Real-world incidence of severe myelosuppression among chronic myeloid leukemia patients treated with imatinib in Ontario

by

Nathan McKenzie

Submitted in partial fulfilment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
April 2024

Dedication

This thesis is dedicated to my wife, Sarah, and to my parents, whose unwavering patience, support, and encouragement made this achievement possible.

Table of contents

List of tables

List of figures

Abstract

Imatinib revolutionized the treatment of chronic myeloid leukemia (CML), transforming a once fatal disease into a manageable condition. The initial clinical trials emphasized its exceptional safety and tolerability, leading to an accelerated approval for CML in 2001. However, imatinib was associated with frequent and severe hematologic adverse events in these studies. These results highlight a lack of emphasis on safety in trials and reveal challenges in generalizing the results from trials with small, restricted patient populations, and short follow-up durations, to a broader, more diverse patient population.

This population-based retrospective cohort study evaluated severe myelosuppression in 1,683 CML patients in Ontario, who initiated treatment between 2002 and 2020. Using administrative data, the real-world incidence of myelosuppression was compared to data from the phase III International Randomized Study of Interferon and STI571 (IRIS) study. This study aimed to enhance the understanding of the risk of myelosuppression in a real-world population of Ontario Drug Benefit (ODB) database subjects by considering the effects of demographic and clinical factors often underrepresented or omitted from RCT patient groups.

The median age of the ODB subjects was 17 years older than the randomized controlled trial (RCT) patients, with three times as many ODB subjects aged 60 or older at treatment initiation. Severe neutropenia and thrombocytopenia were less frequent among ODB subjects (2.5% and 1.8%, respectively) than in the IRIS study (14.3% and 7.8%). Conversely, severe anemia was more prevalent among ODB subjects (8.3%) compared to RCT patients (3.1%). The risk of myelosuppression increased with age, daily dose, and severity of comorbidities, with no difference between sexes. These results highlight the limitations of generalizing RCT results to broader populations, emphasizing the importance of ongoing pharmacovigilance research to develop a more comprehensive understanding drug safety beyond clinical trials.

Abbreviated abstract

Imatinib, approved in 2001 for the treatment of chronic myeloid leukemia (CML) based on its remarkable efficacy, was associated with severe hematologic adverse events in clinical trials. This retrospective study compared the incidence of severe imatinib-induced myelosuppression in 1,683 Ontario CML patients, who initiated treatment between 2002 and 2020, to the incidence reported in imatinib's phase III randomized controlled trial (RCT). The impact of demographic factors on myelosuppression risk was evaluated among the Ontario Drug Benefit (ODB) subjects.

The ODB subjects differed in demographics and had lower incidences of neutropenia and thrombocytopenia, but a higher incidence of anemia compared to the RCT patients. The risk of myelosuppression increased with age, mean daily dose, and severity of comorbidities, with no difference between sexes. These results emphasize the limitations of generalizing RCT results to broader populations and the importance of continued pharmacovigilance research for better understanding drug safety beyond clinical trials.

List of abbreviations and symbols used

CCI	Charlson comorbidity index
CI	Confidence interval
CIF	Cumulative incidence function
CIHI	Canadian Institute for Health Information
CML	Chronic myeloid leukemia
CTCAE	Common Terminology Criteria for Adverse Events
DAD	Discharge Abstract Database (CIHI)
DIN	Drug identification number
FDA	United States Food and Drug Administration
ICD	International classification of disease
ICD-O	International classification of diseases for oncology
ICES	Institute for Clinical Evaluative Sciences
IQR	Interquartile range
KM	Kaplan-Meier
NACRS	National Ambulatory Care Reporting System (CIHI)
OCR	Ontario cancer registry
ODB	Ontario Drug Benefit program
OHIP	Ontario Health Insurance Plan
REB	Research Ethics Board
RCT	Randomized-Controlled Trial
RPDB	Registered persons database
TKI	Tyrosine Kinase Inhibitor

Acknowledgements

First and foremost, I would like to thank my supervisor, Dr. Adrian Levy, for his guidance, support, and patience over the course of my thesis. His mentorship not only enable the successful completion of this thesis but equipped me with invaluable knowledge and skills that will undoubtedly serve as a sturdy foundation for any future endeavors.

I would also like to extend my gratitude to the members of my supervisory committee, Dr. Sanja Stanojevic and Dr. Martin Chasen, for offering their time, support, and invaluable insight. Their feedback, knowledge, and expertise were instrumental in guiding me through this thesis.

I want to express my deepest gratitude to my parents for their boundless unconditional support, love, and encouragement throughout the entirety of this process, and throughout every single step I've taken to get where I am today.

Finally, I cannot express enough how truly grateful I am to have had my wife, Sarah, by my side throughout this journey. Her truly endless patience, love, and support through every challenge and triumph gave me the motivation to see this project through. I will forever be grateful for the sacrifices she has made to help us reach this point, all while consistently supporting and encouraging me through this chapter in our lives. Without her, this accomplishment would not have been possible.

1. Introduction

The introduction of imatinib mesylate, commonly known as imatinib, has revolutionized the treatment of chronic myeloid leukemia (CML). It transformed a once incurable and uniformly fatal condition, with a 20% annual mortality rate and a median survival of 3 to 4 years without treatment, into a manageable condition with a life expectancy comparable to the general population.[1–3]

CML is a myeloproliferative neoplasm, a cancer affecting the blood-forming cells of the bone marrow, with an estimated annual incidence of one to two cases per 100,000 adults.[4–6] Prior to 1983, CML had an eight-year survival rate of less than 15%, which increased to 65% following the introduction of interferon-α in 1983.[4,6] CML is characterized by the Philadelphia chromosome, a genetic abnormality resulting from a translocation between chromosomes 9 and 22, creating the BCR-ABL fusion gene.[4,6] Present in over 90% of CML patients, this mutation results in a constitutively active tyrosine kinase enzyme which leads to uncontrolled proliferation of white blood cells in the bone marrow.[2,7–9] The BCR-ABL gene, identified as the sole oncogenic driver of CML,[10–15] was the first specific genetic alteration associated with a specific cancer and drug target with known oncogenic activity.[16–18] This discovery shifted research towards targeting this specific tyrosine kinase, resulting in the discovery of imatinib which selectively and effectively inhibited BCR-ABL activity.[12,18]

Imatinib was the first rationally developed, molecularly targeted cancer treatment.[1,2,7] In a 1998 phase I trial, 98% of interferon-α resistant patients treated with a dose of at least 300 mg achieved a complete hematologic response, typically within four weeks of starting treatment.[9,19,20] These results were further validated in three large phase II studies, in which 95% of chronic-phase CML patients achieved a complete hematologic response, with fewer toxicities than interferon-α.[19,21–23] Imatinib was granted an accelerated FDA approval in 2001, less than three years after the first trial started and prior to the completion of the ongoing Phase III trial, the fastest cancer drug approval at that time.[2,20]

Imatinib's rapid approval was driven by compelling efficacy data from the phase I and II trials, supported by claims of safety and tolerability in these trials. However, despite imatinib being lauded for its "exceptional" tolerability, severe (grade 3 or higher) hematologic toxicities were

reported in 35 to 45% of chronic phase CML patients and in 50 to 62% of patients with advanced phases of CML.[19–22]

This discrepancy in perceived tolerability is linked to how toxicity was defined in these trials. The classification of myelosuppression during imatinib treatment as an adverse effect is contentious, as it may be a direct result of its intended pharmacological action, potentially indicating efficacy rather than toxicity.[7,19,24–26] Therefore, these trials limited the definition of intolerance to solely nonhematologic effect, reporting hematologic toxicity separately as "laboratory abnormalities".[21,22] This restricted adverse events to the occurrence of rare extramedullary toxicities, suggesting a more favorable safety profile.[19–22,26] While myelosuppression may be the result of the intended pharmacological action, in these instances the effects of imatinib exceed the desired outcome, leading to adverse events that are far from benign with complication that can be life-threatening.[24,27–29] Severe myelosuppression, can have substantial impacts on quality of life due to fatigue, susceptibility to infection, or severe hemorrhaging which can be life-threatening if untreated.[24,27,30] Treating these severe outcomes as routine aspects of treatment reflects a disconnect in acknowledging patient perceptions of toxicity and highlights inadequacies in the assessment and reporting of safety data in clinical trials.[30–33]

While the efficacy of imatinib made it a suitable candidate for an accelerated approval, this decision raised concerns as most robust clinical data is usually collected during phase III trials. Historically, drugs approved before completing a phase III randomized controlled trial (RCT) were often associated with unexpected toxicities or inadequate efficacy in broader populations.[34–36] However, RCTs, while held as the gold standard in clinical research, often emphasize efficacy over safety, resulting in inadequate assessments of adverse events.[32,33,37,38]

RCTs typically have strict eligibility criteria and controlled setting not reflective of the diversity of real-world populations, often excluding older patients and those with comorbidities.[39–41] Their limited duration and sample size hinder the detection of rare or latent adverse events, which become apparent only once a drug is used more broadly.[37,42,43] Despite these limitations, regulatory authorities are advocating for "alternative trial designs" to expedite drug approvals and more timely access to treatments.[44–46] Therefore, targeted therapies are increasingly seeking approval through smaller, shorter, and single-arm trials, raising concerns about the reliability and applicability of safety data from future trials under these less stringent standards.[35,44,47]

Although imatinib has considerably improved CML treatment, it is not without severe adverse events. Frequent severe hematologic toxicities including neutropenia, thrombocytopenia, and anemia can lead to serious complications and greatly impact quality of life.[24,27,30] However, imatinib safety data is primarily derived from RCTs which is limited in its generalizability to real-world populations.[32,33,39] This study aimed to address this gap by comparing the real-world incidence of severe myelosuppression during imatinib treatment to the incidence reported in the phase III International Randomized Study of Interferon and STI571 (IRIS) trial. This study evaluated the variation in the risk of myelosuppression based on factors such as age, sex, comorbidity, mean daily dose, cumulative dose, and the changes in the risk of myelosuppression over time, factors typically unexplored or underrepresented in RCTs. This complements the current understanding of imatinib's real-world safety and highlights the limitations of RCT drug safety evaluations and the need for ongoing, post-market pharmacovigilance to confirm and maintain the safety and effectiveness of approved drugs.

2. Background

2.1. Chronic Myeloid Leukemia (CML)

2.1.1. Epidemiology

CML, a myeloproliferative neoplasm, is characterized by the uncontrolled proliferation of myeloid cells in the bone marrow, leading to elevated white blood cell counts in the bloodstream.[5] CML accounts for approximately 15% of newly diagnosed adult leukemias, with an annual diagnosis rate of one to two individuals per 100,000.[5] The median age at diagnosis is 64 years and it is predominately diagnosed between the ages of 65 and 74. In 2018, 585 Canadians were diagnosed with CML, consisting of 360 men and 225 women, ranking it as the third most common leukemia in adults in Canada.[48] Canadian mortality data reported 124 Canadians deaths due to CML in 2020, 70 of which were men and 54 were women.[48] Historically, the prognosis for CML patients was grim, with a median untreated survival of only 2.4 years, and until the 1980s, it was considered incurable and inexorably fatal.[3,49] Treatments options were at the time were limited in effectiveness. Hydroxyurea and interferon-α did improve survival, but were associated with substantial toxicities and often still led to disease progression within three to five years of diagnosis.[49,50] Allogeneic bone marrow transplantation was a potentially curative option but had a high risk of mortality and was limited to young, healthy patients with suitable donors.[50]

2.1.2. The Philadelphia chromosome

CML is primarily characterized by the presence of the Philadelphia chromosome, or the *BCR-ABL1* gene, a result of translocation between chromosomes 9 and 22.[2,7,51,52] The result of this genetic abnormality is the creation of a continuously active tyrosine kinase protein, which promotes the uncontrolled proliferation of leukemic myeloid cells in the bone marrow, identified as the sole oncogenic driver of CML.[10–15] This discovery was a breakthrough in oncology, as it marked the first time a specific genetic alteration was directly associated with causing a specific cancer, and the first drug target recognized to have distinctly differing activity between normal and leukemic cells.[2,5] As a result, research efforts pivoted towards developing a drug that could specifically target and inhibit the activity of this specific tyrosine kinase.[1,2,16]

2.2. Imatinib Mesylate

2.2.1. Development of imatinib clinical trials

In the late 1980s, Ciba-Geigy (now Novartis) developed STI571, later called imatinib, which demonstrated selective inhibition of *BCR-ABL1* both *in-vitro* and *in-vivo* with minimal impact on normal cells.[2,7,12,16] In June 1998, a phase I dose-escalation trial in 83 chronic-phase CML patients unresponsive to interferon-α, reported that, at a daily dose of 300 mg or higher, 98% achieved complete hematologic responses.[2,19,20] Hematologic responses were durable, typically occurring within a month of treatment, which prompted three single-arm phase II studies in 1999.[19,20,53] These studies involved 532 chronic-phase CML patients following interferon-α failure, 235 accelerated-phase patients, and 260 patients in blast crisis.[2,7,19] Complete hematologic responses were achieved in 95% of chronic-phase patients.[2,7,19] Treatment responses were initially promising in patients with more advanced CML, however relapse was frequent, with most patients in blast crisis relapsing within the first year.[7,54,55]

Imatinib received accelerated market authorization for the treatment of all three phases of CML in May 2001, less than three years from the start of the first phase I study.[2,20] This approval was based on Subpart H of the United States Code of Federal Regulations which permits approvals for drugs treating serious or life-threatening diseases which have no alternative treatment options.[20] Accelerated approvals are based on surrogate endpoints that are "reasonably likely to predict clinical benefit", in addition to post-market studies required to confirm ongoing safety and efficacy, including the International Randomized Study of Interferon and STI571 (IRIS) study for imatinib.[2,20,56] In this phase III trial involving 1,106 patients with newly diagnosed chronic-phase CML, imatinib demonstrated superior efficacy, tolerability, and safety across all measures compared to interferon-α and low-dose cytarabine.[56,57] After 19 months, 95.3% of patients treated with imatinib achieved a complete hematologic response, as did 82.4% of those who switched to imatinib, with a median time to response of 1 month.[56]

2.2.2. Imatinib safety in clinical trials

In oncology clinical trials, the urgency to find and approve effective treatments for life-threatening conditions often leads to a focus on the efficacy related outcomes over the potential risks of adverse events.[38] This emphasis can result in an underrepresentation of the risks

associated with these treatments, as those with demonstrable efficacy may face less scrutiny regarding safety data.[27]

The phase II RCTs consistently reported imatinib to be “well-tolerated”, with a mild toxicity profile, minimal extramedullary adverse events, low discontinuation rates, and no treatment-related deaths.[16,21,22,55,56] While imatinib had fewer toxicities compared to interferon-α, the treatment was not free from adverse events. In contrast with the statements emphasizing imatinib’s tolerability, hematologic toxicities of grade 3 or 4 severity were reported in over a third of the phase II trial patients with chronic-phase CML and over two-thirds of the trial patients in the blast-phase.[19–22] Specifically, 35% of chronic-phase patients had severe neutropenia, 20% severe thrombocytopenia, and 7% severe anemia.[21,22,24,55,56,58] These incidences worsened with disease severity, increasing to 58%, 43%, and 39% for neutropenia, thrombocytopenia, and anemia, respectively, in the accelerated phase, and further increasing to 64%, 62%, and 52% in patients in blast crisis. Treatment discontinuation due to adverse events increased correspondingly from 2% in chronic-phase CML patients, to 3% in accelerated-phase CML, and 5% in blast crisis.[19–22]

The Common Terminology Criteria for Adverse Events (CTCAE), used during the imatinib trials, categorizes low-grade (grade 1 or 2) adverse events as "tolerable and manageable”.[29] In contrast, grade 3 events are considered "severe and very undesirable," often requiring or prolonging hospitalization, or immediate “serious interventions”, while grade 4 events are defined as “potentially life threatening, disabling, or resulting in loss of organ, organ function, or limb”.[29] Therefore, despite reporting that over 60% of blast-phase CML patients experienced severe, potentially life-threatening hematologic complications, the study concluded that imatinib was “well tolerated” with an “acceptable level of toxicity” as it was deemed to be less myelosuppressive than conventional chemotherapy.[21,22]

2.2.3. Myelosuppression during imatinib treatment

Although phase II and III trials routinely classify severe neutropenia, thrombocytopenia, and anemia as tolerable or manageable outcomes, these conditions are far from benign and can post serious, potentially fatal risks or complications for CML patients (See Appendix 1 for myelosuppression laboratory definitions). Severe neutropenia, defined by an absolute neutrophil count below 1,000 cells per microliter, compromises immune function and increases susceptibility to infections.[24,28,59] While sometimes asymptomatic in early stages, it can lead to

neutropenic fever, sepsis, or oral ulcers stemming from an impaired immune response. In untreated, these conditions can be life-threatening, leading to hospitalization, and treatments including blood transfusions, granulocyte colony-stimulating factor treatment, intensive antibiotics, and adjustments to the imatinib treatment.[24,28,59,60]

Severe thrombocytopenia is defined by a platelet count below 50,000 per microliter, a type of blood cell involved in blood clotting and wound healing.[24,28,59] Thrombocytopenia can similarly remain asymptomatic in early stages or mild cases, but can lead to symptoms including easy bruising, petechiae (small red spots under the skin), prolonged bleeding from cuts, and spontaneous bleeding from the gums or nose. In severe cases, there is a risk of life-threatening hemorrhaging in critical organs, such as the brain. Treatment generally requires hospitalization for intensive measures such as platelet transfusions and adjustments in imatinib therapy.[24,59,60]

Severe anemia is characterized by a substantial reduction in the number of red blood cells or hemoglobin concentration, vital for oxygen transport throughout the body.[24,28,59] Symptoms typically include fatigue, weakness, and shortness of breath, which can substantially impact a patient's quality of life, affecting physical energy, cognitive function, and placing strain on the cardiovascular system. While low-grade anemia may be mild or transient, management of severe anemia may require blood transfusions, erythropoiesis-stimulating agents, and adjustments to the imatinib treatment.[24,28,59,61]

The burden of myelosuppression extends beyond its direct symptoms and risks, encompassing indirect factors which can adversely affect patient health and well-being. Symptom management strategies, including blood transfusions, growth factor treatments, and hospitalizations, to address complications, carry further risks and can adversely impact a patient's quality of life.[24,59,60] While early detection and treatment of symptoms can often prevent the worsening of symptoms, myelosuppression often requires dose adjustments or temporary cessation of treatment. However, these dose reductions or treatment pauses have been associated with diminished treatment efficacy, highlighting the challenging balance between mitigating the risk or progression of adverse events and maintaining therapeutic efficacy.[24,26]

2.2.4. Implications of imatinib safety data

The discrepancy between the frequent cases of severe myelosuppression, and seemingly unsubstantiated claims that adverse events during imatinib treatment were rare likely is a result

of how adverse events are defined.[21,22,29,31] Classifying myelosuppression during imatinib treatment as an adverse event can be contentious, as it could be viewed as a direct result of the drug's intended pharmacological action. Imatinib inhibits the activity of the deregulated tyrosine kinase, suppressing the uncontrolled proliferation of myeloid cells, which can lead to sustained bone marrow hypocellularity until normal hematopoiesis can recover. Therefore, myelosuppression may be considered an indication of efficacy rather than toxicity.[19,24–26]

This disconnect highlights a broader issue in clinical research and the drug approval processes, where drug efficacy and regulatory compliance are often prioritized at the expense of a comprehensive evaluation of drug safety, and the patient's perspective on tolerability and quality of life.[30,31,34] This disconnect was apparent in the definition of imatinib intolerance applied in the phase II trials. In these trials, imatinib intolerance was strictly defined as “nonhematologic toxic effects of grade 3 or higher”.[21,22,55] This narrow definition restricted adverse events to rare extramedullary toxicities, implying a more favorable drug safety profile compared to if the hematologic events had been included.[21,22,30] Therefore, despite the frequent occurrence of severe hematologic toxicities, the studies concluded that adverse effects, as per their toxicity criteria, were mild and infrequent.[21,22,24,30]

In clinical trials, the use of the term "tolerability" often diverges from its traditional regulatory meaning. Statements labeling a treatment as "well-tolerated" have been criticized for implying an acceptable safety profile without considering tolerability from the perspective of the patient.[31] These assessments are typically seen as informal, often “colloquial”, conclusions emphasizing a favorable safety-efficacy balance for the purposes of regulatory approvals, rather than accurately reflecting patient experiences or to contribute to a detailed risk-benefit assessment.[31] This issue was also made apparent in imatinib’s phase II trials, where severe myelosuppression was considered an acceptable and "manageable" outcome as long as full treatment discontinuation could be avoided through dose adjustments and symptomatic treatment, irrespective of severity or patient perceptions.[21,22,30]

Assessing a drug's risk-benefit ratio is a complex process and is subject to differing perspectives among regulatory authorities, healthcare professionals, and patients.[62–64] With severe diseases, such as cancer, there is often a higher tolerance for adverse event risks, provided the benefits of treatment are substantial.[31,62,63] Therefore, in the context of oncology, the focus is often on efficacy due to the life-threatening nature of the diseases and lack of alternative treatment

options outside of conventional chemotherapy, resulting in a somewhat diminished emphasis on drug's safety profile.[21,22,30] However, categorizing severe, potentially life-threatening events as manageable or acceptable outcomes minimizes the patient's perspective on safety and their tolerance for acceptable levels of risk. Patient perspectives are essential in assessing drug tolerability and the lack of emphasis on these insights further highlight the inadequacies in drug safety data, which is already limited at the time of approval, hindering the potential for truly informed decision making.[30,31,63–65]

2.3. Drug development and approval

2.3.1. Canadian drug development and approval process

In Canada, all new drugs are evaluated by Health Canada's Health Products and Food Branch for safety, and efficacy.[66,67] Phase I and II trials evaluate the safety, optimal dosage, and initial efficacy of a drug in a small group of typically healthy volunteers, followed by patients with the disease or condition of interest.[66] Phase III trials enroll hundreds to thousands of subjects to confirm a treatment's efficacy compared to placebo or standard care, monitor for adverse events and estimate the risk-benefit balance of the treatment.[66] Following the successful completion of these trials, a Notice of Compliance and Drug Identification Number are issued, indicating the market authorization of the drug in Canada.[66]

RCTs are the gold standard in pharmaceutical evaluation, providing the highest level of clinical evidence for regulatory decisions.[68–71] Their strength lies in two practices: randomization, which minimizes selection bias by evenly distributing patient variables, and blinding, which reduces bias related to expectations by keeping treatment details hidden from participants and researchers.[72,73] RCTs use strict inclusion and exclusion criteria to create a homogeneous study population, improving internal validity by eliminating variability from patients with comorbidities or other factors confounding the association between the treatment and the outcome being studied.[72–75] RCTs have set the standard for phase III trials, providing controlled, reproducible, and minimally biased results. These studies are unparalleled in identifying causal relationships between a treatment and health outcomes when compared to existing standards of care.[72–75]

2.3.2. Balancing timely approvals and patient safety

New drugs typically take 12 years from the time of application to market authorization, with additional delays due to provincial regulatory reviews and funding negotiations further delaying

patient access even after efficacy has been proven.[76–82] However, Imatinib received FDA approval in 32 months, the fastest approval for a cancer drug at the time, and was subsequently approved in many other markets, including Canada within the year.[83,84] This expedited approval was possible as imatinib bypassed the completion of a phase III trial, traditionally necessary for validating a drug's safety and efficacy on a larger scale prior to widespread distribution.[2,16,85] Therefore, imatinib's approval without robust results from an RCT was initially met with apprehension, as historically, drugs approved prior to the completion of RCTs were often later associated with severe toxicity or inadequate efficacy in wider populations.[34–36] The accelerated approval was conditional on the timely completion of an ongoing phase III trial, the preliminary results of which were promising, and commitments to phase IV pharmacovigilance studies and ongoing long-term follow-up.[83,86] Nonetheless, critics expressed concerns about the safety of patients treated before more comprehensive safety data from the phase III trial study were available.[35,36,85,87]

In contrast, the drug approval process is typically criticized for delaying access to potentially life-saving treatments, leading to the loss of overall and progression-free life-years.[47,76,77] Therefore, regulatory agencies are tasked with balancing timely access to treatments for unmet medical needs while ensuring thorough evaluations of safety and efficacy.[36,88,89] To address this, the FDA has introduced several initiatives to expedite drug approvals for rare or severe diseases, including the Orphan Drug Program (1984), Fast-Track Program (1988), FDA Accelerated Approval Program (1992), Breakthrough Therapy designation (2012), and the 21st Century Cures Act (2016).[47,90] These initiatives established frameworks to allow market authorization based on phase II trials, non-randomized studies, or surrogate endpoints, particularly when a phase III RCT may not be feasible.[47,91–93] In Canada, despite the absence of a specific orphan drug framework, systems such as Health Canada's Special Access Program allow access to treatments not listed provincial formularies for severe conditions lacking adequate alternatives. Additionally, Health Canada can issue a "Notice of Compliance with Conditions" (NOC/c), permitting conditional market authorization based on post-market commitments to monitor safety and efficacy.[87,89,91,92,94–96]

2.3.3. Concerns of faster drug approvals

Accelerated drug approvals, which aim to expedite access to potentially life-saving treatments, have raised concerns about the reliability of the study results.[36,47,70,97] Drugs approved through

Fast-Track and Accelerated Approval designations have had higher rates of severe black-box warnings or market withdrawals in the years following their authorization.[35] A review of these initiatives reported a direct correlation between shorter review times and increased rates of severe adverse events.[88] Within 25 years of approval, one out of every three drugs approved since the introduction of the accelerated approval process were issued black-box warnings or had market authorization revoked due to serious safety issues, half of which occurred after 12 years of market availability.[35] Despite these concerns, there has been a notable increase in the number of treatments which qualify for accelerated approval programs in recent years.[35,36,44,88] It was initially anticipated that this designation would apply to approximated two drugs each year, however, 24% of the 108 FDA approvals between 2014 and 2016 were granted to breakthrough therapies.[47] A review of the 31 breakthrough therapies approved between 2013 and 2016 reported that 52% were based on phase I and II trials, 45% relied on a single trial, and 42% relied on trials without a comparator or control group.[71] The ambiguous criteria for granting accelerated approvals has raised concerns about the reliability of safety data in future clinical trials with lower evidentiary standards.[35,44,47]

Regulatory agencies are increasingly adopting "alternative" and "more efficient" trial designs to keep pace with advancements in cancer treatment.[44–46] These designs include small single-arm trials, and innovative protocol designs such as "master protocols," which include basket, umbrella, and platform trials.[98,99] Master protocols enable the development and approval of novel targeted therapies by evaluating multiple drugs across various patient subgroups within a single, cost-effective trial.[100–102] These trials facilitate the study of rare cancers with specific genetic abnormalities where conventional RCTs would be impractical.[44,99,103] However, while alternative trial designs facilitate clinical research, they pose challenges for the adequate detection of adverse events, potentially resulting in an under representation of risk, especially for rare or serious adverse events in newly approved drugs.[44,103,104]

2.4. Limitations of RCT safety data

While RCTs have long been considered the highest level of clinical evidence, they have several limitations in accurately identifying and reporting drug-related harms.[32,33,37] Strict eligibility criteria, essential for ensuring valid results, inevitably limits the generalizability of RCT findings to more diverse post-market populations.[37,42,43] RCT populations are typically younger, with fewer complications, milder disease stages, and fewer comorbidities.[37,105–107] Despite the substantial

proportion of elderly patients within the overall cancer population, they are typically underrepresented or excluded from clinical trials due to eligibility criteria based on age, comorbidities, organ-system abnormalities, or functional limitations.[40,41,108,109] The systematic exclusion of certain patient groups from clinical trials, particularly older patients or those with severe comorbidities who may be more susceptible to drug-related toxicity, limits the generalizability of the study results outside of the context of the controlled RCT setting. This practice may result in an inaccurate understanding of a drug's safety profile, potentially obscuring potential risks until the drug is made available in a broader market, putting already at-risk patients at greater risk of unforeseen toxicity.[105,110]

Similarly, there are concerns about the generalizability of results from trials in specialized settings like secondary or tertiary care settings, or academic centers, which may limit the applicability of the RCT findings outside of those settings. Differences in healthcare delivery systems, the selection of participating clinicians and centers, differences in level of monitoring, and even differences in the way that healthcare professionals interact with patients, may vary greatly from real-world practice in a primary care settings.[111]

RCTs are designed with sufficient statistical power to detect even marginal differences in efficacy and identify common adverse events but are inadequately powered for the detection of rare or delayed adverse events due to limited sample sizes. Therefore, rare or latent events often remain undetected or fail to meet reporting thresholds.[32,33,42,107,112] RCTs typically feature short, predefined follow-up periods, ranging from months to a few years, which prove inadequate for assessing long-term safety, particularly for rare events that may manifest only after prolonged latency periods or repeated exposures.[33,107] Therefore, a drug's safety profile at the time of its approval is typically incomplete, with many rare adverse events only becoming apparent once used in a broader population.[106,107,110] This concern is particularly relevant with the rise of novel systemic drugs, such as imatinib. Given that patients may rely on these medications for years, or even their entire lifetimes, initiating treatment without fully understanding the associated risks can be concerning, leaving patients exposed to unknown risks of rare adverse events.[3,113]

Reporting of safety data in published RCT data is essential for assessing the benefits and risks of treatments. However, compared to efficacy data, much less emphasis is placed on safety.[32] Despite efforts to enhance and standardize safety data reporting in RCTs, such as the introduction of the Consolidated Standards of Reporting Trials (CONSORT) checklist and its

subsequent updates for "harms-related issues", safety reporting remains suboptimal and inconsistent.[32,75,114–117] Inadequate reporting has largely been attributed to inadequate pharmacovigilance training and professional attitudes that may include complacency or fear of being perceived as incompetent or overly cautious.[118–121]

Publication bias further exacerbate this problem, as studies reporting severe adverse events, or failing to demonstrate sufficient treatment benefits, often remain unpublished. This can lead to discrepancies between what is reported in published data and the more complete data from corresponding unpublished sources, resulting in an incomplete portrayal of adverse events actually observed during RCTs.[122–124] The underreporting of safety data compromises the ability of physicians, and patients, who rely on this data to assess treatment risks and benefits, to make adequately informed treatment decisions.[32]

2.5. Rationale

The introduction of imatinib mesylate revolutionized CML treatment, greatly extending life expectancy for patients. However, while most studies have focused on imatinib's efficacy, available safety data is primarily derived from RCT data. Although RCTs are considered the gold standard for clinical evidence and are essential for informing treatment decisions for new drugs, RCTs are limited in the detection and reporting of adverse events, limiting the generalizability of the results to a broader context.[32,33,39] Consequently, there is a gap in the literature regarding imatinib's safety profile, particularly regarding the burden of severe myelosuppression, in a real-world population.

Therefore, this retrospective study aimed to address this knowledge gap by assessing the real-world incidence of severe myelosuppression during imatinib treatment among CML patients in Ontario and comparing it to the incidence reported in the phase III IRIS trial. This study assessed the effects of demographic and clinical factors on the risk of myelosuppression in a patient population with risk factors typically underrepresented in RCT populations. This research not only enhances the current understanding of imatinib's safety in real-world scenarios but also highlights the limitations of solely relying on RCT data for drug safety evaluations and the necessity for continuous, post-market research to ensure the ongoing safety and efficacy of approved drugs.

3. Objectives

The objectives of this study were:

1) to compare the incidence of severe (grade 3 or 4) neutropenia, thrombocytopenia, or anemia, as reported in the phase III IRIS study, with the post-market occurrence of these events
2) to assess the effects of demographic and clinical factors including sex, age, comorbidity, mean daily dose, and cumulative dose, on the risk of severe myelosuppression during imatinib treatment

among subjects enrolled in the Ontario Drug Benefit (ODB) program who initiated imatinib treatment between April 1, 2002, and March 31, 2020.

4. Methods

4.1. Study design

This study was a population-based retrospective cohort study of adult CML patients in Ontario, treated with imatinib from April 1, 2002, to March 31, 2020, based on prescription records from the ODB database. This study adopted an incident user design which began at each subject's earliest imatinib prescription. Any patients previously treated with a tyrosine kinase inhibitor other than imatinib were excluded to prevent the influence of myelosuppression attributable to second or third-generation tyrosine kinase inhibitors.

4.2. Data sources

4.2.1. Administrative datasets

This study used Ontario's administrative health data, accessed through the Institute for Clinical Evaluative Sciences (ICES) in Toronto. Funded by the Ministry of Health, ICES maintains Canada's largest repository of administrative health data, capturing records from all residents of Ontario with valid health card numbers. ICES Data and Analytic Services staff used encoded patient identifiers to link several administrative health databases while ensuring patient confidentiality. This produced detailed health profiles for the study subjects, including demographic and clinical characteristics, healthcare utilization and outcomes, and prescription history. Linked administrative data facilitates large-scale, longitudinal research of the healthcare system in Ontario by providing a diverse and representative sample population.[125,126] The creation of the ICES dataset was requested in June 2021. Based on guidance from the analysts at ICES, the study population was restricted to subjects who initiated imatinib treatment by March 2020 to mitigate the potential influence of the COVID-19 pandemic on the study results.

The data was made available through the ICES Data and Analytic Virtual Environment, a secure virtual desktop infrastructure accessible via an encrypted internet connection.[125] This virtual environment allows researchers to securely analyze the coded data remotely and in compliance with the Personal Health Information Protection Act.[125,127] This infrastructure allowed for remote research from Dalhousie University using Ontario's comprehensive administrative health data.

Ontario Drug Benefit database:

The Ontario Drug Benefit (ODB) database, managed by the Ontario Ministry of Health and Long-Term Care, captures details of prescription medications dispensed to Ontario residents eligible for the ODB program. This includes seniors aged 65 and over, long-term care home residents, those on disability support or social assistance, and those with high prescription drug costs relative to their income.[128,129] Each claim in the ODB database includes the drug identification number, quantity, days supplied, prescription date, cost information, and details about the patient and prescriber. The drug identification number identifies the brand name, active ingredients, strength, and dosage form. An audit of approximately 100 randomly selected prescriptions reported an error rate of 0.7% (95% confidence interval 0.5 to 0.9%), indicating a high level of coding accuracy and supporting the reliability of study conclusions drawn using ODB data.[130]

In this study, the Ontario Drug Benefit database was used to identify subjects dispensed imatinib during the study period. Using the drug identification number, subsequent study variables including mean daily dose, cumulative dose, and treatment duration were calculated. Any records for the prescription of tyrosine kinase inhibitors other than imatinib were identified and used for subject exclusion or for the censoring of follow-up. Any records for the prescription of drugs reported to have potential drug-drug interactions with imatinib were also identified.[131]

Canadian Institute for Health Information - Discharge Abstract Database:

The Discharge Abstract Database, managed by the Canadian Institute for Health Information, is a national repository for inpatient hospitalization data in Canada, excluding Quebec. It captures detailed demographic, administrative, and clinical data related to hospital inpatient discharges, deaths, sign-outs, and transfers**.** All data is derived from patient charts, encoded, and reported to the Canadian Institute for Health Information.[132] Until 2002, diagnosis and procedure data was coded using the International Classification of Diseases, Ninth Revision (ICD-9) system, transitioning to the Tenth Revision, Canadian Version (ICD-10-CA) thereafter. Each hospital discharge record captures the most responsible diagnosis alongside up to fifteen other diagnoses or comorbidities. To ensure data quality, the Canadian Institute for Health Information conducts annual data quality assessments, supporting its suitability for research.[132]

In this study, the Discharge Abstract Database was used to identify cases of severe myelosuppression using ICD diagnostic codes. This methodology for identifying outcomes related to myelosuppression in Ontario has been validated in previous research.[133–137] Additionally, when available, ICD codes were used as a secondary source to confirm or verify cancer diagnoses data.

Canadian Institute for Health Information - National Ambulatory Care Reporting System:

The National Ambulatory Care Reporting System, managed by the Canadian Institute for Health Information, captures data related to hospital and community-based ambulatory care. In Ontario, detailed demographic, administrative, and clinical data have been systematically recorded from emergency departments, day surgeries, and outpatient clinics since 2001.[138] The data extraction and encoding process is consistent with that of the Discharge Abstract Database. Annual quality assessments are conducted by the Canadian Institute for Health Information to ensure data accuracy and consistency. The data quality analysis for 2019 to 2020 indicated that the coverage of records submitted by participating Canadian facilities was 84%, with an over-coverage rate of 0.11% due to duplicate records.[138]

In this study, the National Ambulatory Care Reporting System database was used to identify cases of severe myelosuppression reported during ambulatory care using ICD diagnostic codes. This methodology for identifying outcomes related to myelosuppression in Ontario has been validated in previous research.[133–137,139,140] Additionally, when available, ICD codes were used as a secondary data source to confirm or verify cancer diagnoses data.

Ontario Cancer Registry:

The Ontario Cancer Registry, managed by Cancer Care Ontario, is the largest provincial cancer registry in Canada. It captures cancer diagnoses and cancer-related mortalities from hospital records, pathology reports, regional cancer centers, and death certificates, providing detailed information on patient demographics, cancer stage at diagnosis, treatment received, and patient outcomes. Diagnoses are encoded and standardized using the International Classification of Diseases for Oncology, third edition (ICD-O-3), indicating morphology and topography.[141] Cancer Care Ontario routinely evaluates data quality using the National Cancer Institute's Surveillance, Epidemiology, and End Results program standards, consistently meeting the criteria for 'Gold' certification across all quality indicators.[142] In 2016, microscopic examination confirmed 81.9% of leukemia cases, with only 0.9% identified from death certificates alone.

In this study, data from the Ontario Cancer Registry was used to confirm CML diagnoses among ODB subjects. All newly diagnosed cases of cancer in Ontario, and 95% of the pathology reports, are recorded in this registry, providing a standardized and validated method of classifying cancer patients using administrative data for clinical research.[143,144]

Ontario Health Insurance Plan claims history database:

The Ontario Health Insurance Plan claims database, managed by the Ontario Ministry of Health and Long-Term Care, is a provincial database which captures data from all billing claims for publicly insured health services in Ontario.[145] This database captures detailed data from routine healthcare interactions, including physician visits, hospital admissions, diagnostic tests, and surgical procedures. Data includes patient demographics, service types and date, healthcare provider details, and administrative data. Capturing billing data from approximately 94% of Ontario's physicians, Ontario Health Insurance Plan claims database represents nearly the entire insured population of Ontario.[146] Therefore, this database provides a rich resource for clinical research, encompassing a wide range of patient ages and demographics. This database is routinely updated through the health care renewal process to ensure the data is accurate and up to date.

In this study, the Ontario Health Insurance Plan claims database was used for the purpose of obtaining demographic information, specifically age, sex, and comorbidities.

Registered Persons Database:

The Registered Persons Database, maintained by the Ministry of Health and Long-Term Care in Ontario, captures vital and demographic information for all residents issued an Ontario Health Insurance Plan card. It includes data on date of birth, sex, location of residence, date of last contact with the healthcare system, and, if applicable, date of death. As this system is used in the management of Ontario's publicly funded healthcare services, the database is continuously updated through registration activities to ensure that all information remains accurate and up to date.[144,147]

In this study, the Registered Persons Database was used for the purpose of determining the date of death, if applicable, and the date of last contact with the healthcare system for each subject. It was also used alongside the Ontario Health Insurance Plan claims database to confirm demographic information, such as age and sex as needed.

4.2.2. RCT data

The RCT data used for this analysis was taken from the phase III IRIS study, published in 2003 following the approval of imatinib in 2001.[56] The earliest safety data used for the approval of imatinib was collected during the phase I clinical trial which began in 1998, which was confirmed in three open-label phase II studies which began in 1999.[19,21,22] The results of these trials, reinforced by preliminary results from the IRIS study, supported the approval of imatinib, establishing it as the standard first-line treatment for all three phases of CML.[20,148] Subsequent RCTs for new tyrosine kinase inhibitors or new treatments for CML were assessed against imatinib comparator arms.[30] Safety data from these phase III RCTs with imatinib comparator arms were aggregated in a review by Steegman et al., which was used to confirm the reliability of the adverse event data reported in the IRIS study.[30]

4.2.3. Ethical considerations

This research was approved by the Health Sciences Research Ethics Board at Dalhousie University, which confirmed the study was conducted in accordance with the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans (REB #2020-5280). Annual ethics reports were submitted to the Research Ethics Board every 12-month following the initial approval. This process ensured ongoing approval of the research throughout the duration of the study.

After receiving approval from Dalhousie University Research Ethics Board, an ICES Data and Analytic Services agreement (#2020-734) was granted, enabling remote access and analysis of the study data. All ICES administrative data was de-identified after linkage to ensure patient confidentiality. In accordance with the terms of the ICES Data and Analytic Services agreement, any result with a cell value less than six was suppressed to further mitigate potential identification.

4.3. Study population

The target population for this study was all adult patients in Canada using imatinib for the treatment of CML. While this study was conducted within the framework of the Canadian healthcare system, the findings may have broader applicability outside of the Canadian context depending on the similarity of prescribing practices and the regulatory guidelines for the treatment of imatinib using CML.

The available population was all adult patients in Ontario diagnosed with CML who were prescribed imatinib for the treatment of CML, identified using prescription records in the ODB database. Administrative health data from Ontario was chosen to identify a large, sample population representative of the broader Canadian target population. The study population in consisted of adult patients in Ontario with a confirmed CML diagnosis in the Ontario Cancer Registry database who, based on ODB database prescription records, initiated imatinib treatment between April 1, 2002, and March 31, 2020.

4.4. Inclusion and exclusion criteria

The selection of the initial study population was done by ICES Data and Analytical Services staff. This preliminary population included any subject with at least one imatinib prescription record between April 1, 2002, and March 31, 2020, recorded in the ODB database. During the initial screening process, subjects were deemed ineligible if they lacked a valid ICES identifier, had incomplete or missing data related to age or sex, were under 18 years of age at initial diagnosis, or a death date which occurred prior to the index date.

Of the subjects initially enrolled in the sample population, subjects included for analysis in the study analysis required a valid CML diagnosis, and valid treatment characteristics. In the context of this study, a valid CML diagnosis was defined as a record in the Ontario Cancer Registry with specific morphology codes indicating CML (ICD-O-3: 98633, 98753), and a topography code indicating a primary site in the bone marrow (ICD-O-3: C421) (See Appendix 2). Select morphology codes for non-specific myelosuppressive leukemias were considered if supported by corroborating CML diagnosis codes from the Discharge Abstract Database or the National Ambulatory Care Reporting System (ICD-10-CA: C92.1). Subjects were excluded from the study if they had a primary cancer diagnosis other than CML, or if their cancer diagnosis data was missing or incomplete. Additionally, inconsistencies in the index or diagnosis dates, particularly cases where treatment with imatinib commenced significantly before the cancer diagnosis date, resulted in exclusion**.** Furthermore, subjects who were prescribed any tyrosine kinase inhibitor other than imatinib before starting imatinib treatment were also excluded from the study.

4.5. Study timeline and follow-up

Beginning on April 1, 2002, the administrative health records of each subject were prospectively analyzed, commencing from the date of their initial imatinib prescription record within the ODB

database, defined as the index date. Subsequent imatinib dispensation dates or outcome event dates were measured as the number of days elapsed since the index date. The inclusion of new subjects concluded on March 1, 2020, with a maximum follow-up date of March 30, 2020, on which the study concluded, ensuring that all subjects had a minimum potential follow-up duration of at least 30 days. Baseline health, comorbidities, and demographic information for the subjects were collected within a two-year lookback period prior to the index date, starting no earlier than April 1, 2000.

Administrative health data was used to monitor each subject's interactions with the healthcare system, from their index date until the completion of their final recorded imatinib prescription, with an additional 14-day period for adverse event monitoring. Follow-up was ended upon a subject's death, or if they initiated treatment with a tyrosine kinase inhibitor other than imatinib, with data collection ending the day prior. Subjects with treatment gaps exceeding 30 days between the completion date of one prescription to the dispensation of the next prescription were censored 14 days after the completion of the previous prescription to mitigate the risk of immortal time bias. This ensured that subjects who paused treatment weren't considered at risk if longer receiving treatment or if dispensation records couldn't be confirmed.

Data from each subject was continuously captured prospectively, including multiple and recurrent events, to be used in comparative and exploratory analyses. However, a time to first-event model was used for the primary survival analysis, therefore, subjects contributed no additional data following the earliest instance of severe myelosuppression, if applicable. The full study timeline is depicted in **Figure 1** and **Figure 2**.

4.6. Exposure

Exposure was defined as the use of imatinib, based on prescription records in the ODB database. Relevant prescriptions records were identified using the drug information number for any imatinib-containing product which was granted market authorization in Health Canada's Drug Product Database, selecting those with drug information numbers for imatinib that had been authorized for market in Canada. This included products that were canceled post-market, dormant at the time of data access, or obtained through special access programs outside the Ontario drug formulary. (See Appendix 3 for the full list of DINs for imatinib identification).

Figure 1: Study observation period in calendar time

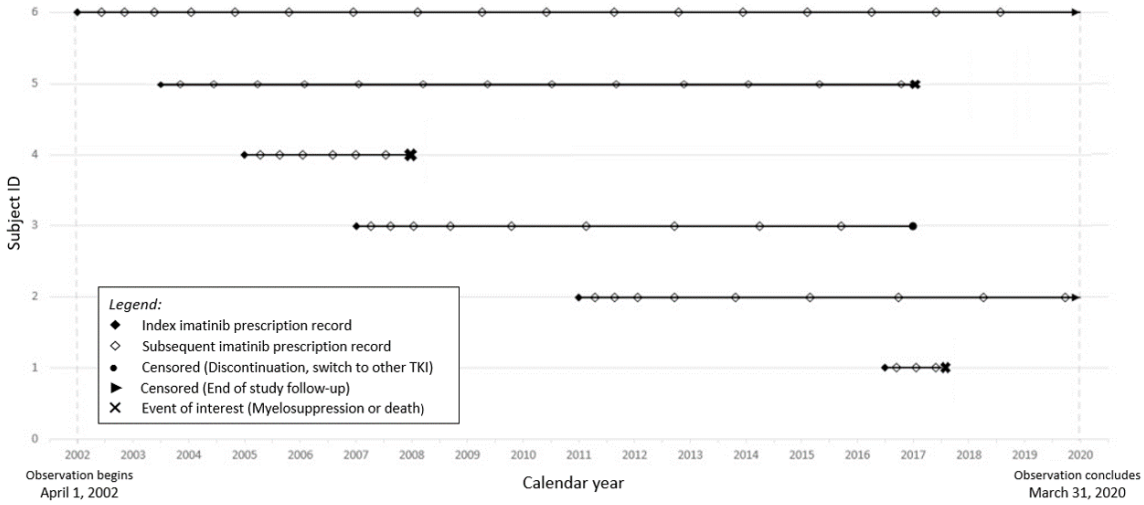
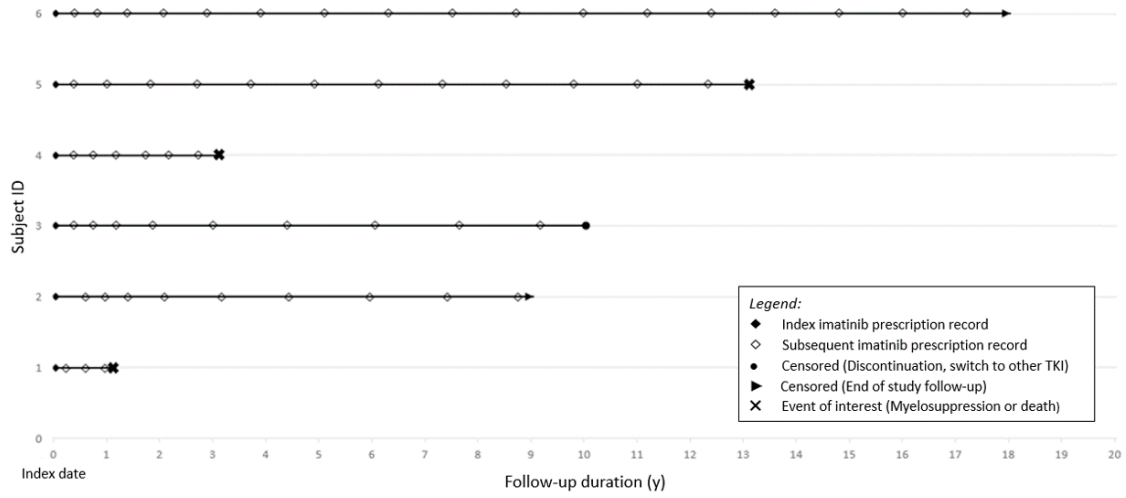


Figure 2: Study observation period in scientific time



In this study, imatinib exposure was determined by the presence of at least one prescription for any imatinib product, including generics, in the ODB database with a valid Health Canada drug information number. Relevant drug information numbers provided insight into the prescription record, allowing for the calculation of variables related to repeated exposure, total cumulative dose, and treatment duration. This definition assumed that dispensed prescriptions had perfect adherence in all subjects, potentially overestimating the true exposure due to non-compliance.

However, one study reported that CML patients had a median adherence of 98%,[149] while another review reported that patient adherence to imatinib was uniformly very high, with an average percentage of prescribed imatinib taken of 90.9%.[150]

4.7. Covariates

This study considered the influence of demographic and clinical characteristics often associated with an increased risk of myelosuppression, which are typically underrepresented or omitted from RCT patient groups. The primary covariates of interested in this study, based on the available data included age, sex, mean daily dose, cumulative dose, and comorbidity.

Previous studies have linked both older age and female sex with a higher risk of myelosuppression.[7,151–153] In this study, to assess the differences in the risk of myelosuppression across different demographics, subjects were stratified by male or female sex, and age at index was categorized into five-year subgroups. As a subgroup analysis, subjects were divided into two categories: those aged 65 and older, who were automatically eligible for the ODB program, and those under 65 years old.

Results from RCTs on imatinib have indicated an association between higher daily doses and increased rates of adverse events, with some evidence suggesting potential long-term adverse effects.[148,154–157] To explore this dose-response relationship, each subject's mean daily dose of imatinib, derived from ODB prescription records, was categorized into four groups increasing in increments of 100 mg per day. Total cumulative exposure to imatinib, from index date to study end, was also calculated to evaluate potential cumulative drug toxicity. While long-term follow-ups have typically demonstrated a stable safety profile after the first year, this has rarely been examined in a real-world context.[24,30,56]

Comorbidities are also associated with an increased risk of myelosuppression.[158–162] To assess this association in a real-world population, Charlson Comorbidity Index scores for each subject were extracted from the Ontario Health Insurance Plan claims database. The risk of myelosuppression was assessed based on CCI scores which were grouped into four categories: no comorbidities, mild, moderate, and severe comorbidities.

The study aimed to assess how concomitant drug use influences the risk of myelosuppression, due to potential interactions with imatinib.[131] Drugs with potential interactions were selected based on the IRIS study exclusion criteria, known contraindications, or drugs with interactions

reported in a study by Récoché et *al*.[131] Prescription records for the drugs of interest dispensed alongside imatinib were identified using Ontario's drug formulary and Health Canada's Drug Product Database (See Appendix 4 for DINs). However, due to the number of characteristically different drug types, and the infrequent use of contraindicated drugs during imatinib treatment among the ODB subjects, this analysis was not included in the current study.

4.8. Outcomes

4.8.1. Outcome definition

The primary outcome of this study was of severe myelosuppression during imatinib treatment. This included severe cases of neutropenia, thrombocytopenia, or anemia, which were the most common severe adverse events reported during the IRIS study.[56] The outcomes were defined and identified using relevant ICD-9 and ICD-10-CA diagnostic codes collected from the Canadian Institute for Health Information's National Ambulatory Care Reporting System or Discharge Abstract Databases.[135,163–165] The outcome definition excluded ICD codes for anemias specified as attributable to nutritional deficiencies, congenital anemia, or otherwise specified as outcomes unrelated to cancer, chemotherapy, or drug use. However, commonly used non-specific ICD codes, such as "anemia, unspecified," were included in the primary analysis. (See Appendix 5 for ICD codes used to identify anemia, neutropenia, and thrombocytopenia).

This study focused on severe adverse events, given that lower-grade adverse events are typically mild and may resolve without intervention. Severe adverse events, classified as grade 3 or higher according to the Common Terminology Criteria for Adverse Events grading system, are typically defined as requiring hospitalization or medical intervention. Therefore these events were expected to be identifiable using ICD diagnostic codes in administrative health data.[28,29] Unlike the IRIS study, which used laboratory blood tests to identify myelosuppressive events and determine severity through precise blood cell counts, such laboratory tests were not available for this study. Outcome events were identified based on ICD diagnostic codes, which are coded by nosologists and recorded primarily for billing purposes. As a result, adverse events were deemed "severe" based on a hospital interaction rather than precise blood cell count thresholds.

In this study, death occurring during imatinib treatment was considered a secondary outcome and treated as a competing event if it precluded the potential observation of the primary study

outcome.[166–168] Subject death data, where applicable, was derived from the Registered Persons Database which records dates of death in Ontario.

4.8.2. Outcome validation

Prior research in Ontario has validated the use of ICD codes in administrative health data to identify myelosuppression during chemotherapy with acceptable levels of misclassification.[133–137] These studies reported high specificity and negative predictive values, however sensitivity varied depending on the specific outcome under investigation and the algorithm used for identification. This variability was anticipated, given the inherent limitations and potential variability of coding in administrative health data.[133–135,139]

An Ontario study conducted by Krzyzanowska *et al*. found that the accurate detection of myelosuppressive events was contingent on how the outcome definition was applied.[133] The algorithm for "moderate" neutropenia had 69% to 97% sensitivity and 83% to 98% specificity, while the algorithm for "general" neutropenia had higher sensitivity (94% to 98%) but lower specificity (64% to 80%).[133,134] These findings suggest that establishing a universal "gold standard" outcome definition for detecting myelosuppression in observational studies is unlikely. The variability in coding, interpretation, and precision of administrative health data means that defining outcomes using secondary administrative data will typically require a trade-off between specificity and selectivity, based on the particular objectives of the study.[29,135] Therefore, this study's outcome definition was focused on severe cases of myelosuppression expected to result in hospitalization or require medical intervention.

4.9. Statistical methods

4.9.1. Incidence of myelosuppression

The occurrence of severe myelosuppression was calculated using incidence proportion and incidence rate, the typical methods for reporting adverse events in RCTs. The frequency of severe adverse events was assessed at six months, one year, and five years to estimate how the incidence rate varies over time in a real-world context.

4.9.2. Objective 1

A one-sample test of proportions, with 95% confidence intervals, was used to compare the incidence of severe myelosuppression observed among the ODB subjects to the incidence proportions for neutropenia, thrombocytopenia, and anemia reported in the IRIS study.

This analysis (objective 1) treated neutropenia, thrombocytopenia, and anemia as distinct myelosuppressive events. The IRIS study provided incidence rates for each event separately without indicating how many patients experienced more than one type of event. Consequently, without data on the overlap between patients affected by each condition, it was not possible to compare the overall occurrence of any-type severe myelosuppression as an aggregate event.

4.9.3. Objective 2

A Fine-Gray subdistribution hazard regression model, with 95% confidence intervals, was used to estimate the risk of severe myelosuppression during imatinib treatment , and to determine if the risk of myelosuppression varied based on demographic and clinical factors including sex, age, comorbidity, mean daily dose, and total cumulative dose. Each regression was conducted as an unadjusted univariate regression model, which estimated the relative risk of severe myelosuppression for each subgroup within each covariate compared to a reference group.

The Fine-Gray subdistribution hazard regression model was used to account for death as a competing event, unlike conventional survival analysis models that treat competing events as censored, potentially leading to an overestimation of risk. While real-world studies involve many events that could be categorized as competing risks, in this analysis, death was considered as the sole competing event based on the available data.[166,169,170]

This analysis considered any instance of severe myelosuppression, including neutropenia, thrombocytopenia, or anemia, as a single aggregate outcome. Despite the established association between imatinib and myelosuppression, the specific mechanisms leading differentiating each type of myelosuppression is not well understood. Therefore, in the context of this study, the occurrence of each event could not reasonably be assumed to be independent of each other.[15,24,171]

4.9.4. Cumulative incidence functions

Cumulative incidence function (CIF) curves were generated for each of the primary covariates of interest to illustrate the probability of a subject developing severe myelosuppression over the course of the study. The CIF derived from estimates of the Fine-Gray subdistribution hazard regression model, accounting for death as a competing event, was also plotted alongside the complement of the survival curve derived from the Cox proportional hazards model. This figure was developed to illustrate and compare the risk of myelosuppression over the course of the study when considering the influence of competing events.[166,172]

4.9.5. Sensitivity analyses

Multiple sensitivity analyses were conducted to evaluate the stability of the findings. In all sensitivity analyses, the same statistical model was applied with additional models fit under the following constraints:

Objective 1 - sensitivity analysis:

To validate the consistency of the study findings, and the replicability of the results from the IRIS study, a sensitivity analysis was conducted for objective 1. This analysis compared the incidence of myelosuppression among the ODB subjects with both the rates reported in the IRIS study and the pooled safety data from nine separate phase III RCTs featuring an imatinib comparator arm. The purpose was to evaluate how the ODB results aligned with those of the IRIS study and assess the generalizability of these findings to other imatinib RCT outcomes.

Objective 2 - sensitivity analyses:

To evaluate the impact of death as a competing event on the association between imatinib and myelosuppression, the Cox Proportional Hazards regression model was also used to estimate the risk of myelosuppression. This model treats competing risks as censored events and estimates risk with cause-specific hazard ratios. The estimates from each model were compared to determine if the use of either model would alter the interpretation of the study results, and to offer methodological insights for future research. If the estimates from both models were consistent, the results from the Fine-Gray competing risks model, deemed more appropriate for survival analysis of adverse events, were treated as primary findings.[166,169,170]

To evaluate if the findings of this analysis differed between subjects automatically enrolled for comprehensive coverage of prescription drug costs through the ODB program, and those under 65 years old with incomplete coverage or incomplete prescription records not captured in the ODB database, a sensitivity analysis was conducted. This sensitivity analysis restricted the regression analysis to subjects who were 65 years of age or older at the time of their index prescription to compare if the results of this analysis were comparable to the results of the full population, to determine if the findings of the study were robust.[130]

To assess if the initial outcome definition for myelosuppression, particularly for anemia, was overly broad, resulting in misclassification of unrelated events as being drug-induced, a sensitivity analysis was conducted using a more precise definition. The initial definition of anemia only excluded ICD codes for types of anemia that specified as unrelated to CML or chemotherapy, such as nutritional or congenital anemia. (See Appendix 6 for the full list of ICD codes defining any-type myelosuppression). This sensitivity analysis was conducted using a refined definition which further excluded unspecified anemia (ICD-10 code: D64.9) and “anemia in other chronic diseases classified elsewhere” (ICD-10 code: D63.8). This analysis aimed to enhance specificity and reduce false positives, and to assess potential impacts on the interpretation of the results.

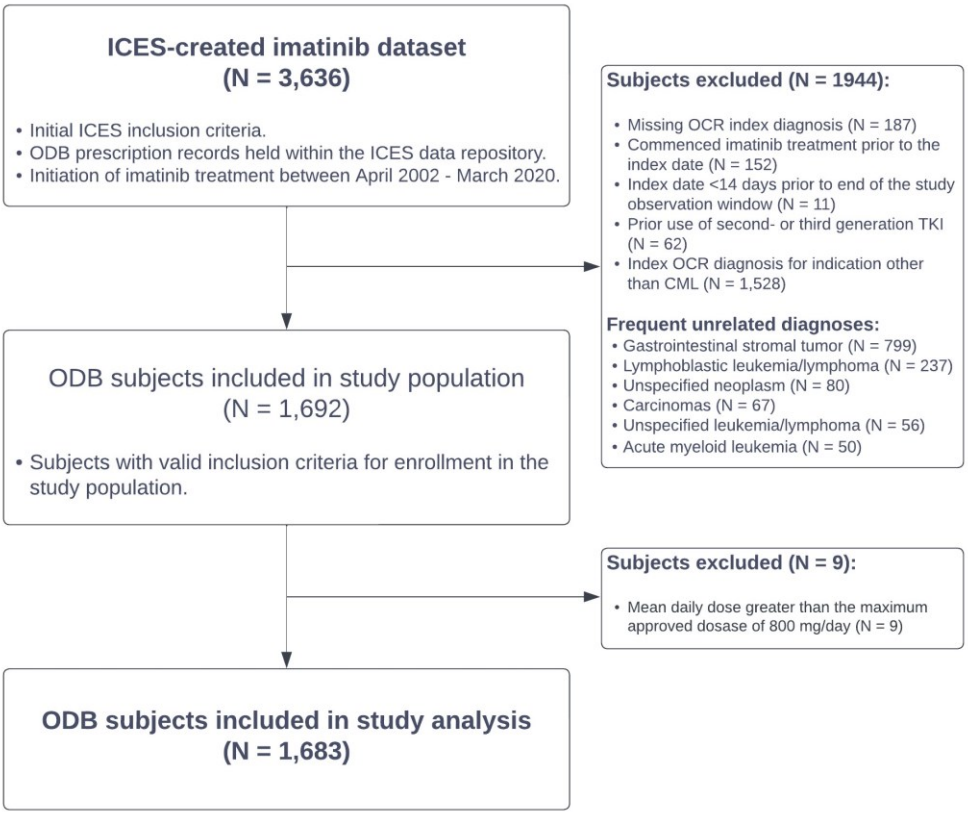
5. Results

5.1. Study population

A preliminary screening of the ODB database prescription records identified 3,636 subjects who initiated imatinib treatment between April 1, 2002, and March 31, 2020. Of these subjects, 1,683 met all the inclusion criteria for the study. A total of 1,944 subjects were excluded, mainly due to having a cancer diagnosis other than CML. **(See Figure 3**).

Based on an initial estimate of over 65,000 imatinib prescriptions in the ODB database, at the onset of this study it was calculated that at least 1,376 CML subjects would be required to detect a 5% difference in the incidence of myelosuppression between the ODB subjects and RCT patients, assuming a significance level (α) of 0.05 and a power (1 – β) of 80%. (Data not shown) Therefore, the inclusion of 1,683 unique subjects exceeds the suggested threshold for adequate statistical power for this analysis.

Figure 3: Flow diagram for the selection of the study population



5.2. Descriptive analysis

Demographic data and clinical characteristics of the ODB subjects and RCT patients are presented in **Table 1**. Noteworthy discrepancies were observed in the age and the distribution of sexes in the ODB subjects compared to the RCT patients. The ODB subjects were generally older, with a proportion of subjects who were 60 years or older at the index date, more than triple the proportion among the RCT patients. Additionally, the ODB subjects had a lower proportion of male subjects compared to the RCT patients.

The RCT data provided detailed information on patient health and disease severity, including laboratory test results, Sokal Index for CML, and ECOG performance status.[56] In contrast, these details were not available for the ODB subjects based on the accessible data. Stratified demographic and clinical data for the ODB subjects is presented in **Table 2**. The predominant age group at study entry, when stratified by decade, was 65 to 75 years old. Notably, 34.1% of the ODB subjects were over 70 years and thus would have been ineligible for the IRIS study, while another 42.0% were under 65 years, indicating their enrollment in a special access program for ODB reimbursement. Comorbidity data, measured by CCI, was available for 53.1% of the study population, 60.7% of which had a CCI score of at least one at study entry.

Table 1: Baseline characteristics of the ODB subjects and the RCT patients

Characteristic	ODB subjects (N = 1,683)	IRIS study (N = 551)
Sex (%)		
Male	55.7	61.7
Female	44.3	38.3
Age (y)		
Median	67	50
Range (IQR)	18 – 87 (52 – 72)	18 – 70
≥ 60 y (%)	65.9	20.4
Daily dose (mg/day)		
Mean	405.2 ± 81.9	400.0
Range (IQR)	100.0 – 800.0 (400.0 – 400.0)	114.0 – 732.0
Follow-up (mo)		
Median	1.9	2.1
Range (IQR)	0.0 – 218.1 (0.8 – 14.8)	0.0 – 10.4

*IQR = Interquartile range

* Variables including ECOG score, CML phase at diagnosis, SOKAL risk for CML, or laboratory test results were not available.

Table 2: Stratified clinical and demographic data of the ODB subjects

Covariate	ODB subjects (N = 1,683) %
Sex	
Male	55.7
Female	44.3
Age group (y)	
<45	15.0
45 - <55	11.4
55 - <65	15.6
65 - <75	37.9
75 - <85	16.3
≥85	3.9
Mean daily dose (mg/day)	
<350	11.3
350 - <450	76.4
450 - <550	5.9
≥550	6.45
Total cumulative dose (g)	
<200	55.1
200 - <400	16.3
400 - <600	8.0
600 - <800	5.9
≥800	14.7
Comorbidity (CCI)	
0	20.9
1 – 2	22.7
3 – 4	7.0
≥5	2.6
Missing	47.0

*Sokal Index for CML, and ECOG performance status scores, or CML phase severity data were not available for this study
*Analyses of comorbidity data were based on the 893 subjects with recorded CCI data

5.3. Incidence of severe myelosuppressive events

The incidence of each event is detailed in **Table 3**. Notable differences in the incidence of each event were observed between ODB subjects and RCT patients. The total incidence of severe neutropenia and thrombocytopenia was lower in ODB subjects (2.5% and 1.8%) compared to RCT patients (14.3% and 7.8%), while the incidence of severe anemia was greater in ODB subjects (8.3%) compared to RCT patients (3.1%).

5.3.1. Sensitivity analysis – IRIS study vs. pooled phase III imatinib data

In a sensitivity analysis, the incidence proportions for each myelosuppressive event reported in the IRIS study were comparable to the proportions determined using pooled data from multiple phase III RCTs.[30] Therefore, the findings of the study analysis are consistent whether using data from the IRIS study or pooled data from multiple phase III studies (See Appendix 7 for demographics and Appendix 8 for results).

Table 3: The incidence of severe myelosuppression reported among the ODB subjects compared to the values reported in the IRIS study

	ODB subjects (N = 1,683)	RCT patients (N = 551)	Mean difference	95% CI of the difference	
Adverse event	**%**	**%**	**%**	Lower	Upper
Total follow-up period					
Neutropenia	3.0	14.3	-11.3	-12.1	-10.5
Thrombocytopenia	2.3	7.8	-5.5	-6.3	-4.8
Anemia	12.7	3.1	9.6	8.0	11.2
RCT-matched follow-up					
Neutropenia	2.5	14.3	-11.8	-12.6	-11.1
Thrombocytopenia	1.8	7.8	-6.0	-6.7	-5.4
Anemia	8.4	3.1	5.3	4.0	6.6

*****Maximum RCT follow-up (25 months) period estimated using the published Kaplan-Meier survival curves

5.4. Risk of severe myelosuppression

Estimates of the Fine-Gray competing risks regression analysis are presented in **Table 4**. The key study covariates associated with the risk of myelosuppression were age, comorbidity, and mean daily dose. The risk of myelosuppression increased with age, most notably in subjects over 85 years old, compared to subjects under 45 years of age. Severe comorbidities (CCI ≥5) and high doses of imatinib (>550 mg/day) were also associated with an increased risk of myelosuppression. There was no observed difference in risk between male and females subjects.

5.4.1. Sensitivity analysis – cause-specific hazard vs. subdistribution hazard

Estimates of the risk of severe myelosuppression derived from the Cox proportional hazards and Fine-Gray subdistribution hazard models were found to be consistent in terms of direction and magnitude across all study covariates. As the estimates were consistent, the Fine-Gray subdistribution hazard model, accounting for death as a competing risk, was selected as the primary model for the analysis (See Appendix 9 for results).

Table 4: Estimates of the risk of severe myelosuppression derived from the Fine-Gray subdistribution hazard model

Demographic/clinical variable	Subdistribution hazard ratio	95% CI
Sex		
Male	1.0 (Reference)	1.0 (Reference)
Female	1.0	0.8 – 1.3
Age group (y)		
<45	1.0 (Reference)	1.0 (Reference)
45 - <55	1.5	0.8 – 3.1
55 - <65	1.3	0.7 – 2.5
65 - <75	2.3	1.4 – 3.9
75 - <85	3.7	2.1 – 6.6
≥85	4.3	2.0 – 9.0
Mean daily dose (mg/day)		
<350	1.1	0.7 – 1.6
350 - <450	1.0 (Reference)	1.0 (Reference)
450 - <550	0.9	0.5 – 1.6
≥550	1.6	1.0 – 2.5
Total cumulative dose (g)		
<200	1.0	0.4 – 2.0
200 - <400	1.0 (Reference)	1.0 (Reference)
400 - <600	3.4	1.4 – 8.1
600 - <800	2.5	0.9 – 6.7
≥800	4.4	1.6 – 12.2
Comorbidity (CCI)*		
0	1.0 (Reference)	1.0 (Reference)
1 – 2	1.3	0.9 – 1.8
3 – 4	1.6	1.0 – 2.7
≥5	3.2	1.8 – 5.7

*CCI was calculated based on the ODB subjects with available CCI data (893/1,683)

5.5. Temporality of events

The incidence proportion and incidence rate of severe myelosuppression at six months, twelve months, five years, and throughout the total observation period are shown in **Table 5**. The rate was highest in the initial six months and lowest across the total period. Notably, within the first five years of imatinib treatment, half of the observed cases of severe myelosuppression occurred in the first six months. Cumulative incidence curves illustrating the risk of severe myelosuppression over time for each study covariate, derived from the Fine-Gray subdistribution hazard model, are presented in **Figure 4.** Compared to the Fine-Gray CIF curves, the survival curves from the complement of the Kaplan-Meier function show a slight increase in risk of myelosuppression over time (See Appendix 10 for results).

Out of 707 cases of severe myelosuppression, 43.5% occurred in the first year of treatment, 37.8% between one and five years, and 18.7% after five years. Interestingly, neutropenia and thrombocytopenia were typically observed within the first 12 months, while anemia was the predominant myelosuppressive event observed following the first year of treatment. Specifically, for neutropenia and thrombocytopenia, 66.7% occurred in the first 12 months, 22.5% within one to five years, and 10.9% after five years of treatment. In contrast, for anemia, 38.4% occurred in the first 12 months, 41.2% between one to five years, and 20.4% after five years. The average time to severe anemia onset within the first five years (19.6 ± 18.3 mo) was more than double that for severe neutropenia or thrombocytopenia (8.4 ± 11.1 mo).

5.5.1. Sensitivity analysis – redefining anemia

When considering a refined definition for the classification of anemia, namely excluding instances of unspecified anemia (ICD-10 code: D64.9) or "anemia in other chronic diseases classified elsewhere" (ICD-10 code: D63.8), a notable reduction in the number of severe anemia cases was observed. However, the incidence of each myelosuppressive event remained statistically different from the IRIS study, and the estimate subdistribution hazard ratios remain consistent with the previous model. (Results not shown).

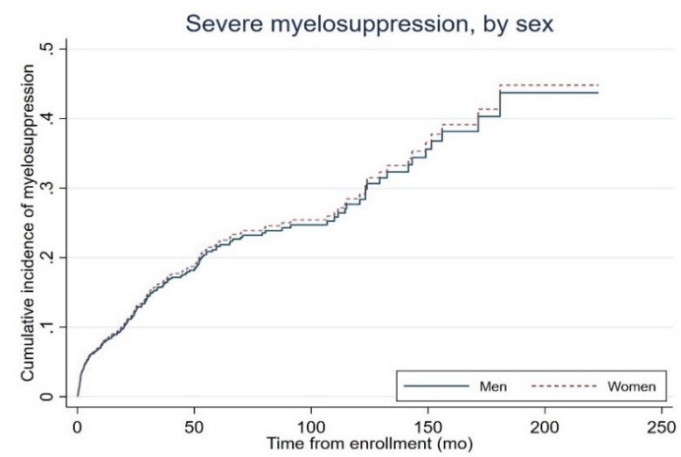
Table 5: Incidence rates of severe myelosuppression among the ODB subjects

	ODB subject follow-up (N = 1,683)			
Myelosuppression	**6 months**	**12 months**	**5 years**	**Total**
Incidence (%)	6.8	8.4	13.7	15.6
Incidence rate*	135.6	105.1	67.5	56.9

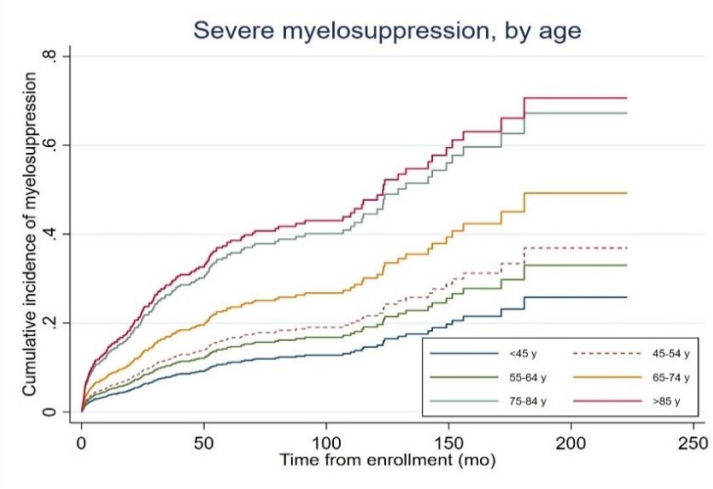
*Incidence rate per 1,000 person years

Figure 4: CIF of the probability of severe myelosuppression over time for each covariate

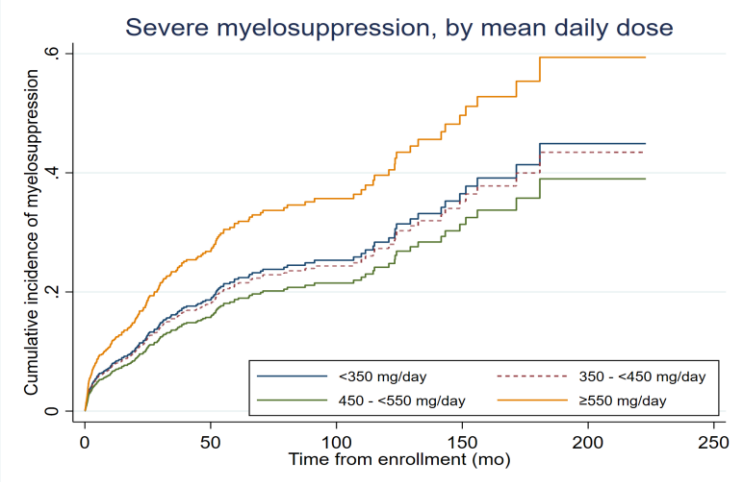
Figure 4a) CIF of the probability of myelosuppression by sex



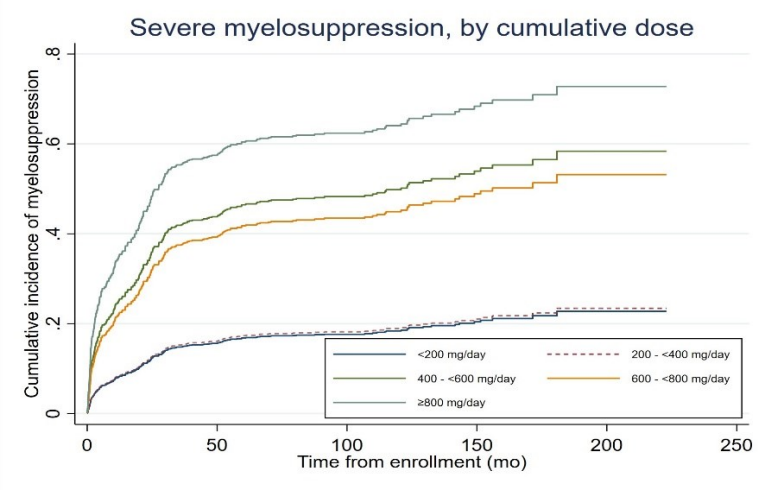
b) CIF of the probability of myelosuppression by age



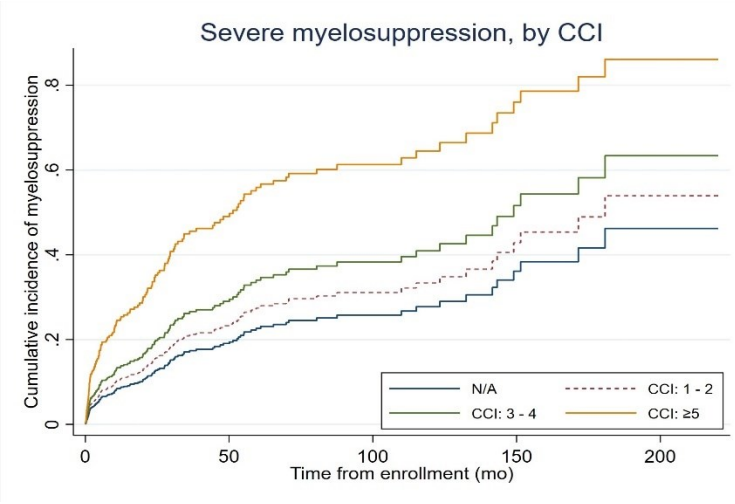
c) CIF of the probability of myelosuppression by mean daily dose



d) CIF of the probability of myelosuppression by cumulative dose



e) CIF of the probability of myelosuppression by CCI



6. Discussion

6.1. Summary of results

In this study it was observed that the ODB subject population was older with a greater proportion of female subjects compared to the RCT patients. The ODB subjects had a lower incidence of severe neutropenia and thrombocytopenia, and a higher incidence of anemia compared to the RCT patients. Discussed in section 6.2.

Among the ODB subjects, severe myelosuppression, particularly neutropenia and thrombocytopenia, was predominantly observed during the initial months of treatment with decreasing incidence over time, consistent with the RCT findings. The risk of myelosuppression increased with age, mean daily dose, and severity of comorbid conditions. No statistical difference in risk was observed between male and female ODB subjects. Discussed in section 6.3.

6.2. Context within literature

The differences in the rates and distribution of myelosuppressive events observed between the ODB subjects and RCT patients may be attributable, in part, to the inherent differences in study design, enrollment criteria, treatment settings, and the overall objectives of these studies. Each study is uniquely designed with specific purposes, strengths, and limitations, which can influence how data is collected and analyzed, which can lead to potential inconsistencies in outcomes and in the interpretation of results.[73,111,173] Methodological differences, including outcome definitions, study design, event detection, and population differences, may be associated with the observed discrepancies in the incidences of myelosuppression.

Differences in protocolized study design

The differences in the rates or distribution of myelosuppressive events between the ODB subjects and the RCT patients may stem from inherent differences in study design. RCTs aim to minimize bias and identify clear cause-and-effect relationships through strict adherence to predefined protocols, ensuring consistent treatment across the study population. In contrast, real-world clinical practice often offers physicians greater flexibility to rely on their experience and tailor treatments to meet individual patient needs.[74,174,175]

In real-world settings, patient assessments and follow-ups are typically symptom-driven rather than based on a predetermined follow-up schedule. Familiarity with a drug's safety profile allows for early recognition and detection of symptoms and timely initiation of treatments or preventive measures, particularly for high-risk patients.[176–179] Increased flexibility in patient management allows for the use of prophylactic treatments, like granulocyte colony-stimulating factors to prevent myelosuppression, and individualized monitoring based on perceived risk.[158,177–179] This approach, unconstrained by RCT protocols, allows physicians to prioritize patient health, potentially mitigating the incidence or reducing the severity of conditions like neutropenia or thrombocytopenia to levels not identified by ICD diagnostic codes.[178,180–182]

Outcome definitions

The observed difference in outcome events is likely attributable to the variations in outcome definitions used across studies. RCTs use strict criteria for defining exposure and outcomes, including clinical endpoints, standardized assessments, and regular monitoring, to ensure accurate and consistent outcome measurements. This process allows for the tailored selection and execution of study methods to address a specific research question, ensuring the available data and collection methods are precise and align with the outcome definitions. The protocol driven structure of an RCT minimizes ambiguity and misclassification through clear, objective definitions and includes additional tests for redundancy.[37,183]

In the IRIS study, hematologic adverse events were defined and graded using the Common Terminology Criteria for Adverse Events (version 3), based on precise blood cell count thresholds.[29,56] Routine blood tests for hematologic toxicity, supplemented by patient chart reviews and baseline health records, enabled accurate and consistent identification of severe myelosuppression. This methodological framework also ensured that the outcomes could be accurately attributed to the drug under investigation, distinguishing them from other potential causes. This framework allowed for precise identification of severe myelosuppression through objective laboratory tests, with supplemental patient data to determine whether the outcomes were related to the drug under investigation or other factors[56]

Studies using administrative health data rely on ICD diagnostic codes for outcome identification, which are primarily collected for billing purposes, rather than to address a specific research question. ICD codes therefore may not fully capture the details required for certain studies, as

the precision of outcome identification depends on the specificity of the codes used and the accuracy of their application by healthcare providers. Without supplemental laboratory results or patient charts, validating outcomes is typically not feasible, providing limited control over the accurate classification of events, introducing variability and potential bias.[39,184]

In this study, outcome detection was not protocol-driven, resulting in non-standardized outcome definitions and reporting processes. Therefore, instances of severe myelosuppression among the ODB subjects represented a wide range of clinical definitions, associated with various ICD codes, and recorded in multiple clinical settings, which complicates direct comparisons with the results of the IRIS study, which used more objective criteria. Severe events were identified using hospitalization or healthcare interactions, based on CTCAE descriptions of the clinical manifestations of severe myelosuppression, corresponding with severity based on hematologic definitions. However, the absence of laboratory test results for further validation highlights the limitations of solely using ICD codes in the identification of clear and interpretable outcomes.

Outcome detection

Differences in the methods used to detect myelosuppression may be partially attributable to the variance in incidence and distribution of events between populations. RCTs consistently and reliably detect myelosuppression using routine lab tests and protocolized follow-up. In contrast, observational studies relying on administrative data are limited to outcomes reported during clinical visits, which likely contributed to the lower incidences of neutropenia and thrombocytopenia among the ODB subjects.

Neutropenia, thrombocytopenia, and anemia are conditions characterized by low counts of white blood cells, platelets, and red blood cells or hemoglobin, respectively.[29,59,60] This study's outcome definitions are based within the CTCAE grading system definition used in RCTs, which defines severe myelosuppression as typically requiring hospitalization or medical intervention.[29] However, neutropenia and thrombocytopenia may initially remain asymptomatic or manifest as nonspecific symptoms, potentially resulting in underreporting in administrative health data. Without regular blood tests and scheduled follow-up, symptomatic subjects may be more inclined to seek medical attention, while even severe asymptomatic conditions may remain undetected until complications arise.[24,59,185] Therefore, the lower incidences of neutropenia and

thrombocytopenia in this study could be attributed to differences in the methods used to detect these outcomes, as well as their clinical manifestations, and healthcare-seeking behaviors.

Differences in study populations

Differences in the incidence of myelosuppression, particularly the increased anemia among the ODB subjects, may be attributed to differences in demographic profiles and clinical risk factors compared to the RCT patients. The ODB subjects reflect a more diverse population with a higher prevalence of risk factors associated with age, sex, comorbidities, and concomitant medication use that can affect drug response and toxicity.[37,42,43,131] While the ODB subjects offer a more representative sample of a diverse post-market population, these differences limit the generalizability of the results to RCTs, where such variables are more tightly controlled.[39]

Neutropenia and thrombocytopenia are often considered as direct or even "inevitable" effects of imatinib.[185,186] However, the increased incidence of anemia among the ODB subjects may reflect the greater prevalence of associated risk factors. Age-related changes, sex-specific differences in drug metabolism, and comorbidities such as renal or liver dysfunction, have all been reported to increase the risk of anemia during imatinib treatment.[131,158,160–162,187] While these factors are typically absent or underrepresent in RCTs, they were more prevalent among the ODB subjects, with many subjects affected by a combination of these risk factors. This could potentially compound the risk of anemia and add complexity to understanding this association.

The IRIS study excluded patients with advanced CML, low baseline blood cell counts, or preexisting blood disorders, as these factors are associated with a greater risk of myelosuppression.[20–22,185] However, these exclusions were not applied to the ODB subjects as baseline blood cell counts were not available, potentially resulting in greater susceptibility to anemia compared to the RCT patients. Subjects with a history of recurrent anemia before starting imatinib might have faced a higher risk of developing anemia during treatment. However, due to the imprecise or nonspecific nature of the ICD codes for anemia, this factor was not addressed, suggesting ODB subjects with recurrent prior anemia may already be more susceptible to anemia during imatinib treatment.

While the complexities of a less controlled study population likely impacted all outcomes, it may have been particularly evident in the incidence of anemia, possibly attributable to more burdensome symptoms and its association with a broader range of prevalent risk factors.[59,60] This

finding is consistent with previous post-market studies which indicated anemia was the most common type of myelosuppression outside of clinical trials.[188,189] This suggests that anemia during imatinib treatment is attributable, in part, to demographic or external factors, rather than solely the myelosuppressive effects of imatinib, especially in long-term or ongoing treatment.[185,186,190] This result is substantiated in this study by the sensitivity analysis which limited the definition of anemia to events specified as being treatment related. Despite the exclusion of non-specific events potentially unrelated to imatinib, the incidence of anemia remained higher among the ODB subjects. This suggests that the ODB population inherently had some level of increased anemia risk, beyond the differences accounted for by variability in study definitions and outcome detection.

6.3. Interpretation of ODB analysis

Among the ODB subjects, the risk of myelosuppression was estimated using a Fine-Gray subdistribution hazard model, accounting for death as a competing event. The risk of myelosuppression was found to have increased with age, mean daily dose, and the severity of comorbid conditions. No difference in risk was observed between male and female subjects.

Age and comorbidity

The observation that older subjects or those with severe comorbidities have an increased risk of severe myelosuppression during imatinib treatment is consistent with existing clinical literature.[30,159–161,187,191–194] Post-market imatinib studies found that elderly CML patients experienced higher rates of both any-grade (24% vs. 9%) and severe (25% vs. 7%) hematologic adverse events compared to younger patients, leading to more frequent treatment adjustments.[187,194] This association is typically attributed to natural, age-related declines in drug receptor sensitivity and in bone marrow reserve and function.[191]

The increased risk of myelosuppression among subjects with severe comorbidities is also consistent with existing literature.[158–162] Comorbidities, particularly those affecting the renal, hepatic, or hematopoietic systems can affect drug metabolism and elimination, resulting in increased imatinib trough levels and an increased risk of myelosuppression.[155] Severe comorbidities often require concomitant medications which may affect the effectiveness or toxicity imatinib.[131] Studies by Breccia *et al*. and Ono *et al*. found that CML patients with more

severe comorbidities, particularly a CCI score of 4 or greater, have a higher risk of hematologic toxicity, both any-grade and severe, and higher rates of toxicity-related discontinuation.[159–161]

High daily dose

The risk of severe myelosuppression also increased with higher doses of imatinib (≥550 mg/day), a finding consistent with RCTs and post-market studies.[30,154,155,181,195–198] This dose-dependent toxicity typically limits dose increases, up to 800 mg/day of imatinib, to patients with advanced CML.[154,155] Consequently, advanced phases of CML are also associated with higher rates of myelosuppression.[30,195–198] Therefore, high dose imatinib and the respective increase in the risk of myelosuppression may indicate treatment of advanced CML. While the absence of disease severity data limits further analysis, the prescribing patterns of high dose imatinib suggest that the severity of the disease may have influenced this association.[56,154,199]

Sex

This study found no statistically significant difference in the risk of myelosuppression between male and female subjects. This is inconsistent with much of the existing literature which typically identifies female sex as a risk factor for hematologic toxicities during imatinib treatment.[109,151,200,201] Notably, however, the studies which identify female sex as a risk factor, seldom publish safety data stratified by sex.[7,151–153] A ten-year follow-up of the CML-study IV trial found that women with chronic phase CML had a 26% greater risk of severe hematologic adverse events compared to men. Sneed *et al*. similarly reported that myelosuppression occurred more frequently in females (43%) than in males (29%).[24] Interestingly, multiple studies have indicated that female patients on imatinib have a greater risk of anemia specifically.[190,202,203] However, the finding that male and female subjects had similar risks of myelosuppression aligns with multiple imatinib pharmacovigilance studies, including a case-control study in Kenya and a study of 200 CML patients in Iraq.[188,189] Both studies reported comparable risks of neutropenia and thrombocytopenia between sexes, while Matti *et al*. reported that female subjects had a greater incidence of anemia only.[188,189]

Standard drug dosages, often determined using male-centric trials, may not be as generalizable to women due to variations in body weight and composition. Pharmacokinetic studies have found that women have different levels of drug-metabolizing enzymes and lower drug elimination capacities than men, often resulting in elevated drug trough concentrations and

increased toxicity.[200,201,204,205] One imatinib dose-concentration study found that female CML patients experienced a 15.2% lower drug clearance rate than men, leading to elevated trough concentrations and a greater risk of toxicity.[200,205] However, anthropometric or pharmacokinetic data was not available for this study to further evaluate these associations. Interestingly, some studies attributed the increased rates of myelosuppression among women to being driven by iron-deficiency anemia, nutritional anemia, or lower baseline hemoglobin levels.[185,190,202,203] An observation that would coincide with the findings of the study by Matti *et al*.[189]

Therefore, the discrepancy between this study's findings and existing literature may again be attributable to how myelosuppression was defined. The inclusion of conditions like iron-deficiency or nutritional anemia, which are more common in women but typically unrelated to imatinib, further highlights the inadequacies in the assessment and reporting of safety data in RCTs.[190,202,203] A protocol-driven RCT should have the resources to delineate treatment-related adverse events from unrelated events, however published adverse event data is remains limited to a single incidence proportion, aggregating unrelated cases of anemia with severe drug-induced hematologic toxicities. In contrast, this study's definition of severe myelosuppression specifically excluded ICD codes for conditions considered unrelated to imatinib treatment, such as iron-deficiency and nutritional anemias, wherever possible. This was done with the intention of refining the analysis to focus on outcomes thought to be attributable to imatinib treatment. In addition, in a real-world population, the remaining association between sex and myelosuppression may be obscured by more biologically relevant confounders with stronger associations.[109,200]

6.4. Strengths

A major strength of this study lies in the use of the ODB database, which includes prescription records for Ontario residents 65 years of age and older, among other special populations, providing a large, diverse sample for analysis. Linking subject ODB prescription records with patient-level data from Ontario's other large population-based administrative health databases provided insights into comprehensive information on subject demographics, comorbidities, healthcare utilization, and clinical outcomes. This integration facilitates research on large, diverse, multicenter populations, making large or long-term studies on rare diseases like CML both practical and more cost-effective.[184] Typically, post-market imatinib research has involved single-center studies with small sample sizes due to the low incidence of CML. Therefore, a long-

term evaluation of adverse event data from 1,683 CML patients offers unique insights into imatinib's safety profile that are generally not feasible in standard research environments.

Another advantage of this study is the emphasis on safety as the primary outcome, providing a more complete understanding of imatinib's safety profile within a diverse post-market population. The findings of this study offer more nuanced analyses of the risk of severe myelosuppression based on patient demographics and temporal factors, which are typically overlooked during RCTs, but relevant to the real-world patient experience.[33,166]

6.5. Limitations

6.5.1. Information bias

A major limitation of this study was the potential for information bias, largely attributable to the dependency on the accuracy, completeness, and validity of the available prescription data and ICD codes. Using data that was not initially collected for the purpose of addressing a specific research question can introduce misclassification bias, and instances of missing, incomplete, or non-specific exposure or outcome data. These limitations can restrict the depth, validity, and specificity of the analysis that can be conducted given the available data.

Misclassification bias

The primary limitation of this study was the potential for misclassification of outcome data, resulting from reliance on the accuracy and validity of ICD codes from administrative health data. Despite having been used and validated for the identification of hematologic adverse events in previous research, since these codes are typically intended for billing purposes, they may not offer the level of granularity or detail required for the precise identification of outcomes in research. Since RCTs use precise, consistent, and clinically validated outcome definitions, accurately identifying outcome events that are defined consistently with the RCT criteria depends on the specificity of the ICD code used and the accuracy with which it is applied. Therefore, inaccurate application of ICD codes, inconsistency between hospitals or coders, and the limited detail provided by these ICD codes can result in misclassification of outcome events and potentially a misinterpretation of their association with exposure.

Most notably, the prevalence of ICD codes for unspecified anemia (D64.9) or "anemia in other chronic diseases classified elsewhere" (D63.8), some of the most common anemia diagnoses, presented a challenge. Due to the lack of specificity, without supplemental patient data it is not

possible to distinguish treatment-related events from unrelated outcomes. The ambiguity of non-specific ICD codes can result in misclassification, regardless of how these codes are handled methodologically. Therefore, the lack of standardization in the outcome definitions between this study and the IRIS study may limit the applicability of the results when compared to the RCT results, where outcomes are precisely defined and standardized. Additionally, inconsistency or inaccuracy of the ICD codes could also lead to a misinterpretation of the association between the study covariates and myelosuppression during imatinib treatment, which can affect the generalizability of the study results to broader contexts.

Identifying subjects with CML in the Ontario Cancer Registry database is similarly limited by the lack of specificity in certain incident cancer diagnoses. This study was focused on patients with CML, therefore, any subjects prescribed imatinib for other cancer indications or with a diagnosis of a non-specific myeloproliferative neoplasm were excluded to maintain diagnostic specificity. While this may have excluded some subjects with CML, favoring specificity over selectivity, it ensured that only subjects with confirmed diagnoses were included. However, this exclusion applied to a very small number of the total subjects.

Physician billing claims from the Ontario Health Insurance Plan database were initially considered for outcome detection but were ultimately not included due to the lack of granularity of the diagnostic codes for outcome events. The diagnostic codes used in the Ontario Health Insurance Plan database have only three digits of specificity, grouping similar conditions under broad diagnostic categories. As a result, they fail to distinguish relevant outcome events from those unrelated to imatinib treatment, limiting the accurate identification of study outcomes.

Missing data/variables

Administrative health data, primarily collected for billing purposes rather than research, is limited due to missing variables and incomplete data. Potentially important demographic and clinical variables including CML phase at diagnosis, Sokal Index scores, and Eastern Cooperative Oncology Group (ECOG) performance scores, standard in imatinib RCTs, were not available. Patient charts or baseline laboratory results, including risk factors for myelosuppression such as baseline blood cell counts or hemoglobin levels, were also not available.[185,188] These variables are essential for better understanding the association between imatinib and myelosuppression in real-world treatment. The association between myelosuppression during imatinib treatment and

daily dose may be more strongly attributable to disease phase or severity. Therefore, this study aimed to conduct a more in-depth assessment of the real-world risk of myelosuppression during imatinib treatment based on the available data. However, the depth of analysis that was possible without more nuanced subject data was limited, and when interpreting these results, it's essential to note that key variables were not included in the study.

Missing data also posed limitations on the available covariates. Approximately half of the ODB subjects were missing comorbidity data, resulting in stratification into four groups based on Charlson Comorbidity Index scores due to smaller sample sizes. An overarching goal of this study was to report the unadjusted risk of myelosuppression as they were observed in a real-world population. Therefore, the univariate regression model for the risk of myelosuppression based on comorbidity was restricted to the subjects with provided CCI scores, rather than using any methods for data imputation. Additionally, age at index was categorized into five-year intervals to protect subject anonymity. These data limitations restricted the depth of the analysis and potentially introduced residual confounding due to the stratification of continuous variables. Results of each analysis were presented with 95% confidence intervals to provide more reliable interpretation of the results, especially considering smaller or restricted subgroups.

Imatinib prescription records were limited to those within the ODB database, which does not capture prescriptions covered under private or employment-based insurance. The first imatinib prescription in the ODB database marked the initial exposure for each subject, establishing their study index date. However, missing prescription records may have misclassified some long-term users of imatinib as being treatment naïve. To address this limitation, a sensitivity analysis compared the rates of myelosuppression rates between the subjects who initiated imatinib treatment within six months of diagnosis and those who started later, reflective of the eligibility criteria used in the IRIS study. This was to ensure that those with longer time to treatment initiation were not characteristically different as a result of being misclassified as unexposed during the period with the greatest risk of myelosuppression. The results of this sensitivity analysis found that the rate of myelosuppression was comparable between both groups, confirming the robustness of the results (Results not shown).

6.5.2. Selection bias

Underrepresentation of subjects under 65 years of age:

The use of the ODB database, which primarily includes Ontario residents 65 years of age and older, did raise some concerns regarding potential under-sampling of subjects under 65 years of age. This source of selection bias may result in study findings which are skewed to align with drug safety and efficacy profiles representative of older adults rather than a more diverse target population. Therefore, caution should always be applied when interpreting the results of studies using a population derived from the ODB database, particularly when considering applying these results beyond the context of the study. Since the ODB database may not capture all subjects under the age of 65 years, a drug's safety profile estimated using a sample population from the ODB database may be inconsistent with that of an RCT population, in which older subjects are routinely underrepresented.[40,41]

Despite these concerns, the sample population of imatinib-treated CML subjects captured by the ODB database was expected to provide a fairly comprehensive sample of the target population, considering the high cost of imatinib as an outpatient cancer drug and the median age of CML diagnosis at approximately 64 years.[129,206,207] Based on this information, it was expected that approximately half of the CML patients in Ontario would qualify for ODB coverage automatically, while its prohibitive prescription costs would account for much of the population under 65 years of age. At the index date, 42.0% of ODB subjects were under the age of 65, likely suggesting enrollment in a reimbursement program, such as the Trillium Drug Program. The age distribution among the ODB subjects was reflective of the estimated median age at diagnosis for CML in Ontario, and therefore the population was considered to be representative.[208–210]

Consistency of eligibility criteria between ODB subjects and RCT patients:

However, while the ODB subject population was considered reasonably representative of the target population, the eligibility criteria for the ODB drug program are not reflective of those for enrollment in the IRIS study.[56] As previously described, RCTs typically have strict eligibility criteria resulting in sample populations that are not reflective of a real-world population. The exclusion criteria applied in the IRIS study were extensive, limiting enrollment based on disease phase, blood cell counts, and previous disease history. Most notably, the study restricted enrollment to patients aged between 18 and 70 years. As the ODB database is primarily comprised of those 65

years of age or older, and the median age at diagnosis for CML is approximately 64 years of age, 34.1% of the ODB subjects were found to be over 70 years old when they started imatinib treatment and would have been ineligible for enrollment in the IRIS study.

This led to an ODB subject population with a median age 17 years older than those in the IRIS study and a much higher proportion of elderly subjects. Therefore, while the ODB subject results may have greater external validity, caution must be exercised when comparing these results to an RCT population, such as the IRIS study, as a different sampling frame was used.

Restriction to Ontario subjects

Limiting this study exclusively to CML patients in Ontario may limit the generalizability of the findings to the broader Canadian context. The specifics of Ontario's healthcare system, population demographics, provincial drug formulary, drug policies, and prescribing patterns may not be fully representative of CML patients in other provinces. These differences could influence drug access, treatment patterns, and the frequency and severity of adverse events.[211,212] Ontario's diverse and extensive administrative databases were expected to be fairly representative of the target population of Canadian CML patients. However, including data from additional provincial databases could increase the population diversity, enhance the external validity, and provide a deeper understanding of imatinib safety across different healthcare systems and drug formularies.

Incident user design

Subjects previously treated with tyrosine kinase inhibitors other than imatinib were excluded to prevent the observation of myelosuppression attributable to second or third generation tyrosine kinase inhibitors and mitigate potential survivorship bias. However, this design may have excluded patients who switched to imatinib due to resistance or intolerance to other treatments, potentially leading to an underreporting of adverse events in subjects with complex treatment histories. Therefore, the findings of this study may not be applicable to patients previously treatment with another tyrosine kinase inhibitor treatment prior to starting treatment with imatinib. However, imatinib is still the front-line treatment for CML and second-generation tyrosine kinase inhibitors were not approved until several years later in Canada, therefore the impact of this limitation was anticipated to be relatively minor. Ultimately, this design resulted in the exclusion of 62 of the 1,944 (3.1%) imatinib-treated CML-subjects.

6.6. Implications

Clinical

This study highlights the need for continuous monitoring of imatinib safety and personalized treatment plans for CML patients. These findings reinforce the importance of safety follow-ups during the initial months of treatment, particularly for patients with increased risk factors such as older age or severe comorbidities. The differences in adverse event rates across patient demographics highlight the importance of tailored treatment approaches. Additionally, given the long-term nature of imatinib therapy, educating patients about potential risks and adverse events, such as myelosuppression, can potentially enable timely intervention and improved patient outcomes.

Research

This study highlights the importance of ongoing, long-term safety research across diverse patient demographics, especially for drugs like imatinib, which were approved based on limited clinical trial data and scarce real-world safety evidence. These findings emphasize the importance of including a broader range of patient demographics in clinical trials to better mirror the real-world patient population. Additionally, this study calls for a more balanced emphasis on both safety and efficacy outcomes in RCTs. More comprehensive and consistent collection and reporting of adverse event data would provide a more complete understanding of the safety risks and potential long-term impacts of new therapies.

Pharmacoepidemiological

This study highlights the importance of real-world pharmacovigilance data for improving the understanding of a drug's safety profile beyond the controlled environment of clinical trials. While improvements in safety data evaluation and reporting in RCTs are necessary, ongoing real-world studies serve as an essential complement to RCT data. Post-market pharmacovigilance studies provide insights into drug safety in a broader, more diverse patient population, and are essential for the detection of rare or latent adverse effects that are typically unknown at the time of a drug's approval.

6.7. Future considerations

The results of this study, and the recognition of its limitations, lay the groundwork for further research into severe myelosuppression during imatinib treatment in subjects with CML. An ideal follow-up study would be a large-scale, multi-center, prospective study. This would enable real-time data collection and a reduction in potential biases, improving the accuracy and validity of the results. This would allow for precise definition of study outcomes and establish pre-determined methods for screening, follow-up, and detection, ensuring outcomes are captures accurately and consistently. This approach would not only identify severe cases of myelosuppression but also detect mild or moderate instances, as well as other rare hematologic events or cytopenias, using laboratory results and screenings.

Future retrospective studies should aim to establish clear, operational definitions for adverse events, particularly by detailing each type and grade of myelosuppression using standardized criteria. These definitions should be validated by clinical experts to ensure their accuracy and practicality for detection in clinical environments. Standardizing these definitions will promote consistent outcome classification within the study and promote replicability in future research. Additionally, these studies should secure access to all relevant test results to validate the accuracy of study outcomes. For myelosuppression, this involves obtaining hematologic laboratory test results, patient charts, baseline blood cell counts, and information on existing hematologic conditions. Having access to this data would allow for more precise identification of relevant outcome events and differentiate them from unrelated outcomes.

Future studies should explore how commonly used drugs interact with imatinib to understand their impact on imatinib toxicity, addressing a gap between real-world and controlled trial subjects. Future research should also aim to evaluate rare or latent adverse events associated with imatinib treatment. While this study focused on the most common severe adverse events due to data constraints, identifying and evaluating rare adverse events is essential for a more comprehensive understanding of imatinib's safety profile. This will enhance proactive safety monitoring and aid in treatment-related decision making.

7. Conclusion

This study revealed substantial differences in the demographic profiles and the distribution of severe myelosuppressive events between ODB subjects and RCT patients. The ODB subjects were typically older, had a more balanced gender ratio, and reported lower incidences of neutropenia and thrombocytopenia but a higher anemia incidence compared to RCT patients. The risk of myelosuppression, which typically occurred during the initial months of treatment, increased with age, mean daily dose, and the severity of comorbidities, with no observed difference in risk based on sex.

These findings augment the understanding of the risk of myelosuppression during imatinib treatment in real-world populations and emphasize the limited generalizability of results derived from RCTs to more diverse populations. When interpreting results, especially for treatment or regulatory decisions, it is essential to consider the constraints of the treated population and limitations of the study design. These findings highlight the importance of ongoing post-market pharmacovigilance research as a necessary complement to RCTs, to help ensure the ongoing safety of patients beyond the context of an RCT.

References

1. Iqbal, N. & Iqbal, N. Imatinib: A Breakthrough of Targeted Therapy in Cancer. *Chemother. Res. Pract.* **2014**, 1–9 (2014).
2. Capdeville, R., Buchdunger, E., Zimmermann, J. & Matter, A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. *Nat. Rev. Drug Discov.* **1**, 493–502 (2002).
3. Bower, H. *et al.* Life Expectancy of Patients With Chronic Myeloid Leukemia Approaches the Life Expectancy of the General Population. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **34**, 2851–2857 (2016).
4. Jabbour, E. & Kantarjian, H. Chronic myeloid leukemia: 2022 update on diagnosis, therapy, and monitoring. *Am. J. Hematol.* **97**, 1236–1256 (2022).
5. Jabbour, E. & Kantarjian, H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. *Am. J. Hematol.* **93**, 442–459 (2018).
6. Granatowicz, A. *et al.* An Overview and Update of Chronic Myeloid Leukemia for Primary Care Physicians. *Korean J. Fam. Med.* **36**, 197–202 (2015).
7. Deininger, M., Buchdunger, E. & Druker, B. J. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. *Blood* **105**, 2640–2653 (2005).
8. Jabbour, E. & Kantarjian, H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. *Am. J. Hematol.* **95**, 691–709 (2020).
9. Druker, B. J. Imatinib as a Paradigm of Targeted Therapies. in *Advances in Cancer Research* vol. 91 1–30 (Elsevier, 2004).
10. Collins, S., Coleman, H. & Groudine, M. Expression of bcr and bcr-abl fusion transcripts in normal and leukemic cells. *Mol. Cell. Biol.* **7**, 2870–2876 (1987).
11. Shtivelman, E., Lifshitz, B., Gale, R. P. & Canaani, E. Fused transcript of abl and bcr genes in chronic myelogenous leukaemia. *Nature* **315**, 550–554 (1985).

12. Druker, B. J. *et al.* Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat. Med.* **2**, 561–566 (1996).
13. Santos, F. P. S. & Quintás-Cardama, A. New Drugs for Chronic Myelogenous Leukemia. *Curr. Hematol. Malig. Rep.* **6**, 96–103 (2011).
14. Daley, G., Van Etten, R. & Baltimore, D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. *Science* **247**, 824–830 (1990).
15. Quintás-Cardama, A. & Cortes, J. Molecular biology of bcr-abl1–positive chronic myeloid leukemia. *Blood* **113**, 1619–1630 (2009).
16. Druker, B. J. Translation of the Philadelphia chromosome into therapy for CML. *Blood* **112**, 4808–4817 (2008).
17. Soverini, S., Mancini, M., Bavaro, L., Cavo, M. & Martinelli, G. Chronic myeloid leukemia: the paradigm of targeting oncogenic tyrosine kinase signaling and counteracting resistance for successful cancer therapy. *Mol. Cancer* **17**, 49 (2018).
18. Rossari, F., Minutolo, F. & Orciuolo, E. Past, present, and future of Bcr-Abl inhibitors: from chemical development to clinical efficacy. *J. Hematol. Oncol.J Hematol Oncol* **11**, 84 (2018).
19. Druker, B. J. *et al.* Efficacy and Safety of a Specific Inhibitor of the BCR-ABL Tyrosine Kinase in Chronic Myeloid Leukemia. *N. Engl. J. Med.* **344**, 1031–1037 (2001).
20. Cohen, M. *et al.* Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **8**, 935–42 (2002).
21. Sawyers, C. L. *et al.* Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. *Blood* **99**, 3530–3539 (2002).

22. Talpaz, M. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* **99**, 1928–1937 (2002).
23. Druker, B. J. Perspectives on the development of a molecularly targeted agent. *Cancer Cell* **1**, 31–36 (2002).
24. Sneed, T. B. *et al.* The significance of myelosuppression during therapy with imatinib mesylate in patients with chronic myelogenous leukemia in chronic phase. *Cancer* **100**, 116–121 (2004).
25. Barber, N. A., Afzal, W. & Akhtari, M. Hematologic toxicities of small molecule tyrosine kinase inhibitors. *Target. Oncol.* **6**, 203–215 (2011).
26. Henkes, M., van der Kuip, H. & Aulitzky, W. E. Therapeutic options for chronic myeloid leukemia: focus on imatinib (Glivec®, Gleevec™). *Ther. Clin. Risk Manag.* **4**, 163–187 (2008).
27. Kronick, O. *et al.* Hematological Adverse Events with Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia: A Systematic Review with Meta-Analysis. *Cancers* **15**, 4354 (2023).
28. Division of Cancer Treatment and Diagnosis (DCTD). Common Terminology Criteria for Adverse Events v3.0 (CTCAE). *https://ctep.cancer.gov/* https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf (2006).
29. Trotti, A. *et al.* CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin. Radiat. Oncol.* **13**, 176–181 (2003).
30. Steegmann, J. L. *et al.* European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia* **30**, 1648–1671 (2016).

31. Stanulović, V., Hodolic, M., Mitsikostas, D. D. & Papadopoulos, D. Drug tolerability: How much ambiguity can be tolerated? A systematic review of the assessment of tolerability in clinical studies. *Br. J. Clin. Pharmacol.* **88**, 551–565 (2022).
32. Wang, Y. *et al.* Adverse Event Reporting Quality in Cancer Clinical Trials Evaluating Immune Checkpoint Inhibitor Therapy: A Systematic Review. *Front. Immunol.* **13**, 874829 (2022).
33. Phillips, R., Hazell, L., Sauzet, O. & Cornelius, V. Analysis and reporting of adverse events in randomised controlled trials: a review. *BMJ Open* **9**, e024537 (2019).
34. Gyawali, B., Parsad, S., Feinberg, B. A. & Nabhan, C. Real-World Evidence and Randomized Studies in the Precision Oncology Era: The Right Balance. *JCO Precis. Oncol.* (2017) doi:10.1200/PO.17.00132.
35. Frank, C. *et al.* Era Of Faster FDA Drug Approval Has Also Seen Increased Black-Box Warnings And Market Withdrawals. *Health Aff. (Millwood)* **33**, 1453–1459 (2014).
36. Chary, K. Expedited drug review process: Fast, but flawed. *J. Pharmacol. Pharmacother.* **7**, 57 (2016).
37. Monti, S., Grosso, V., Todoerti, M. & Caporali, R. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. *Rheumatology* **57**, vii54–vii58 (2018).
38. Singh, S. & Loke, Y. K. Drug safety assessment in clinical trials: methodological challenges and opportunities. *Trials* **13**, 138 (2012).
39. Karim, S. *et al.* Generalisability of Common Oncology Clinical Trial Eligibility Criteria in the Real World. *Clin. Oncol. R. Coll. Radiol. G. B.* **31**, e160–e166 (2019).
40. Lewis, J. H. *et al.* Participation of Patients 65 Years of Age or Older in Cancer Clinical Trials. *J. Clin. Oncol.* **21**, 1383–1389 (2003).

41. Yee, K. W. L., Pater, J. L., Pho, L., Zee, B. & Siu, L. L. Enrollment of older patients in cancer treatment trials in Canada: why is age a barrier? *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **21**, 1618–1623 (2003).
42. Wahab, I., Pratt, N., Kalisch Ellett, L. & Roughead, E. The Detection of Adverse Events in Randomized Clinical Trials: Can we Really Say New Medicines are Safe? *Curr. Drug Saf.* **8**, (2013).
43. Borrelli, E. P. & McGladrigan, C. G. Differences in safety profiles of newly approved medications for multiple myeloma in real-world settings versus randomized controlled trials. *J. Oncol. Pharm. Pract.* 107815522094193 (2020) doi:10.1177/1078155220941937.
44. Strzebonska, K. & Waligora, M. Umbrella and basket trials in oncology: ethical challenges. *BMC Med. Ethics* **20**, 58 (2019).
45. Expedited Programs for Serious Conditions – Drugs and Biologics. 40.
46. Lipsky, M. S. & Sharp, L. K. From idea to market: the drug approval process. *J. Am. Board Fam. Pract.* **14**, 362–367 (2001).
47. Darrow, J. J., Avorn, J. & Kesselheim, A. S. FDA Approval and Regulation of Pharmaceuticals, 1983-2018. *JAMA* **323**, 164–176 (2020).
48. Canadian Cancer Society. Chronic Myelogenous Leukemia Statistics. *www.cancer.ca* https://www.cancer.ca:443/en/cancer-information/cancer-type/leukemia-chronic-myelogenous-cml/statistics/?region=on.
49. Laneuville, P. *et al.* Recommendations of the Canadian Consensus Group on the Management of Chronic Myeloid Leukemia. *Curr. Oncol.* **13**, 201–221 (2006).
50. Goldman, J. M. & Melo, J. V. Chronic myeloid leukemia--advances in biology and new approaches to treatment. *N. Engl. J. Med.* **349**, 1451–1464 (2003).

51. Rowley, J. D. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. *Nature* **243**, 290–293 (1973).

52. Heisterkamp, N., Stam, K., Groffen, J., de Klein, A. & Grosveld, G. Structural organization of the bcr gene and its role in the Ph' translocation. *Nature* **315**, 758–761 (1985).

53. Sacha, T. Imatinib in Chronic Myeloid Leukemia: an Overview. *Mediterr. J. Hematol. Infect. Dis.* **6**, e2014007 (2014).

54. Capdeville, R., Silberman, S. & Dimitrijevic, S. Imatinib: the first 3 years. *Eur. J. Cancer* **38**, S77–S82 (2002).

55. Kantarjian, H. *et al.* Hematologic and Cytogenetic Responses to Imatinib Mesylate in Chronic Myelogenous Leukemia. *N. Engl. J. Med.* **346**, 645–652 (2002).

56. O'Brien, S. G. *et al.* Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. *N. Engl. J. Med.* **348**, 994–1004 (2003).

57. Hahn, E. A. *et al.* Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: results from the IRIS Study. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **21**, 2138–2146 (2003).

58. Peng, B., Lloyd, P. & Schran, H. Clinical Pharmacokinetics of Imatinib: *Clin. Pharmacokinet.* **44**, 879–894 (2005).

59. Epstein, R. S. *et al.* Patient Burden and Real-World Management of Chemotherapy-Induced Myelosuppression: Results from an Online Survey of Patients with Solid Tumors. *Adv. Ther.* **37**, 3606–3618 (2020).

60. Goldschmidt, J. *et al.* Burden of chemotherapy-induced myelosuppression among patients with ES-SCLC in US community oncology settings. *Future Oncol.* **18**, 3881–3894 (2022).

61. Liu, Z. *et al.* Impact of anemia on the outcomes of chronic phase chronic myeloid leukemia in TKI era. *Hematology* **25**, 181–185 (2020).

62. Mt-Isa, S. *et al.* Balancing benefit and risk of medicines: a systematic review and classification of available methodologies. *Pharmacoepidemiol. Drug Saf.* **23**, 667–678 (2014).

63. Ulrich, C. M. *et al.* Cancer clinical trial participants' assessment of risk and benefit. *AJOB Empir. Bioeth.* **7**, 8–16 (2016).

64. Pignatti, F., Jonsson, B., Blumenthal, G. & Justice, R. Assessment of benefits and risks in development of targeted therapies for cancer — The view of regulatory authorities. *Mol. Oncol.* **9**, 1034–1041 (2015).

65. Johnson, F. R., Hauber, B., Siegel, C. A., Hass, S. & Sands, B. E. Are Gastroenterologists Less Tolerant of Treatment Risks than Patients? Benefit-Risk Preferences in Crohn's Disease Management. *J. Manag. Care Pharm.* **16**, 616–628 (2010).

66. Health Canada. How Drugs are Reviewed in Canada. *www.canada.ca* https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada.html (2001).

67. Lee, P. R. & Herzstein, J. International Drug Regulation. *Annu. Rev. Public Health* **7**, 217–235 (1986).

68. Camm, A. J. *et al.* Real-world vs. randomized trial outcomes in similar populations of rivaroxaban-treated patients with non-valvular atrial fibrillation in ROCKET AF and XANTUS. *EP Eur.* **21**, 421–427 (2019).

69. Burns, P. B., Rohrich, R. J. & Chung, K. C. The Levels of Evidence and Their Role in Evidence-Based Medicine. *Plast. Reconstr. Surg.* **128**, 305 (2011).

70. Ciociola, A. A. *et al.* How Drugs are Developed and Approved by the FDA: Current Process and Future Directions: *Am. J. Gastroenterol.* **109**, 620–623 (2014).

71. Darrow, J. J., Avorn, J. & Kesselheim, A. S. The FDA Breakthrough-Drug Designation — Four Years of Experience. *N. Engl. J. Med.* **378**, 1444–1453 (2018).

72. Sibbald, B. & Roland, M. Understanding controlled trials: Why are randomised controlled trials important? *BMJ* **316**, 201 (1998).

73. Blonde, L., Khunti, K., Harris, S. B., Meizinger, C. & Skolnik, N. S. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. *Adv. Ther.* **35**, 1763–1774 (2018).

74. Godwin, M. *et al.* Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med. Res. Methodol.* **3**, 28 (2003).

75. Schulz, K. F., Altman, D. G., Moher, D., & the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med.* **8**, 18 (2010).

76. Gotfrit, J., Shin, J. J. W., Mallick, R., Stewart, D. J. & Wheatley-Price, P. Potential Life-Years Lost: The Impact of the Cancer Drug Regulatory and Funding Process in Canada. *The Oncologist* **25**, e130–e137 (2020).

77. Gotfrit, J., Dempster, W., Chambers, J. & Wheatley-Price, P. The Pathway for New Cancer Drug Access in Canada. *Curr. Oncol.* **29**, 455–464 (2022).

78. Government of Ontario, M. of H. and L.-T. C. How Drugs Are Approved - Health Care Professionals - MOHLTC. https://www.health.gov.on.ca/en/pro/programs/drugs/how_drugs_approv/how_drugs_approv.aspx.

79. Menon, D., Stafinski, T. & Stuart, G. Access to Drugs for Cancer: Does Where You Live Matter? *Can. J. Public Health.* **96**, 454–458 (2005).

80. Chafe, R. *et al.* Access to Cancer Drugs in Canada: Looking Beyond Coverage Decisions. *Healthc. Policy Polit. Santé* 27–35 (2011) doi:10.12927/hcpol.2011.22177.

81. MacPhail, C. & Snow, S. Not All Canadian Cancer Patients Are Equal—Disparities in Public Cancer Drug Funding across Canada. *Curr. Oncol.* **29**, 2064–2072 (2022).

82. Lexchin, J. Time to market for drugs approved in Canada between 2014 and 2018: an observational study. *BMJ Open* **11**, e047557 (2021).

83. Cohen, M. H., Moses, M. L. & Pazdur, R. Gleevec™ for the Treatment of Chronic Myelogenous Leukemia: U.S. Food and Drug Administration Regulatory Mechanisms, Accelerated Approval, and Orphan Drug Status. *The Oncologist* **7**, 390–392 (2002).

84. News in Brief. *Expert Rev. Anticancer Ther.* **1**, 3–5 (2001).

85. Chabner, B. Approval of New Agents after Phase II Trials. *Am. Soc. Clin. Oncol. Educ. Book* e1–e3 (2012) doi:10.14694/EdBook_AM.2012.32.114.

86. Cohen, M. H., Johnson, J. R. & Pazdur, R. U.S. Food and Drug Administration Drug Approval Summary: Conversion of Imatinib Mesylate (STI571; Gleevec) Tablets from Accelerated Approval to Full Approval. 9.

87. Lexchin, J. Quality of evidence considered by Health Canada in granting full market authorisation to new drugs with a conditional approval: a retrospective cohort study. *BMJ Open* **8**, e020377 (2018).

88. Chary, K. & Pandian, K. Accelerated approval of drugs: ethics versus efficacy. *Indian journal of medical ethics* vol. 2 https://pubmed.ncbi.nlm.nih.gov/28661403/ (2017).

89. Ho, C., Lim, H. J. & Regier, D. A. FDA Accelerated Approval for Malignant Hematology and Oncology Indications in the Canadian Environment. *Curr. Oncol.* **29**, 402–410 (2022).

90. Ward, L. M., Chambers, A., Mechichi, E., Wong-Rieger, D. & Campbell, C. An international comparative analysis of public reimbursement of orphan drugs in Canadian provinces compared to European countries. *Orphanet J. Rare Dis.* **17**, 113 (2022).

91. Kesselheim, A. S. Characteristics of Clinical Trials to Support Approval of Orphan vs Nonorphan Drugs for Cancer. *JAMA* **305**, 2320 (2011).

92. McPhail, M., Weiss, E. & Bubela, T. Conditional Drug Approval as a Path to Market for Oncology Drugs in Canada: Challenges and Recommendations for Assessing Eligibility and Regulatory Responsiveness. *Front. Med.* **8**, 818647 (2022).

93. Herink, M. C., Irwin, A. N. & Zumach, G. M. FDA Breakthrough Therapy Designation: Evaluating the Quality of the Evidence behind the Drug Approvals. *Pharmacother. J. Hum. Pharmacol. Drug Ther.* **38**, 967–980 (2018).

94. McMillan, H. J. & Campbell, C. We need a "made in Canada" orphan drug framework. *Can. Med. Assoc. J.* **189**, E1274–E1275 (2017).

95. Lexchin, J. Harmony in Drug Regulation, but Who's Calling the Tune? An Examination of Regulatory Harmonization in Health Canada. *Int. J. Health Serv.* **42**, 119–136 (2012).

96. Cheung, R. Y. & Goodwin, S. H. An Overview of Canadian and U.S. Approaches to Drug Regulation and Responses to Postmarket Adverse Drug Reactions. *J. Diabetes Sci. Technol.* **7**, 313–320 (2013).

97. Moore, T. J. & Furberg, C. D. The Safety Risks of Innovation: The FDA's Expedited Drug Development Pathway. *JAMA* **308**, 869 (2012).

98. Redman, M. W. & Allegra, C. J. The Master Protocol Concept. *Semin. Oncol.* **42**, 724–730 (2015).

99. Cunanan, K. M., Iasonos, A., Shen, R., Begg, C. B. & Gönen, M. An efficient basket trial design: K. M. CUNANAN *ET AL. Stat. Med.* (2017) doi:10.1002/sim.7227.

100. Demeyin, W. A., Frost, J., Ukoumunne, O. C., Briscoe, S. & Britten, N. N of 1 trials and the optimal individualisation of drug treatments: a systematic review protocol. *Syst. Rev.* **6**, 90 (2017).

101. Kyr, M., Svobodnik, A., Stepanova, R. & Hejnova, R. N-of-1 Trials in Pediatric Oncology: From a Population-Based Approach to Personalized Medicine—A Review. *Cancers* **13**, 5428 (2021).

102. Gouda, M. A., Buschhorn, L., Schneeweiss, A., Wahida, A. & Subbiah, V. N-of-1 Trials in Cancer Drug Development. *Cancer Discov.* **13**, 1301–1309 (2023).

103. Renfro, L. A. & Sargent, D. J. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. *Ann. Oncol.* **28**, 34 (2017).

104. Park, J. J. H. *et al.* Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols. *Trials* **20**, 572 (2019).

105. Martin, K. *et al.* Differences between clinical trials and postmarketing use: Differences between clinical trials and postmarketing use. *Br. J. Clin. Pharmacol.* **57**, 86–92 (2003).

106. Baldo, P., Fornasier, G., Ciolfi, L., Sartor, I. & Francescon, S. Pharmacovigilance in oncology. *Int. J. Clin. Pharm.* **40**, 832–841 (2018).

107. Berlin, J. A., Glasser, S. C. & Ellenberg, S. S. Adverse Event Detection in Drug Development: Recommendations and Obligations Beyond Phase 3. *Am. J. Public Health* **98**, 1366–1371 (2008).

108. Davies, E. A. & O'Mahony, M. S. Adverse drug reactions in special populations - the elderly. *Br. J. Clin. Pharmacol.* **80**, 796–807 (2015).

109. Unger, J. M., Vaidya, R., Hershman, D. L., Minasian, L. M. & Fleury, M. E. Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. *J. Natl. Cancer Inst.* **111**, 245–255 (2019).

110. Seruga, B., Sterling, L., Wang, L. & Tannock, I. F. Reporting of Serious Adverse Drug Reactions of Targeted Anticancer Agents in Pivotal Phase III Clinical Trials. *J. Clin. Oncol.* **29**, 174–185 (2011).

111. Rothwell, P. M. External validity of randomised controlled trials: 'to whom do the results of this trial apply?' *Lancet Lond. Engl.* **365**, 82–93 (2005).

112. Maillet, D. *et al.* The reporting of adverse events in oncology phase III trials: a comparison of the current status versus the expectations of the EORTC members. *Ann. Oncol.* **27**, 192–198 (2016).

113. Claudiani, S. & Apperley, J. F. The argument for using imatinib in CML. *Hematology* **2018**, 161–167 (2018).

114. Haddad, C., Sigha, O. B., Lebrun-Vignes, B., Chosidow, O. & Fardet, L. Reporting of harm and safety results in randomized controlled trials published in 5 dermatology journals. *J. Am. Acad. Dermatol.* **77**, 98-104.e1 (2017).

115. Lineberry, N. *et al.* Recommendations to improve adverse event reporting in clinical trial publications: a joint pharmaceutical industry/journal editor perspective. *BMJ* i5078 (2016) doi:10.1136/bmj.i5078.

116. Ioannidis, J. P. A. *et al.* Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann. Intern. Med.* **141**, 781–788 (2004).

117. Haidich, A.-B., Birtsou, C., Dardavessis, T., Tirodimos, I. & Arvanitidou, M. The quality of safety reporting in trials is still suboptimal: survey of major general medical journals. *J. Clin. Epidemiol.* **64**, 124–135 (2011).

118. Gahr, M., Eller, J., Connemann, B. J. & Schönfeldt-Lecuona, C. Underreporting of adverse drug reactions: Results from a survey among physicians. *Eur. Psychiatry* **41**, S369–S369 (2017).

119. García-Abeijon, P. *et al.* Factors Associated with Underreporting of Adverse Drug Reactions by Health Care Professionals: A Systematic Review Update. *Drug Saf.* **46**, 625–636 (2023).

120. Varallo, F. R., Guimarães, S. D. O. P., Abjaude, S. A. R. & Mastroianni, P. D. C. Causes for the underreporting of adverse drug events by health professionals: a systematic review. *Rev. Esc. Enferm. USP* **48**, 739–747 (2014).

121. Lopez-Gonzalez, E., Herdeiro, M. T. & Figueiras, A. Determinants of Under-Reporting of Adverse Drug Reactions: A Systematic Review. *Drug Saf.* **32**, 19–31 (2009).

122. Golder, S., Loke, Y. K., Wright, K. & Norman, G. Reporting of Adverse Events in Published and Unpublished Studies of Health Care Interventions: A Systematic Review. *PLOS Med.* **13**, e1002127 (2016).

123. Parsons, R., Golder, S. & Watt, I. More than one-third of systematic reviews did not fully report the adverse events outcome. *J. Clin. Epidemiol.* **108**, 95–101 (2019).

124. Rising, K., Bacchetti, P. & Bero, L. Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation. *PLoS Med.* **5**, e217 (2008).

125. Ishiguro, L., Saskin, R., Vermeulen, M. J., Yates, E. & Victor, N. G. and J. C. Increasing Access to Health Administrative Data with ICES Data & Analytic Services. *Healthc. Q.* **19**, (2016).

126. Schull, M. J. *et al.* ICES: Data, Discovery, Better Health. *Int. J. Popul. Data Sci.* **4**, 1135 (2020).

127. Schull, M., Paprica, A. P., Victor, C. J. & Saskin, R. Institute for Clinical Evaluative Sciences (ICES) Exploratory Data & Analytic Services Private Sector Pilot Project: IJPDS (2017) Issue 1, Vol 1:069, Proceedings of the IPDLN Conference (August 2016). *Int. J. Popul. Data Sci.* **1**, (2017).

128. Cheng, S. Y. *et al.* Demographic characteristics and cost of treatment among oncology patients in a publicly funded system, the Ontario Trillium Drug Program: a retrospective cohort study. *CMAJ Open* **7**, E516–E523 (2019).

129. Tadrous, M. *et al.* Catastrophic drug coverage: utilization insights from the Ontario Trillium Drug Program. *CMAJ Open* **6**, E132–E138 (2018).

130. Levy, A. R., O'Brien, B. J., Sellors, C., Grootendorst, P. & Willison, D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can. J. Clin. Pharmacol. J. Can. Pharmacol. Clin.* **10**, 67–71 (2003).

131. Récoché, I. *et al.* Drug–drug interactions with imatinib: An observational study. *Medicine (Baltimore)* **95**, e5076 (2016).

132. Canadian Institute for Health Information. Data Quality Documentation, Discharge Abstract Database — 2019–2020. (2020).

133. Krzyzanowska, M. K. *et al.* Can Chemotherapy-Related Acute Care Visits Be Accurately Identified in Administrative Data? *J. Oncol. Pract.* **14**, e51–e58 (2018).

134. Grant, R. C. *et al.* Development and Validation of a Score to Predict Acute Care Use After Initiation of Systemic Therapy for Cancer. *JAMA Netw. Open* **2**, e1912823 (2019).

135. Hohl, C. M., Karpov, A., Reddekopp, L. & Stausberg, J. ICD-10 codes used to identify adverse drug events in administrative data: a systematic review. *J. Am. Med. Inform. Assoc.* **21**, 547–557 (2014).

136. Weycker, D. *et al.* Technical evaluation of methods for identifying chemotherapy-induced febrile neutropenia in healthcare claims databases. *BMC Health Serv. Res.* **13**, 60 (2013).

137. Segal, J. B. & Powe, N. R. Accuracy of identification of patients with immune thrombocytopenic purpura through administrative records: a data validation study. *Am. J. Hematol.* **75**, 12–17 (2004).

138. Data Quality Documentation, National Ambulatory Care Reporting System — Current-Year Information, 2019–2020.

139. Quan, H. *et al.* Assessing Validity of ICD-9-CM and ICD-10 Administrative Data in Recording Clinical Conditions in a Unique Dually Coded Database. *Health Serv. Res.* **43**, 1424–1441 (2008).

140. Wijeratne, D. T. *et al.* Using health administrative data to identify patients with pulmonary hypertension: A single center, proof of concept validation study in Ontario, Canada. *Pulm. Circ.* **12**, e12040 (2022).

141. Hall, S., Schulze, K., Groome, P., Mackillop, W. & Holowaty, E. Using cancer registry data for survival studies: the example of the Ontario Cancer Registry. *J. Clin. Epidemiol.* **59**, 67–76 (2006).

142. Cancer Care Ontario. Data Sources - Ontario Cancer Statistics. https://www.cancercareontario.ca/en/statistical-reports/ontario-cancer-statistics-2020/data-sources (2016).

143. Robles, S. C., Marrett, L. D., Aileen Clarke, E. & Risch, H. A. An application of capture-recapture methods to the estimation of completeness of cancer registration. *J. Clin. Epidemiol.* **41**, 495–501 (1988).

144. Rabeneck, L. *et al.* Ontario's ColonCancerCheck: Results from Canada's First Province-Wide Colorectal Cancer Screening Program. *Cancer Epidemiol. Biomarkers Prev.* **23**, 508–515 (2014).

145. Ontario Ministry of Health. OHIP Personal Health Information. http://www.ontario.ca/page/ohip-personal-health-information.

146. Schwartz, K. L. *et al.* Using physician billing claims from the Ontario Health Insurance Plan to determine individual influenza vaccination status: an updated validation study. *Can. Med. Assoc. Open Access J.* **4**, E463–E470 (2016).

147. Ontario Community Health Profiles Partnership. The Registered Persons Database (RPDB) vs. Statistics Canada, Census Counts: Why the Ontario Community Health Profiles Partnership (OCHPP) Project Uses RPDB instead of Census as the Source for Population (Denominator). https://www.ontariohealthprofiles.ca/o_documents/aboutTheDataON/RPDB_vs_Census.pdf (2022).

148. Hochhaus, A. *et al.* Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. *N. Engl. J. Med.* **376**, 917–927 (2017).

149. Marin, D. *et al.* Adherence Is the Critical Factor for Achieving Molecular Responses in Patients With Chronic Myeloid Leukemia Who Achieve Complete Cytogenetic Responses on Imatinib. *J. Clin. Oncol.* **28**, 2381–2388 (2010).

150. Noens, L. *et al.* Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood* **113**, 5401–5411 (2009).

151. Lee, E. & Wen, P. Gender and sex disparity in cancer trials. *ESMO Open* **5**, e000773 (2020).

152. Vinay, K. *et al.* Long-term mucocutaneous adverse effects of imatinib in Indian chronic myeloid leukemia patients. *Int. J. Dermatol.* **57**, 332–338 (2018).

153. Adattini, J. A., Gross, A. S., Wong Doo, N. & McLachlan, A. J. Real-world efficacy and safety outcomes of imatinib treatment in patients with chronic myeloid leukemia: An Australian experience. *Pharmacol. Res. Perspect.* **10**, e01005 (2022).

154. Kantarjian, H. M. *et al.* Efficacy of Imatinib Dose Escalation in Patients With Chronic Myeloid Leukemia in Chronic Phase. *Cancer* **115**, 551–560 (2009).

155. Cheng, F. *et al.* Imatinib dose optimization based on therapeutic drug monitoring in Chinese patients with chronic-phase chronic myeloid leukemia. *Cancer* **128**, 3951–3958 (2022).

156. Mughal, T. I. & Schrieber, A. Principal long-term adverse effects of imatinib in patients with chronic myeloid leukemia in chronic phase. *Biol. Targets Ther.* **4**, 315–323 (2010).

157. Xu, J., Ju, B., Yang, X.-D., Xiu, N.-N. & Zhao, X.-C. Imatinib-induced severe hematological toxicity: Prolonged myelosuppression resulting from extraordinary sensitivity in an old age. *Eur. J. Inflamm.* **21**, 1721727X231158468 (2023).

158. Lipton, J. H. *et al.* Long-term safety review of tyrosine kinase inhibitors in chronic myeloid leukemia - What to look for when treatment-free remission is not an option. *Blood Rev.* **56**, 100968 (2022).

159. Breccia, M. *et al.* Age influences initial dose and compliance to imatinib in chronic myeloid leukemia elderly patients but concomitant comorbidities appear to influence overall and event-free survival. *Leuk. Res.* **38**, 1173–1176 (2014).

160. Breccia, M. *et al.* Age Influences Initial Dose and Compliance to Imatinib In Chronic Myeloid Leukemia Elederly Patients but Concomitant Comorbidities Appear to Influence Overall and Event-Free Survival. *Blood* **118**, 2751 (2011).

161. Ono, T. *et al.* Prognostic effect of comorbidities in patients with chronic myeloid leukemia treated with a tyrosine kinase inhibitor. *Cancer Sci.* **111**, 3714–3725 (2020).

162. Chao, C. *et al.* History of chronic comorbidity and risk of chemotherapy-induced febrile neutropenia in cancer patients not receiving G-CSF prophylaxis. *Ann. Oncol.* **25**, 1821–1829 (2014).

163. Hougland, P. *et al.* Using ICD-9-CM Codes in Hospital Claims Data to Detect Adverse Events in Patient Safety Surveillance. 18.

164. Krive, J. *et al.* The complexity and challenges of the International Classification of Diseases, Ninth Revision, Clinical Modification to International Classification of Diseases, 10th Revision, Clinical Modification transition in EDs. *Am. J. Emerg. Med.* **33**, 713–718 (2015).

165. Quan, H. *et al.* Mining administrative health databases to advance medical science: geographical considerations and untapped potential in Canada. *Can. J. Cardiol.* **28**, 152–154 (2012).

166. Allignol, A., Beyersmann, J. & Schmoor, C. Statistical issues in the analysis of adverse events in time-to-event data. *Pharm. Stat.* **15**, 297–305 (2016).

167. Abdel-Qadir, H. *et al.* Importance of Considering Competing Risks in Time-to-Event Analyses: Application to Stroke Risk in a Retrospective Cohort Study of Elderly Patients With Atrial Fibrillation. *Circ. Cardiovasc. Qual. Outcomes* **11**, e004580 (2018).

168. Schuster, N. A., Hoogendijk, E. O., Kok, A. A. L., Twisk, J. W. R. & Heymans, M. W. Ignoring competing events in the analysis of survival data may lead to biased results: a nonmathematical illustration of competing risk analysis. *J. Clin. Epidemiol.* **122**, 42–48 (2020).

169. Stegherr, R., Schmoor, C., Lübbert, M., Friede, T. & Beyersmann, J. Estimating and comparing adverse event probabilities in the presence of varying follow-up times and competing events. *Pharm. Stat.* **20**, 1125–1146 (2021).

170. Southern, D. A. *et al.* Kaplan–Meier methods yielded misleading results in competing risk scenarios. *J. Clin. Epidemiol.* **59**, 1110–1114 (2006).

171. Paul, T. R. *et al.* Evaluation of Cytopenias Occurring in Imatinib Treated Chronic Myeloid Leukemia (CML) Patients. *Indian J. Hematol. Blood Transfus.* **26**, 56–61 (2010).

172. Bender, R., Beckmann, L. & Lange, S. Biometrical issues in the analysis of adverse events within the benefit assessment of drugs. *Pharm. Stat.* **15**, 292–296 (2016).

173. Franklin, J. M. & Schneeweiss, S. When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials? *Clin. Pharmacol. Ther.* **102**, 924–933 (2017).

174. Treweek, S. & Zwarenstein, M. Making trials matter: pragmatic and explanatory trials and the problem of applicability. *Trials* **10**, 37 (2009).

175. Tunis, S. R., Stryer, D. B. & Clancy, C. M. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA* **290**, 1624–1632 (2003).

176. Booth, C. M. & Tannock, I. F. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. *Br. J. Cancer* **110**, 551–555 (2014).

177. Efficace, F. *et al.* Chronic fatigue is the most important factor limiting health-related quality of life of chronic myeloid leukemia patients treated with imatinib. *Leukemia* **27**, 1511–1519 (2013).

178. Aapro, M. S. *et al.* 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur. J. Cancer Oxf. Engl. 1990* **47**, 8–32 (2011).

179. Lyman, G. H. Impact of chemotherapy dose intensity on cancer patient outcomes. *J. Natl. Compr. Cancer Netw. JNCCN* **7**, 99–108 (2009).

180. Leleu, X., Gay, F., Flament, A., Allcott, K. & Delforge, M. Incidence of neutropenia and use of granulocyte colony-stimulating factors in multiple myeloma: is current clinical practice adequate? *Ann. Hematol.* **97**, 387–400 (2018).

181. Dotsu, Y. *et al.* Real-World Incidence of Febrile Neutropenia among Patients Treated with Single-Agent Amrubicin: Necessity of the Primary Prophylactic Administration of Granulocyte Colony-Stimulating Factor. *J. Clin. Med.* **10**, 4221 (2021).

182. Abboud, C. N. *et al.* Real-world safety experience of tevagrastim/ratiograstim/biograstim and tbo-filgrastim, short-acting recombinant human granulocyte colony-stimulating factors. *Support. Care Cancer* **27**, 2569–2577 (2019).

183. Kim, H.-S., Lee, S. & Kim, J. H. Real-world Evidence versus Randomized Controlled Trial: Clinical Research Based on Electronic Medical Records. *J. Korean Med. Sci.* **33**, (2018).

184. Johnson, E. K. & Nelson, C. P. Values and pitfalls of the use of administrative databases for outcomes assessment. *J. Urol.* **190**, 17–18 (2013).

185. Mohammed, A. H., Abdulsalam, A. H. & Abdulbaqee, A. G. Types of Anemia in Patients with Chronic Myeloid Leukemia- Chronic Phase on Imatinib Mesylate. (2012).

186. Tong, W.-G. *et al.* Imatinib front-line therapy is safe and effective in patients with chronic myelogenous leukemia with pre-existing liver and/or renal dysfunction. *Cancer* **116**, 3152–3159 (2010).

187. Latagliata, R. *et al.* "Real-life" results of front-line treatment with Imatinib in older patients (≥65 years) with newly diagnosed chronic myelogenous leukemia. *Leuk. Res.* **34**, 1472–1475 (2010).

188. McLigeyo, A. *et al.* Baseline blood count levels increase odds of cytopenia among CML patients in Kenya: a case control study. *BMC Cancer* **22**, 128 (2022).

189. Matti, B. F., Alwan, A. F. & Alwan, A. F. Evaluation of the safety of imatinib mesylate in 200 iraqi patients with chronic myeloid leukemia in the chronic phase: single-center study. *Turk. J. Haematol. Off. J. Turk. Soc. Haematol.* **30**, 387–393 (2013).

190. Moura, M. S. *et al.* Evaluation of anemia after long-term treatment with imatinib in chronic myeloid leukemia patients in chronic phase. *Hematol. Transfus. Cell Ther.* **41**, 329–334 (2019).

191. Hurria, A. *et al.* Predicting Chemotherapy Toxicity in Older Adults With Cancer: A Prospective Multicenter Study. *J. Clin. Oncol.* (2011) doi:10.1200/JCO.2011.34.7625.

192. Balducci, L. & Extermann, M. Management of Cancer in the Older Person: A Practical Approach. *The Oncologist* **5**, 224–237 (2000).

193. Flores, I. Q. & Ershler, W. Managing Neutropenia in Older Patients With Cancer Receiving Chemotherapy in a Community Setting. *Clin. J. Oncol. Nurs.* **14**, 81–86 (2010).

194. Eşkazan, A. E. Tyrosine kinase inhibitors (TKIs) used in the management of chronic myeloid leukaemia are associated with haematologic toxicities—Which TKI is the safest? *Br. J. Clin. Pharmacol.* **85**, 2241–2243 (2019).

195. Cortes, J. E. *et al.* Phase III, Randomized, Open-Label Study of Daily Imatinib Mesylate 400 mg Versus 800 mg in Patients With Newly Diagnosed, Previously Untreated Chronic Myeloid Leukemia in Chronic Phase Using Molecular End Points: Tyrosine Kinase Inhibitor Optimization and Selectivity Study. *J. Clin. Oncol.* **28**, 424–430 (2010).

196. Hehlmann, R. *et al.* Tolerability-Adapted Imatinib 800 mg/d Versus 400 mg/d Versus 400 mg/d Plus Interferon-α in Newly Diagnosed Chronic Myeloid Leukemia. *J. Clin. Oncol.* **29**, 1634–1642 (2011).

197. Deininger, M. W. *et al.* Imatinib 800mg Daily Induces Deeper Molecular Responses Than Imatinib 400mg Daily: Results of Swog S0325, an Intergroup Randomized Phase Ii Trial in

Newly Diagnosed Chronic Phase Chronic Myeloid Leukaemia. *Br. J. Haematol.* **164**, 223–232 (2014).

198. Kantarjian, H. *et al.* High-dose imatinib mesylate therapy in newly diagnosed Philadelphia chromosome–positive chronic phase chronic myeloid leukemia. *Blood* **103**, 2873–2878 (2004).

199. Petzer, A. L. *et al.* High-dose imatinib induction followed by standard-dose maintenance in pre-treated chronic phase chronic myeloid leukemia patients – final analysis of a randomized, multicenter, phase III trial. *Haematologica* **97**, 1562–1569 (2012).

200. Özdemir, B. C., Csajka, C., Dotto, G.-P. & Wagner, A. D. Sex Differences in Efficacy and Toxicity of Systemic Treatments: An Undervalued Issue in the Era of Precision Oncology. *J. Clin. Oncol.* **36**, 2680–2683 (2018).

201. Özdemir, B. C., Gerard, C. L. & Espinosa da Silva, C. Sex and Gender Differences in Anticancer Treatment Toxicity: A Call for Revisiting Drug Dosing in Oncology. *Endocrinology* **163**, bqac058 (2022).

202. Cortes, J. *et al.* Erythropoietin is effective in improving the anemia induced by imatinib mesylate therapy in patients with chronic myeloid leukemia in chronic phase. *Cancer* **100**, 2396–2402 (2004).

203. Latagliata, R. *et al.* Incidence of persistent/late chronic anemia in newly diagnosed patients with chronic myeloid leukemia responsive to imatinib. *Am. J. Hematol.* **90**, 105–108 (2015).

204. Kim, H.-I., Lim, H. & Moon, A. Sex Differences in Cancer: Epidemiology, Genetics and Therapy. *Biomol. Ther.* **26**, 335–342 (2018).

205. Gotta, V. *et al.* Large-scale imatinib dose–concentration–effect study in CML patients under routine care conditions. *Leuk. Res.* **38**, 764–772 (2014).

206. Government of Canada, S. C. Distribution of total income by census family type and age of older partner, parent or individual. *www150.statcan.gc.ca* https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1110001201 (2020).

207. Kantarjian, H., Mathisen, M. S. & Lipton, J. H. Having “Skin in the Game” and Allowing Cross-Border Importation of Drugs to Lower High Prices of Cancer Drugs. *JAMA Oncol.* **1**, 729 (2015).

208. Gugliotta, G. *et al.* First-Line Treatment of Newly Diagnosed Elderly Patients with Chronic Myeloid Leukemia: Current and Emerging Strategies. *Drugs* **74**, 627–643 (2014).

209. Hijiya, N., Schultz, K. R., Metzler, M., Millot, F. & Suttorp, M. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. *Blood* **127**, 392–399 (2016).

210. Siegel, R. L., Miller, K. D. & Wagle, N. S. Cancer statistics, 2023. *CA. Cancer J. Clin.* **73**, 17–48 (2023).

211. Brandt, J., Shearer, B. & Morgan, S. G. Prescription drug coverage in Canada: a review of the economic, policy and political considerations for universal pharmacare. *J. Pharm. Policy Pract.* **11**, 28 (2018).

212. Hajizadeh, M. & Edmonds, S. Universal Pharmacare in Canada: A Prescription for Equity in Healthcare. *Int. J. Health Policy Manag.* **9**, 91–95 (2019).

Appendices

Appendix 1: Clinical and laboratory symptoms of myelosuppression

Adverse event	Characteristics (grade 3+)
Neutropenia	**Laboratory indications:** - Low levels of neutrophils - Grade 3: Absolute neutrophil count <1.0 to 0.5 x 10^9/L - Grade 4: Absolute neutrophil count <0.5 x 10^9/L **Clinical symptoms:** - Neutropenic fever (febrile neutropenia) - Neutropenic colitis - Mouth sores and ulcers - Elevated risk of opportunistic infections - Signs of infection without inflammatory response due to low levels of neutrophils
Thrombocytopenia	**Laboratory indications:** - Low levels of platelets - Grade 3: Platelet count <50,000 to 25,000/mm^3 - Grade 4: Platelet count <25,000/mm^3 **Clinical symptoms:** - Excessing bruising - Excessive superficial or prolonged bleeding - Bleeding from gums, nose, or gastrointestinal tract (blood in urine or stool) - Petechiae (Small blood spots cause by bleeding under the skin)
Anemia	**Laboratory indications:** - Low levels of red blood cells or hemoglobin (Hb) - Grade 3: Hemoglobin level <8.0 g/dL - Grade 4: Life-threatening consequences; urgent intervention indicated **Clinical symptoms:** - Severe fatigue or weakness which limits functional status - Cardiac symptoms: shortness of breath, heart palpitations, or chest pain - Syncope or near-syncope: Fainting spells, dizziness, or light-headedness

Appendix 2: ICD-O-3 codes used for the identification of CML

Diagnosis	Morphology	ICD-O-3 code	Topography	ICD-O-3 code
CML	Chronic myeloid leukemia, nos	98633	Bone marrow	C421
	Chronic myeloid leukemia, BCR-ABL+	98753		

Appendix 3: Canadian DINs used for the identification of imatinib prescription records in the ODB program database

DIN	Product name	Manufacturer	Active ingredient	Strength (mg)	In Ontario formulary
02244724	GLEEVEC	Novartis	Imatinib mesylate	50	Yes
02244725	GLEEVEC	Novartis	Imatinib mesylate	100	Yes
02253275	GLEEVEC	Novartis	Imatinib mesylate	100	Yes
02253283	GLEEVEC	Novartis	Imatinib mesylate	400	Yes
02355337	APO-IMATINIB	Apotex	Imatinib mesylate	100	Yes
02355345	APO-IMATINIB	Apotex	Imatinib mesylate	400	Yes
02397285	NAT-IMATINIB	Natco Pharma	Imatinib mesylate	100	Yes
02397293	NAT-IMATINIB	Natco Pharma	Imatinib mesylate	400	Yes
02399806	TEVA-IMATINIB	Teva Pharmaceuticals	Imatinib mesylate	100	Yes
02399814	TEVA-IMATINIB	Teva Pharmaceuticals	Imatinib mesylate	400	Yes
02424495	MYLAN-IMATINIB	Mylan Pharmaceuticals	Imatinib mesylate	100	Yes
02424509	MYLAN-IMATINIB	Mylan Pharmaceuticals	Imatinib mesylate	400	Yes
02428318	RAN-IMATINIB	Ranbaxy Pharmaceuticals	Imatinib mesylate	100	Yes
02428326	RAN-IMATINIB	Ranbaxy Pharmaceuticals	Imatinib mesylate	400	Yes
02431114	PMS-IMATINIB	Pharmascience	Imatinib mesylate	100	Yes
02431122	PMS-IMATINIB	Pharmascience	Imatinib mesylate	400	Yes
02490986	ACH-IMATINIB	Accord Healthcare	Imatinib mesylate	100	Yes
02490994	ACH-IMATINIB	Accord Healthcare	Imatinib mesylate	400	Yes
02492334	MINT-IMATINIB	Mint Pharmaceuticals	Imatinib mesylate	100	Yes
02492342	MINT-IMATINIB	Mint Pharmaceuticals	Imatinib mesylate	400	Yes
02495066	JAMP IMATINIB	JAMP Pharma	Imatinib mesylate	100	No
02495074	JAMP IMATINIB	JAMP Pharma	Imatinib mesylate	400	No
02504596	IMATINIB	Sanis Health	Imatinib mesylate	100	No
02504618	IMATINIB	Sanis Health	Imatinib mesylate	400	No
02515547	SANDOZ IMATINIB	Sandoz Canada	Imatinib mesylate	100	No
02515555	SANDOZ IMATINIB	Sandoz Canada	Imatinib mesylate	400	No
09857444	APO-IMATINIB	Apotex	Imatinib mesylate	100	EAP Eligible
09857445	GLEEVEC	Novartis	Imatinib mesylate	400	EAP Eligible
09857446	APO-IMATINIB	Apotex	Imatinib mesylate	400	EAP Eligible
09857447	GLEEVEC (GIST-ON)	Novartis	Imatinib mesylate	100	EAP Eligible
09857448	GLEEVEC (GIST-ON)	Novartis	Imatinib mesylate	400	EAP Eligible
09857449	TEVA-IMATINIB	Teva Pharmaceuticals	Imatinib mesylate	100	EAP Eligible
09857450	TEVA-IMATINIB	Teva Pharmaceuticals	Imatinib mesylate	400	EAP Eligible
09857468	CO-IMATINIB	Cobalt Pharmaceuticals	Imatinib mesylate	100	EAP Eligible
09857469	CO-IMATINIB	Cobalt Pharmaceuticals	Imatinib mesylate	400	EAP Eligible
92099987	GLEEVEC (GIST-CAN)	Novartis	Imatinib mesylate	400	EAP Eligible
92099988	GLEEVEC (GIST-CAN)	Novartis	Imatinib mesylate	100	EAP Eligible
99100982	GLEEVEC	Novartis	Imatinib mesylate	100	EAP Eligible
99100983	GLEEVEC	Novartis	Imatinib mesylate	400	EAP Eligible

Appendix 4: Canadian DINs used for the identification of potentially interacting prescription drugs record in the ODB database

Drug type	Drug class	DINs
Imatinib	Tyrosine kinase inhibitor	02244725, 02515547, 02515555, 02521202, 02521210, 02253275, 02253283, 02355337, 02355345, 02397285, 02397293, 02399806, 02399814, 02431114, 02431122, 02490986, 02490994, 02492334, 02492342, 02495066, 02495074, 02504596, 02504618
Dasatinib	Tyrosine kinase inhibitor	02293129, 02293137, 02293145, 02320193, 02360810, 02360829, 02470705, 02470713, 02470721, 02478307, 02478315, 02478323, 02478331, 02478358, 02481499, 02481502, 02499282, 02499304, 02499312, 02499320, 02499339, 02499347, 02514737, 02514745, 02514753, 02514761, 02514788, 02514796
Bosutinib	Tyrosine kinase inhibitor	02419149, 02419157, 02483793
Nilotinib	Tyrosine kinase inhibitor	02315874, 02368250, 02481715
Ponatinib	Tyrosine kinase inhibitor	02437333, 02437341
Hydroxyurea	Antimetabolite	02343096, 02530260, 00465283, 02242920, 02247937
Interferon-α	Immunomodulator	00705896, 00705918, 00705926, 00812498, 00812501, 00891002, 01911988, 01911996, 01912003, 01959069, 01959077, 02019914, 02217015, 02217023, 02217031, 02217058, 02217066, 02223384, 02223392, 02223406, 02223414, 02231651, 02238674, 02238675, 02239832, 02240693, 02240694, 02240695, 02242966, 02242967, 02242968, 02242969, 02248077, 02248078, 02253410, 02253429
Anagrelide	Antiplatelet	02253054, 02260107, 02281155, 02281287, 02236859, 02274949
Dexamethasone	Corticosteroid	00016217, 00042676, 00140732, 00229679, 00285471, 00295094, 00358177, 00379689, 00489158, 00627763, 00716715, 00732885, 00732893, 00739839, 00751863, 00783900, 00785261, 00874582, 01946897, 01947044, 01964968, 01995022, 02023865, 02095114, 02095122, 02095130, 02095149, 02097281, 02150654, 02204266, 02204274, 02212978, 02237044, 02237045, 02237046, 02239534, 02240684, 02240685, 02240687, 02260298, 02260301, 02279363, 02311267, 02363445, 02387743, 02412888, 02412896, 02528584, 00016462, 00042560, 00042579, 00213624, 00354309, 00664227, 01964070, 01964976, 01977547, 02250055, 02261081
Warfarin	Anticoagulant	01918311, 01918338, 01918346, 01918354, 01918362, 02007959, 02240205, 02240206, 02242680, 02242681, 02242682, 02242683, 02242684, 02242685, 02242686, 02242687, 02242924, 02242925, 02242926, 02242927, 02242928, 02242929, 02245618
Rosuvastatin	Statin	02247162, 02247163, 02247164, 02265540, 02337975, 02337983, 02337991, 02338009, 02338726, 02338734, 02338742, 02338750, 02339765, 02339773, 02339781, 02339803, 02354608, 02354616, 02354624, 02354632, 02378523, 02378531, 02378558, 02378566, 02382644, 02382652, 02382660, 02382679, 02391252, 02391260, 02391279, 02391287, 02397781, 02397803, 02397811, 02397838, 02399164, 02399172, 02399180, 02399199, 02405628, 02405636, 02405644, 02405652, 02411628, 02411636, 02411644, 02411652, 02413051, 02413078, 02413086, 02413108, 02438917, 02438925, 02438933, 02438941, 02442574, 02442582, 02442590, 02442604, 02477483, 02477491, 02477505, 02477513, 02496534, 02496542, 02496550, 02496569, 02498332, 02498340, 02498359, 02498367, 02505576, 02505584, 02505592, 02505606
Clopidogrel	Antiplatelet	02238682, 02252767, 02293161, 02303027, 02330555, 02348004, 02359316, 02379813, 02385813, 02388065, 02398591, 02400553, 02408910, 02415550, 02416387, 02422255, 02482037, 02502283
Mercaptopurine	Immunomodulator	00004723, 02415275
Omeprazole	Proton-pump inhibitor	02016788, 02242461, 02242462, 02260859, 02310252, 02310260, 02320843, 02329425, 02329433, 02333422, 02333430, 02339927, 02364352, 02365677, 02372274, 02374870, 02385384, 02402416, 02422212, 02422220, 02432404, 02432765, 02433281, 02435683, 02436728, 02438968, 02439018, 02449919, 02449927, 02484617, 02490692, 00846503, 02119579, 02190915, 02230737,

		02245058, 02260867, 02295407, 02295415, 02296438, 02296446, 02320851, 02348691, 02403617, 02411857, 02416549, 02420198, 02439549, 02501880, 02504294, 09857195, 09857267, 09857285, 09857314, 09857342, 09857464, 09857500, 09857536, 09857640, 09857656, 09858131
Esomeprazole	Proton-pump inhibitor	02300524, 02379163, 02383039, 02383047, 02394839, 02394847, 02417480, 02417499, 02438461, 02438488, 02444712, 02528479, 02528487, 02244521, 02244522, 02339099, 02339102, 02379171, 02423855, 02423863, 02423979, 02423987, 02431173, 02442493, 02442507, 02460920, 02460939, 02479419, 02479427, 02520109, 02520117, 02520699, 02520702
Lansoprazole	Proton-pump inhibitor	02238525, 02249464, 02249472, 02366274, 02366282, 02369028, 02385775, 02392402, 02392410, 02395258, 02395266, 02410370, 02414767, 02414775, 02422808, 02422816, 02433672, 02470780, 02489805, 02489813, 02165503, 02165511, 02280515, 02280523, 02293811, 02293838, 02353830, 02353849, 02357682, 02357690, 02385643, 02385651, 02385767, 02402610, 02402629, 02410389, 02433001, 02433028
Pantoprazole	Proton-pump inhibitor	02239616, 02291665, 02294672, 02299585, 02306727, 02307863, 02308681, 02308703, 02309858, 02309866, 02309998, 02310007, 02310201, 02316463, 02318687, 02318695, 02336308, 02339072, 02352214, 02363410, 02363429, 02385740, 02385759, 02412969, 02415232, 02415240, 02415259, 02415267, 02417421, 02425378, 02428164, 02431319, 02431327, 02439107, 02441527, 02445867, 02453401, 02458969, 02469138, 02478773, 02478781, 02481561, 02498715, 02498723, 02515857, 02528835, 02229453, 02241804, 02267233, 02285479, 02285487, 02292912, 02292920, 02300486, 02301075, 02301083, 02305038, 02305046, 02307871, 02357054, 02370808, 02392615, 02392623, 02408414, 02408570, 02415208, 02416557, 02416565, 02417448, 02428172, 02428180, 02437945, 02440628, 02441853, 02466147, 02467372, 02471825, 02481588, 02519534
Rabeprazole	Proton-pump inhibitor	02315181, 02315203, 02320452, 02320460, 02320614, 02320622, 02330083, 02330091, 02381737, 02381745, 02408392, 02408406, 02415283, 02415291, 02419785, 02419793, 02422638, 02422646, 02484161, 02484188, 02243796, 02243797, 02296632, 02296640, 02298074, 02298082, 02310805, 02310813, 02314177, 02314185, 02345579, 02345587, 02356511, 02356538, 02385449, 02385457
Amlodipine	Calcium channel blocker	02273233, 02273241, 02273268, 02273276, 02273284, 02273292, 02273306, 02273314, 02280124, 02295148, 02297477, 02326760, 02326779, 02326787, 02326795, 02326809, 02326817, 02326825, 02326833, 02326841, 02330474, 02331071, 02331098, 02331489, 02331497, 02331500, 02331934, 02331942, 02339374, 02339382, 02340178, 02340186, 02341093, 02341107, 02342790, 02342804, 02343193, 02343207, 02343215, 02355582, 02355590, 02355604, 02357186, 02357704, 02362759, 02362775, 02362783, 02362791, 02362805, 02362813, 02362821, 02366436, 02366452, 02369222, 02369230, 02369249, 02371332, 02371340, 02371359, 02371707, 02378744, 02378760, 02378779, 02385783, 02392127, 02392135, 02392143, 02398877, 02404222, 02404230, 02404249, 02404257, 02404435, 02411253, 02411261, 02411288, 02411296, 02411318, 02411326, 02411334, 02411342, 02419556, 02421151, 02421178, 02426986, 02426994, 02427702, 02427710, 02427729, 02427737, 02444445, 02444453, 02444461, 02451549, 02468018, 02469022, 02476452, 02478587, 02484307, 02484706, 02490781, 02490803, 02490811, 02492199, 02503271, 02503298, 02503301, 02522500, 00878928, 00878936, 02250497, 02250500, 02259605, 02259613, 02272113, 02272121, 02273373, 02273381, 02280132, 02280140, 02284065, 02284073, 02284383, 02284391, 02297485, 02297493, 02321858, 02321866, 02331284, 02331292, 02357194, 02357208, 02357712, 02357720, 02362651, 02362678, 02371715, 02371723, 02385791, 02385805, 02397072, 02397080, 02419564, 02419572, 02429217, 02429225, 02468026, 02468034, 02469030, 02469049, 02476460, 02476479, 02522519, 0252252
Alprazolam	Benzodiazepine	00677477, 00677485, 01908170, 01908189, 01913239, 01913247, 02137534, 02137542, 02229813, 02229814, 02230074, 02230075, 02248706, 02248707, 02349191, 02349205, 02397021, 02397048, 02397056, 02397064, 02400111, 02400138, 02400146, 02400154, 02404877, 02404885, 02404893, 02404907, 00548359, 00548367, 00723770, 00813958, 00865397, 00865400, 01913484, 01913492, 02243611, 02243612, 02417634, 02417642, 02417650, 02417669, 02434636, 02434644

Prednisone	Corticosteroid	00156876, 00177091, 00271381, 00508586, 00598194, 00607517, 00610623, 00868426, 00868434, 00868442, 00021695, 00210188, 00232378, 00252417, 00271373, 00312770, 00550957
Levothyroxine	Hormone	00012289, 00012297, 00012300, 00012319, 00295582, 01953591, 01953605, 01953613, 01953621, 01953656, 01953664, 01953680, 01953699, 01980890, 01980904, 01980912, 01980920, 01980939, 01980947, 01980955, 01980963, 01980971, 01980998, 01981005, 01981013, 02187574, 02187582, 02187590, 02187604, 02187612, 02187620, 02187639, 02187647, 02233852, 02237213, 02237214, 02237215, 02237216, 02237217, 02237218, 02237219, 02237220, 02237221, 02237222, 02245947, 02245948, 02264323, 02264331, 02264358, 02264366, 02264374, 02264390, 02264404, 02264412, 02264420, 02264439, 02264447, 02264455, 02461714, 02461722, 02499916, 02499924, 02508486, 02508494, 02508508, 02508516, 02508524, 02508532, 02508540, 02508559, 02508567, 02508575, 02508583, 02508591, 02171228, 02172062, 02172070, 02172089, 02172097, 02172100, 02172119, 02172127, 02172135, 02172143, 02172151, 02213192, 02213206, 02213214, 02213222, 0221323

Appendix 5: ICD codes used for the identification of myelosuppression

Event	**ICD-10 code**	**ICD definition**
Anemia	D592	Drug-induced nonautoimmune hemolytic anemia
	D594	Other nonautoimmune hemolytic anemias
	D598	Other acquired hemolytic anemias
	D599	Acquired hemolytic anemia, unspecified
	D611	Drug-induced aplastic anemia
	D612	Aplastic anemia due to other external agents
	D630	Anemia in neoplastic disease
	D648	Other specified anaemias
	D6481	Chemotherapy induced anemia
	D649	Anemia, unspecified
	ICD-9 code	**ICD definition**
	2824	[ICD-9] Other specified aplastic anemias
	2858	[ICD-9] Other specified anemias
	2859	[ICD-9] Anemia, unspecified
Event	**ICD-10 code**	**ICD definition**
Thrombocytopenia	D634	Other primary thrombocytopenia
	D695	Secondary thrombocytopenia, unspecified
	D6959	Secondary thrombocytopenia due to drugs
	D696	Thrombocytopenia, unspecified
	ICD-9 code	**ICD definition**
	2874	[ICD-9] Secondary thrombocytopenia
	2875	[ICD-9] Thrombocytopenia, unspecified
Event	**ICD-10 code**	**ICD definition**
Neutropenia	D700	Neutropenia
	D708	Neutropenia, unspecified
	ICD-9 code	**ICD definition**
	2880	[ICD-9] Neutropenia

*ICD-9, introduced in 1979. uses a three-to-five character code to classify diseases.
*ICD-9 was replaced by ICD-10-CA in Canada in 2002 as ICD-9 was not robust enough to adequately define future diagnoses or procedures.
*ICD-10-CM contains nearly 5 times more diagnosis codes allowing for greater specific and laterality.

Appendix 6: All ICD diagnostic codes used for the identification of severe myelosuppressive events.

Code	Description	Y/N*	Code	Description	Y/N*
ICD-10	**Anemia**		**ICD-10**	**Thrombocytopenia**	
D500	Iron deficiency anemia secondary to blood loss	N	D691	Quality platelet defects	N
D501	Sideropenic dysphagia	N	D692	Other non-thrombocytopenia purpura	N
D508	Other iron deficiency anemias	N	D6938	Idiopathic thrombocytopenia purpura	N
D509	Iron deficiency anemia, unspecified	N	D634	Other primary thrombocytopenia	Y
D510	Vitamin B12 def. anemia due to intrinsic factor def.	N	D695	Secondary thrombocytopenia, unspecified	Y
D513	Other vitamin B12 deficiency anemias	N	D6959	Secondary thrombocytopenia due to drugs	Y
D520	Dietary folate deficiency anemia	N	D696	Thrombocytopenia, unspecified	Y
D521	Drug-induced folate deficiency anemia	N	D699	Hemorrhagic condition, unspecified	N
D529	Folate deficiency anemia, unspecified	N			
D539	Nutritional anemia, unspecified	N	**ICD-10**	**Neutropenia**	
D550	Anemia due to enzyme disorders	N	D700	Neutropenia	Y
D563	Thalassemia (minor), inherited	N	D708	Neutropenia, unspecified	Y
D571	Sickle cell	N	D7281	Other decreased white blood cell count	N
D582	Other hemoglobinopathies, unspecified	N			
D589	Hereditary hemolytic anemia, unspecified	N	**ICD-9**	**Anemia**	
D591	Oth. autoimmune hemolytic anemias, unspecified	N	2824	Thalassemia, unspecified	N
D592	Drug-induced nonautoimmune hemolytic anemia	Y	2829	Hereditary hemolytic anemia, unspecified	N
D594	Other nonautoimmune hemolytic anemias	Y	2848	Other specified aplastic anemias	Y
D598	Other acquired hemolytic anemias	Y	2851	Acute posthemorrhagic anemia	N
D599	Acquired hemolytic anemia, unspecified	Y	2858	Other specified anemias	Y
D600	Chronic acquired pure red cell aplasia	Y	2859	Anemia, unspecified	Y
D601	Transient acquired pure red cell aplasia	N			
D611	Drug-induced aplastic anemia	Y	**ICD-9**	**Thrombocytopenia**	
D612	Aplastic anemia due to other external agents	Y	2871	Qualitative platelet defects	N
D613	Idiopathic aplastic anemia	N	2872	Other nonthrombocytopenic purpuras	N
D618	Other aplastic anemia / bone marrow failures	Y	2873	Primary thrombocytopenia	N
D619	Aplastic anemia, unspecified	Y	2874	Secondary thrombocytopenia	Y
D620	Post-Hemorrhagic anemia	N	2875	Thrombocytopenia, unspecified	Y
D630	Anemia in neoplastic disease	Y			
D638	Anemia in other chronic diseases	N	**ICD-9**	**Neutropenia**	
D641	Secondary sideroblastic anemia due to disease	N	2880	Neutropenia	Y
D648	Other specified anemia	Y	2885	Decreased white blood cell count	N
D6481	Chemotherapy induced anemia	Y	2888	Other specified disease of white blood cells	N
D649	Anemia, unspecified	Y			

Appendix 7: Baseline and clinical characteristics of ODB, RCT, and pooled phase III populations.

Characteristic	ODB subjects (N = 1,683)	RCT patients (N = 551)	Pooled RCT data (N = 1,955)
Sex (%)			
Male	55.7	61.7	60.1
Female	44.3	38.3	39.9
Age (y)			
Median	67	50.0	50.0
Range (IQR)	18 - 87 (52 - 72)	18 – 70	16 – 89
≥ 60 (%)	65.9	20.6	-
Daily dose (mg/day)			
Mean	405.2 ± 81.9	400.0	400.0
Median	400	400.0	400.0
Range min/max (IQR)	100.0 - 800.0 (400.0 - 400.0)	114.0 – 732.0	114.0 – 732.0
Follow–up (mo)			
Median	15.4	19.0	19.0
Range min/max (IQR)	0.1 - 222.9 (5.5 - 45.1)	0.0 – 25.0	0.0 – 10.4
Time from diagnosis (mo)			
Median	1.9	2.1	1.0
Range min/max (IQR)	0.0 - 218.1 (0.8 - 14.8)	0.0 – 10.4	0.0 – 10.4

*ECOG score, SOKAL risk for CML, CML phase, and laboratory tests results were unavailable for the ODB subjects.

*CCI scores were unavailable for the RCT patients.

Appendix 8: The incidence of myelosuppression among ODB subjects compared to the IRIS study and the pooled phase III trials.

Adverse event (%)	ODB subjects (N = 1,683)	Registration trial data (N = 551)	Pooled phase III trials (N = 1,955)	95% CI
Total observed time				
Myelosuppression	15.6	-	-	13.8 - 17.3
Neutropenia	3.0	14.3	17.3	2.2 - 3.8
Thrombocytopenia	2.3	7.8	10.2	1.5 - 3.0
Anemia	12.7	3.1	4.9	11.1 - 14.3
RCT-matched follow up (25 mo)*				
Myelosuppression	10.8	-	-	9.3 - 12.3
Neutropenia	2.5	14.3	17.3	1.7 - 3.2
Thrombocytopenia	1.8	7.8	10.2	1.1 - 2.4
Anemia	8.4	3.1	4.9	7.1 - 9.7

*Two-tailed single-sample proportion test prodivent sufficient evidence to reject the null hypothesis. ($Pr(|Z| > |z|) < 0.01$ for all)

**Maximum RCT follow-up time was estimated using the Kaplan-Meier survival curves published in the clinical trial data.

Appendix 9: The risk of myelosuppression using a Cox proportional hazard model and Fine-Gray competing risks model.

Variable	Cause-specific hazard ratio HR[†]	95% CI	Subdistribution hazard ratio SHR[†]	95% CI
Sex				
Male	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Female	1.01	(0.78 - 1.31)	1.03	(0.80 - 1.34)
Age Group (y)				
< 45	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
45 - <55	1.59	(0.81 - 3.12)	1.54	(0.78 - 3.07)
55 - <65	1.36	(0.72 - 2.54)	1.34	(0.72 - 2.53)
65 - <75	2.43	(1.43 - 4.12)*	2.30	(1.35 - 3.92)*
75 - < 85	4.35	(2.48 - 7.61)*	3.74	(2.12 - 6.62)*
≥85	5.94	(2.89 - 12.23)*	4.28	(2.03 - 9.03)*
Mean Daily Dose (mg/day)				
<350	1.14	(0.76 - 1.73)	1.07	(0.71 - 1.62)
350 - <450	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
450 - <550	0.85	(0.46 - 1.57)	0.86	(0.47 - 1.57)
≥550	1.56	(0.98 - 2.48)	1.57	(0.98 - 2.52)
Total Cumulative Dose (g)				
<200	1.69	(0.67 - 4.30)	0.95	(0.44 - 2.03)
200-400	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
400-600	2.79	(1.21 - 6.46)*	3.39	(1.41 - 8.14)*
600 - 800	1.61	(0.49 - 5.32)	2.51	(0.94 - 6.66)
>800	2.18	(0.49 - 9.67)	4.41	(1.59 - 12.19)*
Comorbidity (CCI)				
0%	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1 - 2	1.26	(0.87 - 1.84)	1.27	(0.88 - 1.84)
3 - 4	1.87	(1.14 - 3.05)*	1.62	(0.98 - 2.67)
≥5	3.76	(2.07 - 6.86)*	3.18	(1.76 - 5.73)*

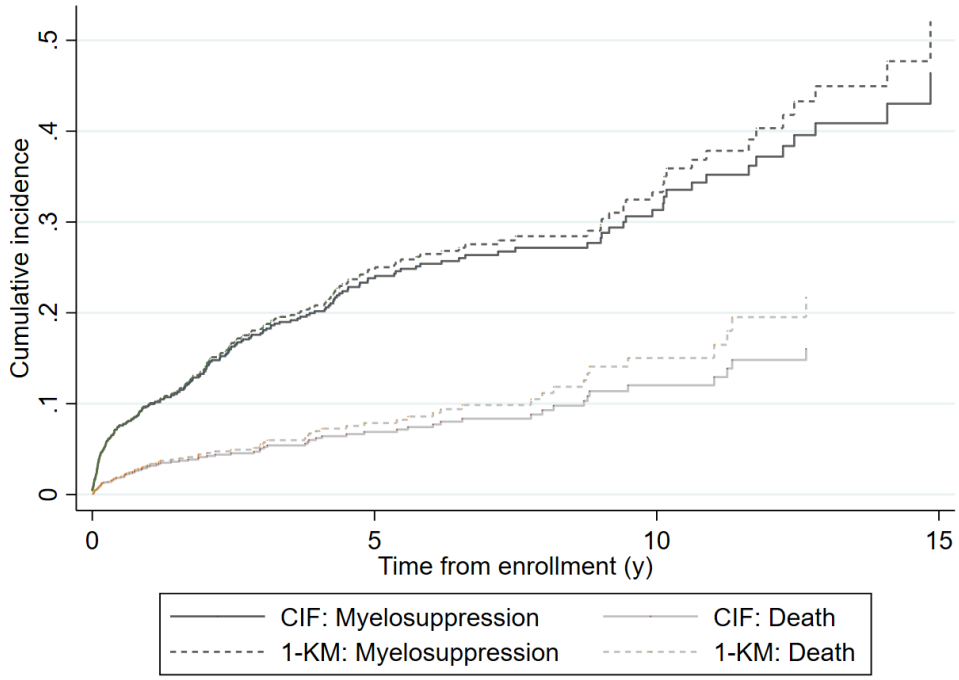
*Denotes statistical significance ($P > |z|) < 0.05$

[†]Subdistribution hazard ratios (SHR) were estmated using the Fine-Gray subdistribution hazard model

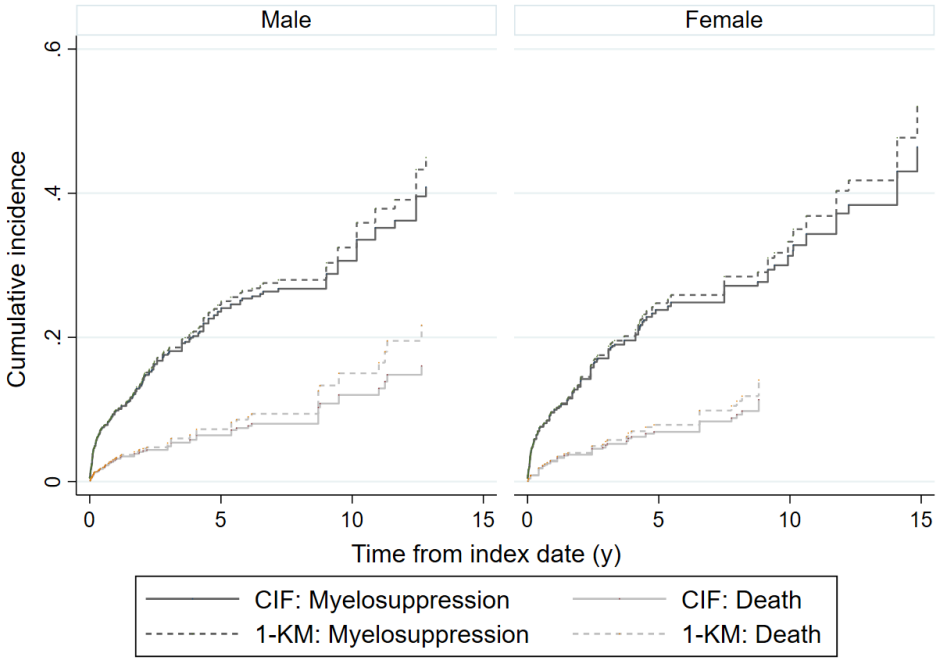
[†]Cause-specific hazard ratios (HR) were estmated using the Cox proportional-hazard model.

Appendix 10: The risk of myelosuppression using a Cox proportional hazard model and Fine-Gray competing risks model.

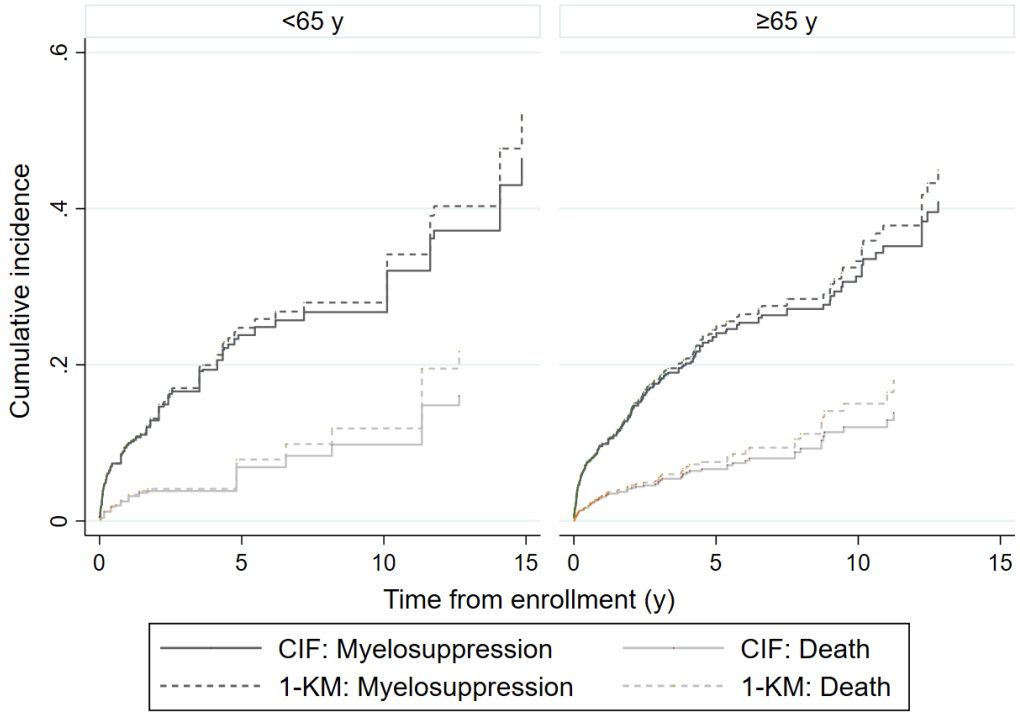
a) overall



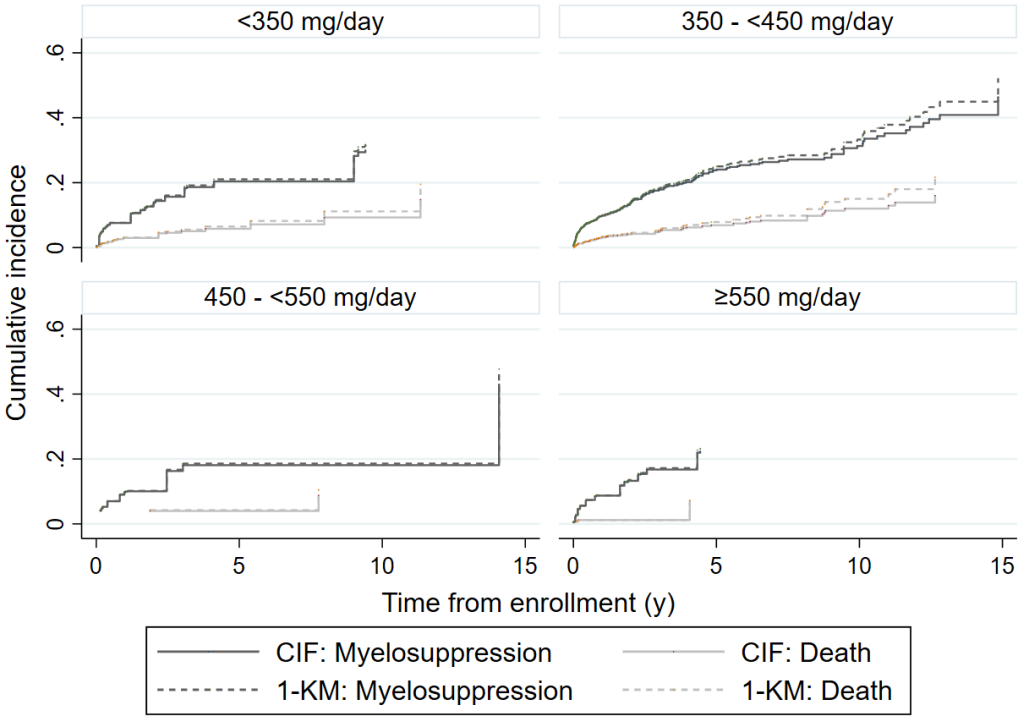
b) by sex



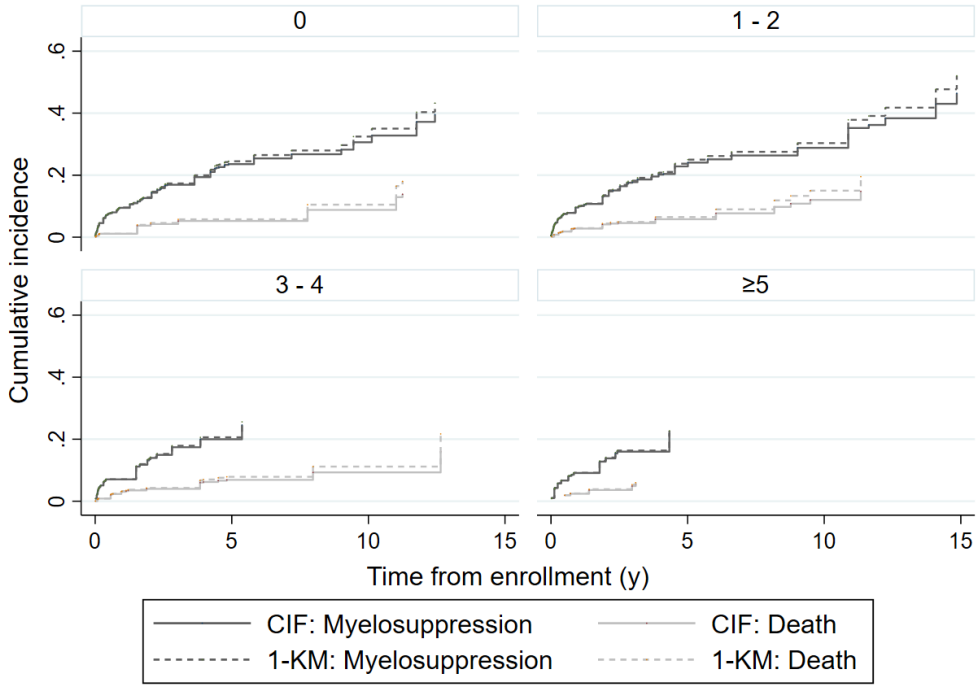
c) by age



d) by mean daily dose



e) by comorbidity (CCI score)



Appendix 11: Incidence of myelosuppression allowing a max. 30-day gap in prescription records, 90-day gap, or allowing any treatment gap.

Adverse event	*Allowing 30-day treatment gaps*	*Allowing 90-day treatment gaps*	*Allowing any treatment gaps*	IRIS study (N = 551)	Pooled phase III (N = 1,955)
		ODB subjects (N = 1,683)			
Total observed time (%)					
Myelosuppression	15.6	19.1	23.0	-	-
Neutropenia	3.0	3.3	3.4	14.3	17.3
Thrombocytopenia	2.2	2.7	3.4	7.8	10.2
Anemia	12.7	16.3	20.1	3.1	4.9
RCT-matched follow up (25 mo)* (%)					
Myelosuppression	10.8	11.3	12.2	-	-
Neutropenia	2.5	2.6	2.6	14.3	17.3
Thrombocytopenia	1.8	1.8	2.0	7.8	10.2
Anemia	8.3	8.8	9.9	3.1	4.9

*Two-tailed single-sample proportion test prodivent sufficient evidence to reject the null hypothesis. ($Pr(|Z| > |z|) < 0.01$ for all)

**Maximum RCT follow-up time was estimated using the Kaplan-Meier survival curves published in the clinical trial data.

Appendix 12: The risk of myelosuppression allowing a maximum 30-day gap in prescription records compared to a maximum 90-day gap in prescription records.

	Cause-specific hazard ratio (Cox PH)						Subdistribution hazard ratio (Fine-Gray CR)					
	Max. 30-day treatment gap*			Max. 90-day treatment gap**			Max. 30-day treatment gap*			Max. 90-day treatment gap**		
VARIABLE	**HR**	95% CI	p	**HR**	95% CI	p	**SHR**	95% CI	p	**SHR**	95% CI	p
Sex												
Male	1	1	1	1	1	1	1	1	1	1	1	1
Female	1.01	(0.78 - 1.31)	0.94	1.08	(0.85 - 1.36)	0.54	1.03	(0.80 - 1.34)	0.80	1.12	(0.88 - 1.41)	0.36
Age Group (y)												
< 45	1	1	1	1	1	1	1	1	1	1	1	1
45 - <55	1.59	(0.81 - 3.12)	0.18	1.80	(0.98 - 3.28)	0.06	1.54	(0.78 - 3.07)	0.21	1.74	(0.95 - 3.19)	0.07
55 - <65	1.36	(0.72 - 2.54)	0.34	1.63	(0.93 - 2.87)	0.09	1.34	(0.72 - 2.53)	0.36	1.60	(0.90 - 2.82)	0.11
65 - <75	2.43	(1.43 - 4.12)	**<0.01**	2.66	(1.64 - 4.32)	**<0.01**	2.30	(1.35 - 3.92)	**<0.01**	2.48	(1.52 - 4.04)	**<0.01**
75 - < 85	4.35	(2.48 - 7.61)	**<0.01**	4.94	(2.96 - 8.23)	**<0.01**	3.74	(2.12 - 6.62)	**<0.01**	4.13	(2.46 - 6.92)	**<0.01**
≥85	5.94	(2.89 - 12.23)	**<0.01**	6.42	(3.24 - 12.71)	**<0.01**	4.28	(2.03 - 9.03)	**<0.01**	4.18	(2.05 - 8.54)	**<0.01**
Mean Daily Dose (mg/day)												
<350	1.14	(0.76 - 1.73)	0.52	1.07	(0.72 - 1.58)	0.73	1.07	(0.71 - 1.62)	0.74	0.98	(0.66 - 1.46)	0.94
350 - <450	1	1	1	1	1	1	1	1	1	1	1	1
450 - <550	0.85	(0.46 - 1.57)	0.60	0.96	(0.58 - 1.57)	0.87	0.86	(0.47 - 1.57)	0.63	0.98	(0.61 - 1.58)	0.95
≥550	1.56	(0.98 - 2.48)	0.06	1.64	(1.10 - 2.44)	0.02	1.57	(0.98 - 2.52)	0.06	1.68	(1.13 - 2.50)	0.01
Total Cumulative Dose (g)												
<200	1.69	(0.67 - 4.30)	0.27	1.45	(0.64 - 3.25)	0.37	0.95	(0.44 - 2.03)	0.89	0.85	(0.45 - 1.63)	0.63
200-400	1	1	1	1	1	1	1	1	1	1	1	1
400-600	2.79	(1.21 - 6.46)	0.02	2.64	(1.25 - 5.58)	0.01	3.39	(1.41 - 8.14)	0.01	3.33	(1.56 - 7.12)	**<0.01**
600 - 800	1.61	(0.49 - 5.32)	0.43	1.99	(0.73 - 5.42)	0.18	2.51	(0.94 - 6.66)	0.07	3.11	(1.32 - 7.29)	0.01
>800	2.18	(0.49 - 9.67)	0.30	2.41	(0.75 - 7.77)	0.14	4.41	(1.59 - 12.19)	**<0.01**	4.97	(2.16 - 11.43)	**<0.01**
Comorbidity (CCI)												
0	1	1	1	1	1	1	1	1	1	1	1	1
1 - 2	1.26	(0.87 - 1.84)	0.23	1.17	(0.83 - 1.66)	0.36	1.27	(0.88 - 1.84)	0.21	1.18	(0.83 - 1.66)	0.35
3 - 4	1.87	(1.14 - 3.05)	0.01	1.92	(1.23 - 2.99)	**<0.01**	1.62	(0.98 - 2.67)	0.06	1.64	(1.05 - 2.56)	0.03
≥5	3.76	(2.07 - 6.86)	**<0.01**	3.47	(1.92 - 6.27)	**<0.01**	3.18	(1.76 - 5.73)	**<0.01**	2.76	(1.52 - 4.99)	**<0.01**

*Maximum 30-day gap between the completion of one subscription to the start of the subsequent prescription, censored after gap >30 days

**Maximum 90-day gap between the completion of one subscription to the start of the subsequent prescription, censored after gap >90 days

Appendix 13: Dalhousie University Health Sciences Research Ethics Board approval (REB #2020-5280).

DALHOUSIE UNIVERSITY

Health Sciences Research Ethics Board
Letter of Approval

January 19, 2021

Nathan McKenzie
Medicine\Community Health & Epidemiology

Dear Nathan,

REB #: 2020-5280
Project Title: Occurrence of adverse events in persons with cancer treated with Imatinib in a real world population.

Effective Date: January 19, 2021
Expiry Date: January 19, 2022

The Health Sciences Research Ethics Board has reviewed your application for research involving humans and found the proposed research to be in accordance with the Tri-Council Policy Statement on *Ethical Conduct for Research Involving Humans*. This approval will be in effect for 12 months as indicated above. This approval is subject to the conditions listed below which constitute your on-going responsibilities with respect to the ethical conduct of this research.

Effective March 16, 2020: Notwithstanding this approval, any research conducted during the COVID-19 public health emergency must comply with federal and provincial public health advice as well as directives from Dalhousie University (and/or other facilities or jurisdictions where the research will occur) regarding preventing the spread of COVID-19.

Sincerely,

Dr. Lori Weeks, Chair

Appendix 14: Dalhousie University Health Sciences Research Ethics Board approval (REB #2020-5280) – Updated February 22, 2024.

DALHOUSIE UNIVERSITY

Health Sciences Research Ethics Board
Annual Renewal - Letter of Approval

February 22, 2024

Nathan McKenzie
Medicine\Community Health & Epidemiology

Dear Nathan,

REB #: 2020-5280
Project Title: Occurrence of adverse events in persons with cancer treated with Imatinib in a real world population.

Expiry Date: January 19, 2025

The Health Sciences Research Ethics Board has reviewed your annual report and has approved continuing approval of this project up to the expiry date (above).

REB approval is only effective for up to 12 months (as per TCPS article 6.14) after which the research requires additional review and approval for a subsequent period of up to 12 months. Prior to the expiry of this approval, you are responsible for submitting an annual report to further renew REB approval. When your project is complete and no longer requires REB approval, please complete a Final Report to close your file in good standing. Forms are available on the Research Ethics website.

I am also including a reminder (below) of your other on-going research ethics responsibilities with respect to this research.

Sincerely,

Dr. Jennifer Isenor
Chair, Health Sciences Research Ethics Board
Dalhousie University