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Original Research

Comparative efficacy and safety of tyrosine kinase inhibitors for chronic myeloid leukaemia: A systematic review and network meta-analysis

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KEYWORDS
Tyrosine kinase inhibitors;
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Abstract ***Background:*** The pharmacotherapy of chronic myeloid leukaemia (CML) is mainly based on tyrosine kinase inhibitors (TKIs). The aim of this study was to compare the efficacy and safety of all TKIs in CML patients.

Methods: We conducted a systematic review with network meta-analysis (NMA) of randomised controlled trials (RCTs), including imatinib, nilotinib, dasatinib, bosutinib, radotinib and ponatinib. Searches were performed in PubMed, Scopus, Web of Science and SciELo (March 2018). The NMAs were built for six outcomes at 12 months: complete cytogenetic response (CCyR), major cytogenetic response (MCyR), deep molecular response, major molecular response (MMR), complete haematologic response and incidence of serious adverse events. We conducted rank order and surface under the cumulative ranking curve (SUCRA) analyses.

Results: Thirteen RCTs were included (n = 5079 patients). Statistical differences were observed for some comparisons in all outcomes. Imatinib 400 mg was considered the safest drug (SUCRA values of 10.3%) but presented low efficacy. Overall, nilotinib 600 mg was superior to the other TKI in efficacy (SUCRA values of 61.1% for CCyR, 81.0% for MMR,

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90.0% for MCyR); however, no data on its safety profile at 12 months were reported.
Interpretation: Our results suggest that nilotinib should be upgraded to first-line therapy for CML, although further cost-effectiveness analyses, including the new TKI (i.e., ponatinib, radotinib), are needed.

1. Introduction

Prevalence of chronic myeloid leukaemia (CML) is about 10–12 per 100,000 people worldwide [1], with an estimated incidence rate in the United States of America (USA) of 8950 cases in 2017 [2]. CML is a clonal haematopoietic stem cell disorder with an abnormal expression of the oncoprotein BCR-ABL1, which is a constitutively active tyrosine kinase [3,4]. The pharmacotherapy of CML is mainly based on tyrosine kinase inhibitors (TKIs). The first BCR-ABL inhibitor to come into use in clinical practice was imatinib mesylate, which demonstrated superior responses rates, tolerability, less probability of progression to accelerated phase, or blast-crisis, and survival benefit compared with interferon-α associated with low-dose cytarabine [5,6].

According to the European Leukemia Net (ELN) and the National Comprehensive Cancer Network (NCCN), the optimal response to TKI is defined as complete haematologic response (CHR; blood counts completely back to normal, no immature cells in blood, and non-palpable spleen), complete cytogenetic response (CCyR; no Ph-positive metaphases by morphologic cytogenetics of at least 20 marrow metaphases) in six months of treatment, and deep molecular response (MR4.5; BCR-ABL1 transcripts non quantifiable, and non-detectable -4.5 log reduction) or major molecular response (MMR; BCR-ABL $\leq$ 0.10 by real quantitative polymerase chain reaction, RQ-PCR) according to the international scale in 12 months of treatment [7–9]. However, many patients using imatinib do not attain treatment goals mainly because of drug resistance [5]. Thus, new drugs have been developed and approved by regulatory agencies.

The new generations of TKI include dasatinib, nilotinib, bosutinib, ponatinib and radotinib. The second generation (dasatinib, nilotinib and bosutinib) is considered more potent and effective than imatinib in newly diagnosed, imatinib-resistant patients [10,11]. Ponatinib and radotinib (third generation TKI) are effective in patients refractory to dasatinib or nilotinib and with T315I mutation [12–14]. However, there are no studies based on an annual response to treatment directly comparing the efficacy and overall safety of all these commercially available TKI.

Network meta-analysis (NMA) has emerged as an effective alternative to compare multiple treatments in one single model. The advantages of this methodology compared with the pairwise meta-analyses include the possibility of comparing interventions that have not been studied head-to-head in clinical trials, and it allows a significant increase in the number of patients compared, comprising a greater amount of evidence [15]. There are currently two NMAs on CML treatment, but they do not include all drugs available on the market and have evaluated few clinical outcomes [16,17]. Therefore, we performed a systematic review and NMA to compare the efficacy and overall safety among commercially available TKI based on haematologic, cytogenetic and molecular responses in CML patients at 12 months.

2. Methods

This systematic review is part of a project on the efficacy and safety of TKI in patients with CML (PROSPERO registration number CRD42017065864). All steps of the systematic review were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [18,19] and Cochrane Collaboration recommendations [20].

2.1. Search strategy and eligibility criteria

We searched PubMed, Scopus, Web of Science and SciELo without time or language limits (last updated on March 2018). Trial registration databases, grey literature (Google Scholar) and the reference lists of other reviews and included studies were also manually searched. The complete search strategy is presented on Supplementary material (Table S1). Two researchers independently screened titles and abstracts to identify all relevant records. In the second stage, full-text articles were independently evaluated by these same researchers, and discrepancies were conciliated in a consensus meeting with a third researcher as a referee.

Studies were included if they met all eligibility criteria: (1) adult patients (>18 years old) diagnosed with CML without other oncologic comorbidities and no prior CML therapy; (2) evaluated any TKI (imatinib, dasatinib, nilotinib, bosutinib, radotinib or ponatinib, in any dose, or regimen) compared head-to-head to another TKI (3) assessed safety (i.e., incidence rates of serious adverse events, SAE); or any clinical efficacy