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Evaluating the endometabolic and bone health effects of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukaemia: a systematic review protocol

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ABSTRACT

Introduction Chronic Myeloid Leukaemia (CML) constitutes 15% of new adult leukaemia cases as well as 2%–3% of leukaemia in children under 15% and 9% of leukaemias in adolescents 15–19 years of age annually. The introduction of Tyrosine Kinase Inhibitors (TKI) therapy has dramatically improved survival in these patients, yet the off-target effects of this treatment may have long-term health impacts on CML survivors. The risk of adverse health outcomes is especially important in children, where TKI exposure may occur during critical windows of growth and puberty, and patients require treatment for prolonged periods of time. The aim of this systematic review protocol is to report on the methods used to conduct a systematic review to investigate the endometabolic and bone health effects of TKI therapy in CML.

Methods and analysis Searches will be conducted in the Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE from inception on August 1st, 2019. Searches may be updated while performing the systematic review to ensure new evidence is included if applicable. Grey literature search will include ClinicalTrials.gov and ProQuest Dissertations and Theses A&I. We will perform a meta-analysis if there are at least two studies reporting similar populations, interventions, methods and tracking the same outcome measures. The studies should also have similar age and sex distributions.

Ethics and dissemination As this is a systematic review protocol, it does not include patient data; therefore, Research Ethics Board approval is not indicated. The systematic review will be published in a peer-reviewed journal and presented at international conferences.

PROSPERO registration number CRD42018091175.

Strengths and limitations of this study

- This systematic review protocol includes a detailed reporting of the methods that will be used to assess the endometabolic and bone health outcomes with Tyrosine Kinase Inhibitors therapy in Chronic Myeloid Leukaemia patients to help the stratification of screening and intervention needs.
- If the relevant studies have small sample sizes, the lack of adequate power will limit the conclusions that can be drawn from this systematic review.
- If there is extensive heterogeneity among studies, it may not be possible to perform a meta-analysis to quantitatively synthesize the data.

INTRODUCTION

Chronic Myeloid Leukaemia (CML) accounts for approximately 15% of all newly diagnosed adult leukaemias as well as 2%–3% of leukaemias in children under the age of 15 years and 9% of leukaemias in those 15–19 years of age.[1 2] In western countries, the annual incidence of CML was approximately 1.9 per 100 000 people in 2016, which translates to around 5600 new cases in the USA alone.[3]

The outcomes of what was uniformly a disease with poor prognosis were transformed with the introduction of Tyrosine Kinase Inhibitors (TKIs).[4–7] As TKI use became more widespread, the estimated 5-year survival rate has more than doubled from 31% in the early 1990s to around 70% in 2015.[3] These innovative drugs inhibit the product of the fundamental mechanism in the genetic aetiology of CML, the fusion of protooncogenes BCR (Breakpoint Cluster Region) and ABL (Abelson murine Leukaemia). The protooncogenes fusion is due to a reciprocal translocation of chromosomes 9 and 22 that forms the Philadelphia chromosome, which houses the gene (BCR-ABL1) with tyrosine kinase activity that drives CML.[8–10]

The selection of TKIs used in CML therapy has evolved over time.[11–18] Imatinib (first generation TKI) and Dasatinib and Nilotinib (second generation TKI) now comprise the mainstay of therapy for patients with CML.[19–22] The third generation of TKIs,

Ponatinib and Bosutinib, have been approved for use in patients resistant to first-line therapies.[23–25] The need for long-term use of TKIs to induce and maintain remission in patients with CML necessitates the assessment of their long-term effects on health.

Despite the major prognostic benefits of TKI use in CML, there are a range of outcomes that may result from their off-target effects, as many important endocrine and metabolic organs have TK receptors as mediators of actions of effector molecules in their signalling pathways.[26 27]

Due to the mechanism of action of TKIs and the need for their long-term use to induce and maintain remission in patients with CML, the aim of this protocol is to report the methods used in a systematic review to assess the endometabolic and bone health effects of TKI use in CML patients.

Objectives

The objective of this protocol is to describe the methods used to conduct a systematic review to quantify the scale of the endometabolic and bone health effects of TKIs in CML patients.

The primary objective includes the assessment of TKI effects on glucose tolerance. The secondary objectives include the assessment of TKI effects on growth, puberty, hypothalamic-pituitary-glandular axes, body mass, lipid homeostasis, and bone health profile.

METHODS AND ANALYSIS

This protocol has been registered with PROSPERO (Registration Number: CRD42018091175), and is presented according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement (online supplementary file 1).[28 29]

Eligibility criteria

We will include studies that recruited male and female patients including paediatric (<18 years of age) and adult (≥18 years of age) populations with CML. Studies that report on the use of the three generations of TKIs (Imatinib (Gleevec, Dasatinib (Sprycel), Nilotinib (Tasigna), ponatinib (Iclusig) and Bosutinib (Bosulif)) will be included.

Eligible study designs will include Randomised Controlled Trials (RCTs), prospective and retrospective cohort studies, case-control studies, cross-sectional studies and studies with before-and after comparisons with and without control groups.[30] We will not restrict paper selection by ethnicity, language of reporting, geographic location of study conduct, or publication timing.

Also, a search of review paper references, conference abstracts and editorials will be performed for relevant studies. Case reports and pilot studies will be excluded.

As TKIs are used in other cancers, in the event that the reported outcomes from patients with CML are aggregated with those from other cancers, we will contact the Principal Investigators of these studies to obtain CML-specific outcomes data.

Outcome measures

Primary outcome

The primary outcome measure for this systematic review is glucose intolerance, defined as prediabetes or diabetes. These outcomes are diagnosed by oral glucose tolerance test, fasting or random plasma glucose, or HbA1c based on the American Diabetes Association criteria.[31]

Secondary outcomes

Secondary outcomes will encompass effects on the hypothalamic-pituitary-target gland axes, metabolic effects and bone health effects including:

1. Growth effects: The effects of TKI therapy on final height and biomarkers of growth hormone axis including IGF-1 or growth hormone levels if formal growth hormone testing is reported.
2. Pubertal development: This will include documentation of precocious puberty and pubertal delay in children and hypogonadism in adults. In addition, we will assess for alterations in luteinising hormone, follicle stimulating hormone, estradiol in females and testosterone in males regardless of age when reported.
3. Thyroid function: This will include history of hypothyroidism or hyperthyroidism or abnormalities in thyroid stimulating hormone, free or total T3 and T4 profiles.
4. Adrenal function: We will collect data on the presence of adrenal insufficiency or hyperfunction. Biomarkers of adrenal outcomes to be collected will include epinephrine and norepinephrine and their metabolites, aldosterone, and cortisol levels.
5. Prolactin: We will assess for history of clinical (amenorrhoea, galactorrhoea) and biochemical (prolactin) evidence of prolactin excess.
6. Antidiuretic hormone: We will assess for history of clinical and biochemical evidence of posterior pituitary gland abnormal profiles including the development of the syndrome of inappropriate antidiuretic hormone secretion and diabetes insipidus (antidiuretic hormone deficiency).
7. Overweight (Body Mass Index (BMI) percentile ≥85th–<95th in children, BMI≥25–<30 kg/m^2 in adults) and obesity (BMI percentile ≥95th in children, BMI≥30 kg/m^2 in adults) data will be collected. In addition, adiposity data will be gathered by assessing for total adiposity with fat mass measured by dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance. Central adiposity if measured using waist-to-hip ratio, waist-to-height ratio, or DXA-based data will also be collected.
8. Dyslipidemia: This will be defined by measuring High Density Lipoprotein, Low Density Lipoprotein, total Cholesterol, Triglycerides and apolipoprotein A and B if reported.
9. Bone health effects: We will report the assessments of bone quantity, quality, and turnover as well as spinal alignment. We will include bone mineral density

measures using DXA scans and x-rays assessing for spinal compression fractures and scoliosis if reported. In addition, the effects of TKIs on biomarkers of bone metabolism will be collected. These will include blood-based markers such as total serum calcium, ionised calcium, phosphate, magnesium, alkaline phosphatase, parathyroid hormone, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. Urine markers of calcium homeostasis including urine calcium/creatinine ratio will also be collected, and blood and urine biomarkers of bone turnover such as N-terminal telopeptide and C-terminal telopeptide will also be collected.

Search strategy

The search strategy will be designed in consultation with a Senior Health Sciences Librarian. Searches will be conducted in the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE from inception on August 1st, 2019. There will be no restriction on the publication date. An updated search will be conducted closer to the time of completion of the systematic review if needed to ensure the most up to date evidence available to address the research question is acquired. A grey literature search will also be conducted in ClinicalTrials.gov and ProQuest Dissertations and Theses A&I. The references of the articles included as well as published review references list will be searched for relevant studies.

A sample search strategy for MEDLINE is presented in table 1.

Data management

Data abstraction and quality assessment will be performed by two independent reviewers. Study records will be organised and duplicates will be removed using Endnote X7.[32] Publication lists will then be exported to an excel spreadsheet to continue with data screening.

Data screening

Titles, abstracts and eligible full text records will be screened in duplicates. Any disagreements following each step will be resolved through discussions or arbitration by a third reviewer. The screening process will be reported in a flow diagram. Figure 1 provides an example of the reporting of the data screening pathway.[33]

Data abstraction

Data abstraction will include title, authors, date of publication, journal name, setting, country, study design, study duration, sample size, eligibility criteria, outcomes measured and sources of funding. TKI treatment details will be extracted involving the TKI administered, dosage, duration of treatment, and health outcomes reported above. A subgroup analysis will be performed for each TKI included and for paediatric and adult populations if sufficient data is available as reported below.

Quality assessment

RCTs will be assessed using the revised Risk of Bias Assessment Tool from the Cochrane Collaboration.[34]

Table 1 MEDLINE search strategy

#	Searches
1	Protein Kinase Inhibitors/
2	Antineoplastic Agents/
3	inase inhibitor*.ti,ab,kf.
4	or/1–3
5	Protein-Tyrosine Kinases/
6	xp receptor protein tyrosine kinases/
7	yrosine kinase*.mp.
8	or/5–7
9	4 and 8
10	((tyrosine adj3 inhibitor*) or (dasatinib or imatinib or sunitinib or nilotinib or bosutinib or ponatinib)).ti,ab,kf.
11	9 or 10
12	Leukemia, Myeloid/
13	Leukemia, Myelomonocytic, Chronic/
14	Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative/
15	eukemia, myelogenous, chronic, bcr-abl positive/ or blast crisis/ or leukemia, myeloid, accelerated phase/ or leukemia, myeloid, chronic-phase/
16	(chronic adj3 myelo* adj3 leuk?emia*).ti,ab,kf.
17	blast crisis.ti,ab,kf.
18	(chronic phase adj3 myelo* adj3 leuk?emia*).ti,ab,kf.
19	chronic myeloleuk?emia*.ti,ab,kf.
20	(ph1* adj4 myelo* adj4 leuk?emia*).ti,ab,kf.
21	(philadelphia negative* adj4 leuk?emia*).ti,ab,kf
22	chronic granulocytic leuk?emia*.ti,ab,kf.
23	or/12–22
24	11 and 23
25	exp Thyroid Hormones/
26	(Dextrothyroxine or Diiodotyrosine or Monoiodotyrosine or “Thyroid (USP)” or Thyronines or Diiodothyronines or Triiodothyronine or Thyroxine).ti,ab,kf.
27	exp Adrenal Cortex Hormones/
28	((adrenal or pituitary or growth or thyroid) adj3 hormone*).ti,ab,kf.
29	cortisol.ti,ab,kf.
30	aldosterone.ti,ab,kf.
31	epinepherine.ti,ab,kf.
32	norepinepherine.ti,ab,kf.
33	adrenaline.ti,ab,kf.
34	noradrenaline.ti,ab,kf.
35	exp Growth Hormone/
36	growth hormone*.ti,ab,kf.
37	somatotropin*.ti,ab,kf.
38	cryotropin.ti,ab,kf.

Continued

Table 1 Continued

#	Searches
39	cryotropin.ti,ab,kf.
40	genotropin.ti,ab,kf.
41	genotonorm.ti,ab,kf.
42	humatrope.ti,ab,kf.
43	nutropin.ti,ab,kf.
44	Insulin-Like Growth Factor I/
45	IGF-1.ti,ab,kf.
46	IGF1.ti,ab,kf.
47	igf-i.ti,ab,kf.
48	igfi smc.ti,ab,kf.
49	insulin like growth factor i.ti,ab,kf.
50	insulin like growth factor 1.ti,ab,kf.
51	igf 1 smc.ti,ab,kf.
52	insulin-like somatomedin peptide i.ti,ab,kf.
53	insulin-like somatomedin peptide 1.ti,ab,kf.
54	somatomedin c.ti,ab,kf.
55	expVasopressins/
56	vasopressin*.ti,ab,kf.
57	antidiuretic hormone*.ti,ab,kf.
58	pitressin.ti,ab,kf.
59	betahypophamine.ti,ab,kf.
60	gonadotropins, pituitary/ or exp follicle stimulating hormone/ or exp luteinizing hormone/ or prolactin/
61	prolactin.ti,ab,kf.
62	follicle stimulating hormone*.ti,ab,kf.
63	luteinizing hormone*.ti,ab,kf.
64	FSH.ti,ab,kf.
65	LH.ti,ab,kf.
66	follitropin.ti,ab,kf.
67	interstitial cell stimulating hormone.ti,ab,kf.
68	lutropin.ti,ab,kf.
69	luteoz?man.ti,ab,kf.
70	ICSH.ti,ab,kf.
71	endocrinopathy.ti,ab,kf.
72	exp Hyperthyroidism/
73	hyperthyroidism.ti,ab,kf.
74	hyperthyroidism.ti,ab,kf.
75	exp Hypothyroidism/
76	hypothyroidism.ti,ab,kf.
77	Hypo thyroidism.ti,ab,kf.
78	expHyperpituitarism/
79	hyperpituitarism.ti,ab,kf.
80	hyper pituitarism.ti,ab,kf.
81	TSH.ti,ab,kf.
82	or/25–81

Continued

Table 1 Continued

#	Searches
83	Osteoporosis/
84	osteoporo*.ti,ab,kf.
85	osteomalacia.ti,ab,kf.
86	(osteoclast adj3 (dysfunction* or activity)).ti,ab,kf.
87	hypocalc?emi*.ti,ab,kf.
88	exp Fractures, Bone/
89	fracture*.ti,ab,kf.
90	((bone* or skull or manidble* or vertebr* or rib or ribs or clavicle* or clavicular or scapula* or humerus or humeral or radius or ulna or carpal* or metacarpal* or femur* or tibia* or fibula* or knee cap* or kneecap* or patella* or tarsals or metatarsal*) adj3 (pain* or malform* or health* or remodel*)).ti,ab,kf.
91	(bone* adj3 density).ti,ab,kf.
92	Scoliosis/
93	scoliosis.ti,ab,kf.
94	scoliotic.ti,ab,kf.
95	Parathyroid Hormone/
96	parathyroid* hormone*.ti,ab,kf.
97	parathyrin.ti,ab,kf.
98	parathormone.ti,ab,kf.
99	“pth(1-34)".ti,ab,kf.
100	“pth (1-34)".ti,ab,kf.
101	“pth (1-84)".ti,ab,kf.
102	“pth(1-84)".ti,ab,kf.
103	or/83–102
104	exp Diabetes Mellitus/
105	(Diabet* or prediabet*).ti,ab,kf.
106	NIDDM.ti,ab,kf.
107	IDDM.ti,ab,kf.
108	T2DM.ti,ab,kf.
109	T2D.ti,ab,kf.
110	hyperinsulinism/ or congenital hyperinsulinism/ or nesidioblastosis/ or insulin resistance/ or metabolic syndrome x/
111	Glucose Metabolism Disorders/
112	hyperinsul*.ti,ab,kf.
113	insulin resist*.ti,ab,kf.
114	insulin sensitiv*.ti,ab,kf.
115	metabolic syndrome x.ti,ab,kf.
116	dyslipid?e?mi*.ti,ab,kf.
117	dyslipoprotein?e?mi*.ti,ab,kf.
118	exp Dyslipidemias/
119	hyperlipidemi*.ti,ab,kf.
120	hypercholesterol?e?mia*.ti,ab,kf.
121	hyperlipoprotein?e?mi*.ti,ab,kf.

Continued

Table 1 Continued

#	Searches
122	hypertriglycerid?e?mi*.ti,ab,kf.
123	(abnormal adj3 (lipid* or cholesterol* or triglyceride* or HDL or LDL or lipoprotein*)).ti,ab,kf.
124	expApolipoproteins/
125	apolioprotein*.ti,ab,kf.
126	cholesterol/
127	Triglycerides/
128	lipoproteins/
129	lipoproteins/ or exp lipoproteins, hdl/ or exp lipoproteins, ldl/
130	expApolipoproteins/
131	cholesterol*.ti,ab,kf.
132	triglyceride*.ti,ab,kf.
133	lipoprotein*.ti,ab,kf.
134	apolioprotein*.ti,ab,kf.
135	hypophosphat?emia.ti,ab,kf.
136	Blood Glucose/
137	blood glucose.ti,ab,kf.
138	or/104–137
139	82 or 103 or 138
140	24 and 139
141	from 140 keep 1–146

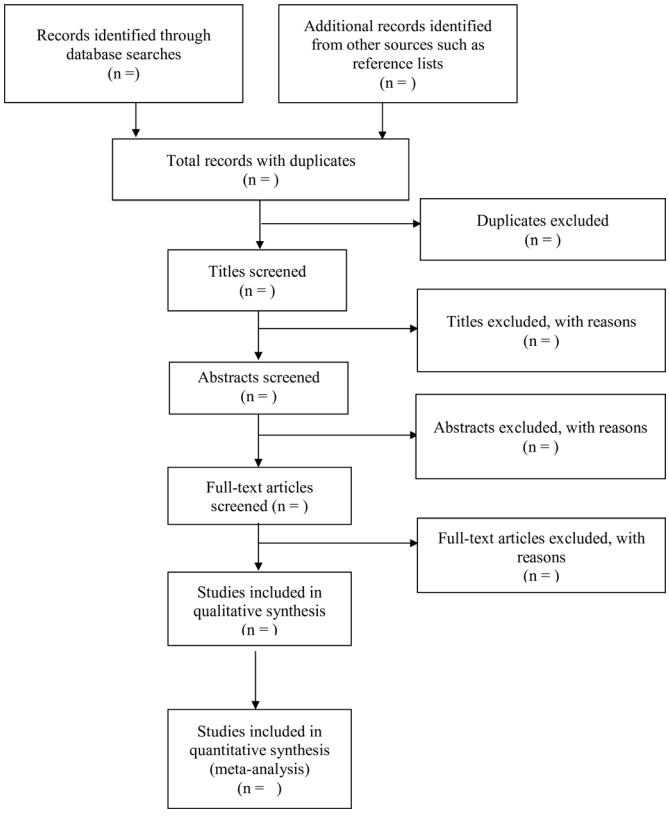

Figure 1 Flow diagram of article screening process.

Non-randomised studies including case-control and cohort studies will be assessed using the Newcastle-Ottawa Scale.[35] Uncontrolled studies reporting before-and-after data will be assessed using the University of Alberta Evidence-based Practice Centre checklist.[36] The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines will be used to evaluate the overall confidence in the evidence for each outcome analysed based on eligible studies. The GRADE guidelines evaluate the risk of bias, inconsistency, indirectness, imprecision and publication bias.[37]

Data analysis

The goal of this systematic review is to determine the pooled prevalence of the primary and secondary endometabolic and bone health outcomes in TKI-treated patients with CML. The results of this review will be reported in accordance with the PRISMA guidelines.[33] Protocol deviations and their rationale will be reported in the full systematic review.

A meta-analysis will be performed for each of the primary and secondary outcomes if two or more studies have reported on populations with a similar age and sex distribution, have used the same TKI with similar dosing and duration, have comparable follow-up periods, and have been studied using a similar study design. For example, we will combine RCT data that fulfil the above criteria together to assess the direction and magnitude of the effect as well as the effect consistency. Even if a minimum of two studies per outcome were available, if there are different treatment and comparison groups reported, diversity of treatment outcomes, or a high risk of bias then a meta-analysis may not be feasible. In this case, a narrative summary of results with tabulated data will be presented.

For studies reporting dichotomous outcomes, we will use risk ratio, OR and risk difference to assess the event rate differences between groups. For continuous outcomes, we will use mean difference to report the differences between groups. For studies with repeated measures of continuous outcomes over time, we will use mean difference as a summary measure. In the presence of a control group, the mean difference is the comparison of change from baseline to follow-up between the two groups. The cases are patients with CML treated with TKIs. The controls are either non-cancer healthy individuals or patients with CML not receiving TKIs. These two control groups will be analysed separately. In the absence of a control group, the mean difference will represent the difference between baseline and follow-up measures.

We predict a high level of heterogeneity that will likely be due to several sources, including age and sex differences of participants between different studies. Age may be a factor in the development of adverse outcomes and children may be more susceptible than adults to certain side-effects when receiving TKIs such as delayed growth.[38] It has also been suggested that there are sex differences in response to TKI in patients with CML, with females being

more susceptible to some side-effects including anaemia and giving birth to infants with congenital abnormalities.[39 40] Therefore, we will analyse our data based on the male and female distribution in the studies.

There are other potential sources of clinical heterogeneity including the different medications used, dosing and duration of treatment when the outcome measures were tested. Furthermore, there are three phases of CML–chronic, accelerated and blast phase. Patients who are on treatment at different phases may experience variable adverse endometabolic and bone health outcomes.[8] Differences in study design, inclusion and exclusion criteria, variation in outcome measurement, and differences in the risk of bias assessment among studies may be other sources of heterogeneity. Statistical heterogeneity may result from heterogeneity in clinical and methodological variations.[41]

Heterogeneity will be evaluated with the χ^2 test for homogeneity and inconsistency index (I^2). A p value of <0.10 and an I^2 ≥75% will represent the thresholds for detecting heterogeneity. To deal with heterogeneity, a random-effects model will be used for the meta-analysis. If the above thresholds for heterogeneity are met, we will attempt to perform sub-group analyses to identify sources of heterogeneity including age, sex, medication used, and CML phase. Of note, high heterogeneity may downgrade the overall confidence in the quality of evidence and the conclusions reached.

When at least ten studies are available for an outcome, we will perform sensitivity analysis by excluding studies with small sample size, are highly-biassed, or with reported outliers to examine their influences on the results. A funnel plot will be used to evaluate publication bias if at least 10 studies are reported. Plot asymmetry will be assessed using both an Egger's test and visual inspection.[42] Additionally, the number of relevant conference abstracts that are lacking published articles will contribute to the estimation of publication bias. We will perform all meta-analyses using Review Manager software V.5.3 (RevMan 5.3).[43] The Egger's test will require the use of Comprehensive Meta-Analysis software V.3 (CMA 3.0).[44]

Patient and public involvement

Patients and the public were not involved in the design of this systematic review protocol.

DISCUSSION

With the improved survival rates of patients with CML on TKI therapy, the endometabolic and bone health effects of these therapies are critical to understand, as they have an influence on the quality of life and the ultimate longevity of these patients.[45–47]

The findings from this systematic review will provide insights regarding which TKIs are associated with what deficits with their use. This will help clinicians personalise the choice of individual TKIs to a given patient with risk factors of an adverse event, predict these adverse effects and screen for them prospectively. This systematic review will also help inform the design of interventions that may prevent or ameliorate the adverse effects of this medication class. Furthermore, this review will provide direction to guide future research on the endometabolic and bone health effects of TKI use in CML.

Ethics and dissemination

No Research Ethics Board approval is necessary for this paper, as this is a systematic review protocol that does not include individual patient identifiers or data. The systematic review will be published in a peer-reviewed journal and presented at international conferences.

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