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Disease-related mortality exceeds treatment-related mortality in patients with chronic myeloid leukemia on second-line or later therapy

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ABSTRACT

Treatment of newly-diagnosed patients with chronic-phase chronic myeloid leukemia (CP-CML) with tyrosine kinase inhibitors (TKIs) results in near-normal life expectancy. However, CP-CML patients resistant to initial TKIs face a poorer prognosis and significantly higher CML-related mortality. We conducted a systematic literature review to evaluate the specific causes of deaths (diseases progression versus drug-related) in CP-CML patients receiving second- or third-line therapy. We identified eight studies based on our criteria that reported causes of death. Overall, 5% of second-line and 10% of third-line patients died during the study follow-up period. For second-line, (7 studies, $n = 1926$), mortality was attributed to disease progression for 41% of deaths, 2% to treatment-related causes, 3% were treatment-unrelated, and 50% were unspecified adverse events (AEs), not likely related to study drug. In third-line, (2 studies, $n = 144$), 71% deaths were attributed to disease progression, 7% treatment-related AEs, 14% treatment-unrelated and 7% unspecified AEs. Annual death rates for second- and third-line therapy were significantly higher than for general population in similar age group. Our findings suggest death attributed to disease progression is approximately 10 times that due to treatment-related AEs in patients with CP-CML receiving second- or third-line therapy. Therefore, the potential benefits of effective treatment for these patients with the currently available TKIs outweigh the risks of treatment-induced AEs.

1. Introduction

Prior to the introduction of tyrosine kinase inhibitors (TKIs), 10–20% of chronic myeloid leukemia (CML) patients progressed from chronic phase (CP) to blast crisis within the first two years after diagnosis. Death would follow shortly thereafter. The risk of progression for patients increased to 20–5% per year in subsequent years post-diagnosis [1]. The median survival of CML patients receiving conventional therapy was less than five years post-diagnosis [1]. Prognosis for CML improved significantly after the introduction of imatinib, the prototype BCR-abl TKI, in 2001. Front-line treatment of CP-CML with imatinib 400 mg per day results in complete cytogenetic response in 66% and major molecular response in 40% of patients at 12 months [2]. After five years, 92% of patients treated with imatinib for CP-CML have major cytogenetic response or complete cytogenetic response, with 89% of patients still alive [3]. Response rates with newer TKIs such as dasatinib and nilotinib in front-line CP-CML are better than for imatinib, but are still not 100% [4,5]. While these novel treatments led to a remarkable progress in CML treatment, a significant challenge remains in improving the prognosis of CML in the fraction of patients who fail first-line therapy [6–9].

Multiple lines of TKI therapy that can target specific resistance-conferring mutations are now available for second- and third-line therapies [10,11]. However, these newer TKIs also have significant and sometimes fatal toxicities that physicians and regulatory bodies must take into account when determining where these new drugs fit in treatment protocols for CML [12]. There is a risk of mortality and morbidity from treatment toxicities particularly in

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pre-treated, later line patients due to greater time since diagnosis, exposure to pharmacologic treatment and advanced age [13–15]. The comparative impact of treatment-related adverse effects (AEs) on mortality in comparison to death from CML disease progression has not been systematically evaluated.

We performed a systematic review of published data to assess and characterize the causes of death linked to TKI therapy in second-line or later therapy in comparison to those linked with progression of CML itself. Our objective was to investigate deaths in patients with CP-CML who were receiving second-line and beyond therapy and compare the risks posed to the patient by the disease and its treatment.

2. Methods

2.1. Search strategy

We searched studies published between January 1999 and January 2014 using PubMed and conference proceedings. Search strategies using primary search/MeSH terms (CML and variations) and secondary search/MeSH terms (treatment-, population-, mortality- and morbidity-related) were used to identify relevant studies (Appendix A). Additionally, an internet search (Google search) targeting mortality and fatal AEs in CML was conducted, conferences proceedings of American Society of Hematology, American Society of Clinical Oncology, European Hematology Association, and International Society for Pharmacoeconomics and Outcomes Research were searched manually for 2006–2013. Two researchers screened the titles and abstracts to determine eligibility for full text review; any disagreements were resolved by consensus with a third researcher [16]. All studies that satisfied our inclusion criteria were reviewed via full-text screening.

2.2. Study selection

Studies were included if they a) enrolled adult patients with CP-CML who were receiving second- or third-line TKI therapy; b) reported mortality data and delineated the causes of mortality; and, c) published in the English language (studies were not limited by geography). Studies were excluded if: a) results for any patient with in accelerated or blast phase CML were not reported separately; b) they were case reports, commentaries or narrative reviews; and, c) causes of death were not clearly reported.

2.3. Data abstraction

Data from selected studies were abstracted on study population, treatment setting, treatment regimen, mortality endpoints, follow-up durations, treatment continuation rate and discontinuation rate at follow-up, and reasons for discontinuation. The mortality endpoints were total all-cause deaths and deaths classified by specific cause. We classified cause of death based on investigator-reported cause as: a) *disease progression* if death was reported as due to CML disease progression; b) *treatment-related* AE if due to the adverse effect of the study drug; c) *treatment-unrelated AE if death occurred due to adverse effect but not due to the study drug*; d) due to an *unspecified AE* if due to adverse effect but its relation to treatment was not specified in the study; and, e) *unknown cause*. For comparison with population mortality measures, we defined *background deaths* as the sum of those due to a *treatment-unrelated AE, unspecified AE* and *unknown cause*.

2.4. Data analysis

Mortality data were analyzed by line of treatment. The overall probability of death and probability of death by cause categories were calculated by direct pooling of data across studies in each therapy line. The frequency of deaths within each therapy line and their respective causes were tabulated.

To allow comparison of our finding to yearly death rates from external sources, we adjusted our death data to calculate yearly rates using the available data. For studies reporting median follow-up, we used this value in the calculation of total follow-up. For studies not reporting median follow-up, we used median time on therapy and added to this value any additional follow-up post discontinuation. For example, if mortality was tracked for 30 days after the last dose, we added 30 days to the median time on therapy. To estimate total patient-years at risk in each study, we converted the median values to means by assuming a constant rate of death, converted this value to years, and multiplied mean years of follow-up by the total number of patients in the study.

Yearly mortality rates for second-line and third-line were estimated by pooling total deaths and total patient-years at risk in each therapy line, and dividing deaths by patient-years. Background death rates were similarly calculated. These rates were then compared to expected mortality of the US population as reported by Centers for Disease Control and Prevention 2011 US census [17].

3. Results

3.1. Study selection

Of the 2531 studies abstracts screened, eight [8,13,18–23] were included in the final assessment. A PRISMA flow diagram summarizing study attrition [24] is shown in Fig. 1.

3.2. Study characteristics

Table 1 shows the characteristics of the eight studies included in the review. Among these studies, seven were full-text studies [8,13,18–20,22,23] and one was a conference poster [21]. Patients receiving second-line treatment were imatinib-resistant or intolerant CP-CML patients, [8,13,18,19,21–23] while those receiving third-line treatments were resistant or intolerant to either dasatinib or nilotinib after second-line therapy [20,23]. The TKI therapy received by patients was dasatinib in five studies [13,18,19,21,22], bosutinib in one study [23], nilotinib in one study [8], and either dasatinib or nilotinib in one study [20]. The discontinuation rates were the same as or lower than treatment continuation rates for dasatinib and high-dose imatinib, while they were higher than treatment continuation rates for nilotinib and bosutinib. The main reasons for discontinuation were disease progression and drug toxicity.

3.3. Comparison of disease-related deaths versus death due to treatment-related adverse event in CP-CML patients

Table 2 reports the mortality data and follow-up period of the included studies. The follow-up period in these studies ranged from 1.0 to 2.3 years. For second-line treatment, a total of 1926 patients were evaluated across all studies, of whom 102 died while on therapy. Investigator-reported mortality cause was disease progression for 42 deaths (41.2%), compared with two patients (2.0%) dying of treatment-related AEs (AE was drug toxicity) and the remaining 58 deaths (56.9%) were due to treatment-unrelated AEs ($n = 3$), unspecified AEs ($n = 51$) or due to unknown cause ($n = 4$) [8,13,18,19,21–23]. The AEs that lead to treatment-unrelated deaths were not specified in the study [23]. Among those who died due to AEs whose relation with the treatment was not specified, deaths were attributed to infection ($n = 19$), cardiovascular diseases ($n = 13$), other malignancies ($n = 4$), bleeding ($n = 3$), suicide