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Comparative efficacy of tyrosine kinase inhibitor treatments in the third-line setting, for chronic-phase chronic myelogenous leukemia after failure of second-generation tyrosine kinase inhibitors

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ABSTRACT

We compared the efficacy of ponatinib and second-generation tyrosine kinase inhibitors (2G-TKIs: bosutinib, dasatinib, and nilotinib) in chronic phase CML resistant/intolerant to ≥1 prior 2G-TKI. Estimated probabilities of CCyR with 2G-TKI ranged from 22% to 26%, compared with 60% (95% CrI 52–68%) with ponatinib. The estimated probability of ponatinib providing higher response rate than all other included treatments was 99% (CCyR) and 97% (MCyR). Use of further 2G-TKI may provide limited benefit in CP-CML patients resistant/intolerant to prior 2G-TKI treatment. Compared with 2G-TKIs, ponatinib is estimated to provide substantially higher probability of achieving CCyR and MCyR; safety was not compared.

1. Introduction

Despite major advances in treatment, resistance and intolerance (R/I) to tyrosine kinase inhibitor (TKI) therapy continue to be significant challenges in the management of chronic phase (CP) chronic myelogenous leukemia (CML). Patients who are R/I to first-line TKI treatment with imatinib are generally treated with a second-generation TKI (2G-TKI), e.g. nilotinib, dasatinib, or bosutinib. Although 2G-TKIs show good efficacy in patients R/I to imatinib, with reported complete cytogenetic response (CCyR) rates of 40–60% [1], at least half of patients receiving dasatinib or nilotinib in the second line experience R/I to these agents over the course of treatment [2–4], and 48-month follow-up data with second-line bosutinib report a 40% incidence of R/I. For patients who experience R/I to 2G-TKIs, treatment options were previously limited to sequential treatment with another 2G-TKI, stem cell transplant, or clinical trials. Because large randomized studies in this setting are few, no TKI is specifically indicated for treatment of CML after failure of both first- and second-generation TKIs. Sequential treatment with 2G-TKIs, although common, may be associated with decreasing clinical response with increasing lines of treatment after failure of a previous 2G-TKI [5]. Newer pharmacologic treatments may provide additional options for patients in this setting.

Ponatinib, a third-generation TKI, is a potent pan-BCR-ABL inhibitor designed to bind with high affinity to both wild-type and mutant BCR-ABL [6]. It is effective in vitro and in vivo against all clinically relevant mutations including the T315I mutation [7], against which no other currently licensed TKI is effective [8]. No single mutation conferring resistance to ponatinib at therapeutic doses has been characterized in CML to date [9]. Although ponatinib has demonstrated clinical efficacy, continuing analyses of the PACE trial of ponatinib in 2013 showed that the cumulative incidence of arterial thrombotic events increased with longer treatment duration [10]. Dasatinib and nilotinib have also been reported to be associated with an increased risk of lung and arterial pathologies, respectively [1].

Abbreviations: 2G, second-generation; CML, chronic myelogenous leukemia; CP, chronic phase; CrI, credible interval; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; R/I, resistant/intolerant; TKI, tyrosine kinase inhibitor.

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As more is learned about the potential for late toxicity from long-term treatment with TKIs [1], understanding the relative efficacy of the available agents in later treatment lines has become increasingly important for clinical decision-making. Among the R/I patient population the overall prognosis is poor, and these patients will likely die from their underlying leukemia. Even though overall survival in newly diagnosed CP-CML has generally increased, patients with advanced disease and patients resistant to prior therapy face a much poorer prognosis and higher likelihood of CML-related death. The median failure-free survival of CP patients receiving their third line of therapy is 20 months, and drops to 3–5 months in patients with advanced disease [11]. Among refractory patients, those with the T315I mutation have been shown to have a worse prognosis than those without the mutation. CP-CML patients with the T315I mutation have a median overall survival of <2 years post detection of T315I mutation; patients with advanced disease have a median OS of <5 months post detection [12]. For patients for whom two prior lines of therapy have failed, CML is the main investigator-reported cause of death in more than 70% of cases, compared with approximately 7% who die of treatment-related causes [13,14]. The potential benefit that patients could receive by effective treatment of their refractory leukemia continues to exceed the potential risk for adverse events associated with treatment; therefore, efficacy is likely to remain the paramount consideration in resistant patients.

Assessment of the relative efficacy of available treatment options is needed in order to weigh the risks and benefits of alternative treatment strategies in individual R/I patients. The current study evaluated the comparative efficacy of ponatinib and 2G-TKIs after failure of at least one previous 2G-TKI in patients with CP-CML using data from clinical trials and other published studies.

2. Methods

2.1. Systematic review

To identify relevant clinical trials, a systematic literature review was conducted in MEDLINE, EMBASE, and the Cochrane Libraries (publication dates 2002–2012), and in the abstracts of the American Society of Hematology, American Society of Clinical Oncology, and European Hematology Association conferences (2008–2012). Studies were included if they were randomized controlled trials, single-arm trials, or observational studies (either retrospective or prospective); enrolled 10 or more adult patients in each arm; and presented results for patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia who were R/I to prior treatments. No restriction was applied with respect to therapy dose due to incomplete reporting of doses in the available studies. The included studies were then screened again to identify those conducted in patients with CP-CML who were R/I to at least one previous 2G-TKI (Fig. 1). In the case of multiple publications from the same study, the publication with the largest patient accrual and/or longest follow-up period was used. Study and patient characteristics were abstracted, as were rates of major (MCyR) and complete (CCyR) cytogenetic response.

2.2. Statistical methods

Measures of cytogenetic response were chosen for synthesis because they are more widely reported than measures of molecular response. Moreover, cytogenetic response by 12 months to treatment with 2G-TKIs has been shown to predict longer-term survival [15]. Only data in CP-CML were analyzed.

2.2.1. Naïve indirect comparison of response

The absence of randomized controlled trials and the considerable heterogeneity in design between studies meant that the data were not suitable for an adjusted indirect comparison. We therefore performed a naive indirect comparison of the data in the form of forest plots depicting reported best response rates (MCyR and CCyR) in individual studies. Node size was determined by the number of patients in the study arm, and line length represented the derived confidence intervals. The time period for reporting response was unspecified in all but one study; responses were therefore plotted regardless of timing. Response probabilities for ponatinib were estimated using individual patient data from the phase 2 PACE study [16,17] and published phase 1 study data [18]. For the PACE study, only patients who had received two prior TKIs were included in the analysis in order to provide an appropriate comparison to the 2G-TKI studies, which were conducted in patients receiving third-line treatment.

2.2.2. Synthesis of response probabilities

In addition to descriptive analyses, we synthesized probabilities of MCyR and CCyR from individual studies, and estimated the overall response probability with 95% credible interval (CrI) for each treatment. A Markov chain Monte Carlo Bayesian analysis was used to obtain estimates of the probability of response to treatment.

After determining that the response to ponatinib was nominally higher than the response to any 2G-TKI treatment, we examined the uncertainty around this conclusion by estimating the probability of ponatinib providing the best response. Response was modeled using a binomial likelihood with fixed treatment effects estimated for each individual treatment. Vague priors were given for treatment effects on the log-odds scale ($N[0,1000]$), i.e. no prior assumption was made regarding the relative efficacy of the treatments. The probability that ponatinib provides the highest response of all the treatments included in the analysis was estimated from the joint posterior distribution of the treatment effects. There were insufficient data to perform random effects analyses.

2.2.3. Sensitivity analysis

The primary analysis included all patients regardless of T315I mutation status. A sensitivity analysis compared response to ponatinib in patients without the T315I mutation with response to 2G-TKIs in all patients.

3. Results

3.1. Systematic review

After de-duplication of multiple publications from the same study, 12 clinical trials and observational studies were identified from the systematic review that met the inclusion criteria in the post-2G-TKI setting (Fig. 1). The treatments represented were the 2G-TKIs bosutinib, dasatinib and nilotinib; the protein translation inhibitor omacetaxine; and ponatinib (Table 1). Use of bafetinib was also reported in a very small number of patients. Four studies reported treatment with any one of two or three different 2G-TKIs. Twelve studies were included in the analysis (the study of omacetaxine was excluded because the analysis was intended as a comparison between TKIs, and Garg et al. [11] was treated as two studies because it contributed two different treatment arms). Overall, 586 patients from 12 treatment arms were included in the analysis (134 for ponatinib and 452 treated with a 2G-TKI).

The included studies consisted of five single-arm trials and seven observational studies (Table 1). No randomized controlled trials were identified. All studies reported use of 2G-TKIs as third line or later; no second-line studies were identified. All studies reported CCyR and seven reported MCyR. Median age ranged from 49 to 58 years where reported. One study reported response at a