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PREDICTING OUTCOMES IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA AT ANY TIME DURING TYROSINE KINASE INHIBITOR THERAPY

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Abstract

Current recommendations for monitoring patients with chronic myeloid leukemia (CML) provide recommendations for response assessment and treatment only at 3, 6, 12, and 18 months. These recommendations are based on clinical trial outcomes computed from treatment start. Conditional survival estimates take into account the changing hazard rates as time from treatment elapses as a continuum. We performed conditional survival analyses among patients with CML to improve prognostication at any time point during the course of therapy. We used two cohorts of patients with CML in chronic phase: one treated in the frontline DASISION phase III study (n=519) and another treated after imatinib failure in the dasatinib dose-optimization phase III CA180-034 study (n=670). Conditional survival estimates were calculated. A modified Cox proportional hazards model was used to build a prognostic nomogram. As the time alive or free from events from commencement of treatment increased, conditional survival estimates changed. No differences were observed regarding future outcomes between patients treated with imatinib or dasatinib in the frontline setting for patients with the same *BCR-ABL1* transcript levels evaluated at the same time-point. Age over 60 years greatly impacted future outcomes particularly in the short-term. Conditional survival-based nomograms allowed the prediction of future outcomes at any time-point. In summary, we designed a calculator to predict future outcomes of patients with CML at any time-point during the course of therapy.

Keywords

CML; BCR-ABL1; nomogram; conditional survival; prognosis

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Introduction

The National Comprehensive Cancer Network (NCCN) and the European LeukemiaNet recommendations for monitoring patients with chronic myeloid leukemia in chronic phase (CML-CP) provide recommendations for response assessment and treatment based on specific milestones at pre-specified time-points based on correlative retrospective evidence from clinical trials.^{1,2}

Studies with frontline imatinib therapy have demonstrated a strong correlation between long-term outcomes and depth of response at early time-points.³ The goal of initial treatment is to achieve complete cytogenetic response (CCyR) by 12 months and major molecular response (MMR) by 18 months of treatment. For instance, patients achieving MMR by 18 months have an event-free (EFS) and progression-free survival (PFS) of 95% and 99%, respectively, after 7 years of follow-up.⁴ Failure to achieve specified responses at specific time-points is categorized as suboptimal response or failure, which are associated with inferior survival, and current recommendations consider a change in therapy.^{1,2}

Useful as they are, these recommendations have important limitations. First, they only provide recommendations at 4 fixed time-points (3, 6, 12, and 18 months) after imatinib start, because those are the time-points customarily used for response assessment in clinical trials of tyrosine kinase inhibitors (TKIs). Second, suboptimal response represents a “grey zone” due to statistical variability and therefore therapeutic recommendations for patients with such response remain controversial. Third, recommendations at 9 months are not available because response assessment at this time-point was not mandatory in TKI clinical trials. Similarly, no recommendations are available beyond 18 months on TKI therapy. Finally, the categorical classifications of response based on crossing certain thresholds (e.g., optimal response <35% Ph+ metaphases at 6 months) assume that all patients with optimal response will have a favorable long-term outcome and all those with a “bad” response (i.e., failure) will have a bad outcome. This is clearly not the case and limits the value of such categorization, as it does not allow physicians to decide on therapy based on the predicted probabilities of a favorable outcome. These issues highlight clear limitations of the recommendations for patients evaluated at time-points different from 3, 6, 12, and 18 months after the start of imatinib therapy, when a bone marrow aspirates are not routinely obtained and monitoring relies on quantitative real-time PCR (qRT-PCR) measurements of *BCR-ABL1* transcript levels alone. Thus, a clear limitation of currently available monitoring recommendations is their applicability at time-points different from those pre-specified in such recommendations, and the grading of responses above and below the given response thresholds. Therefore, tools to predict survival with any level of response at any time-point are warranted.

Overall survival calculations in oncology in general, and in CML in particular, are anchored to the time of diagnosis or that of initiation of TKI therapy. However, the hazard of mortality or that of having an event changes with every fraction of time that elapses since the start of TKI therapy. Conditional survival estimates, which derive from the mathematical concept of conditional probability, account for the latter as they represent the probability that a patient with CML will survive an additional length of time, given that the patient has

already survived a given length of time.⁵ Therefore, conditional survival estimates reflect more accurately than conventional survival estimates the survival probability of patients who are being evaluated at any given time after the start of CML therapy.

In order to overcome the limitations of current CML monitoring recommendations and to refine the prediction of outcomes for patients, we used the principle of conditional survival to devise a calculator of outcomes at any time during the course of TKI therapy.

Patients and methods

Patients

For the present analyses, we used data from 1189 patients enrolled in two previously published large phase III clinical trials. For the analysis of outcomes of patients receiving frontline therapy we evaluated data from 519 patients treated in the DASISION study, which compared dasatinib 100 mg daily (n=259) versus imatinib 400 mg daily (n=260) in a randomized fashion in newly diagnosed patients with CML-CP.⁶ For the analyses of outcomes of patients receiving second line TKI therapy, we used data from 670 patients treated in the dose optimization study CA180-034, comparing different dose schedules of dasatinib in patients with CML-CP who had failed therapy with imatinib. A 6-year update of this study has been presented showing similar efficacy results across the 4 dose-schedules tested in the study.⁷

Statistical analyses

The probabilities of survival were calculated according to the Kaplan-Meier method. Estimates of cumulative survival were utilized to obtain estimates of conditional survival by means of the multiplicative law of probability. Briefly, knowing the probability of event A and event B occurring $\Pr(A \text{ and } B)$ and the probability of event A occurring $\Pr(A)$ facilitates the calculation of the conditional probability of event B occurring in the event that event A has already occurred: $\Pr(B|A) = \Pr(A \text{ and } B) / \Pr(A)$.⁵ For instance, to estimate the additional 10-year conditional survival of patients who have survived 3 years, the 13-year cumulative survival (event A and B) is divided by the 3-year cumulative survival (event A). Given that age is a major predictor of survival, all estimates of survival were adjusted for age.⁸ A modified Cox proportional hazards model was used to build a prognostic nomogram.^{9,10} Progression-free survival (PFS) was defined as any of the following: doubling of white cell count to $>20 \times 10^9/L$ in the absence of complete hematologic response (CHR); loss of CHR; increase in Philadelphia chromosome-positive bone marrow metaphases to $>35\%$; transformation to AP/BP; or death. Overall survival (OS) was defined as the elapsed time between the start of TKI therapy and either the date of death or the last follow-up.

Results

Analysis of outcomes in the frontline setting

First we evaluated the dynamics of molecular response over time for the entire patient population enrolled in the DASISION study segregated by logarithmic reductions in *BCR-ABL1* transcript levels (Figure S1). Most patients started dasatinib with transcript levels

between 10% and 100%, but over time most achieved *BCR-ABL1* levels below 1%, and in fact, as previously reported, most achieved MMR (i.e., *BCR-ABL1/ABL1* 0.1%). Next, we linked *BCR-ABL1* transcript level reduction to the concept of conditional survival. Given the very low number of deaths in both arms of the DASISION trial, we limited our prediction analyses in the frontline cohorts to PFS. As previously reported, no significant difference in PFS was observed in PFS between the cohorts of patients treated with imatinib or dasatinib (Figure S2). To assess whether such assumption held true at specific time-points, we calculated future PFS at random time-points using random *BCR-ABL1* transcript levels. For instance, the probability that a patient with CML-CP treated with TKI therapy for 3 months, who achieved a *BCR-ABL1/ABL1* transcript ratio of 0.17%, and has not yet progressed be free from progression 24 or 36 months later was 91.6% and 90.9% if such patient received frontline therapy with dasatinib and 87.8% and 87.5% if the TKI used was imatinib (Figure 1). No statistically apparent differences were observed between dasatinib- and imatinib-treated patients at any of those time-points. Similar observations were made when a different *BCR-ABL1* transcript level (e.g. 7.9%) was tested at the same time-point (Figure S3). Since the 3-month time-point is already contemplated in current monitoring recommendations, we next calculated the outcomes of a hypothetical patient presenting with similar qRT-PCR values but this time at random time-points. Figure 2 illustrates the probabilities of a hypothetical patient to be free from progression 24 or 36 months after having completed dasatinib or imatinib therapy for 8.7 months if such patient had no evidence of progression at the 8.7-month time-point. PFS for such patient is shown at 8.7 months for the same qRT-PCR values tested at the 3-month time-point (i.e. 0.17% and 7.9%, Figure S4). While the predicted probability of being free from progression at 24 or 36 months were inferior for a *BCR-ABL1* transcript level of 7.9% compared with 0.17%, again, no differences were observed in PFS between dasatinib and imatinib when the same qRT-PCR value was considered at the same time-point.

These data demonstrate the feasibility of predicting PFS in the frontline TKI setting in patients with CML-CP who have not yet progressed at any time-point for any given qRT-PCR value. With available follow-up in the DASISION trial, calculations using the principle of conditional survival predict similar PFS rates for patients treated with dasatinib or imatinib that have reached equal reductions in *BCR-ABL1* allele burden at the same time-points. Finally, we could also calculate how a patient would hypothetically rank against the whole cohort of patients with CML-CP in the DASISION trial with regards to the depth of the molecular response achieved at a specific time-point. For instance, a patient with a *BCR-ABL1* transcript level of 0.17% at 8.7 months is predicted to be at the 64 percentile of molecular response for the entire DASISION cohort, or in other words, approximately one third of patients are projected to have a better molecular response at that time-point.

Analysis of outcomes in the second line setting

Next, we analyzed the outcome of patients receiving second line dasatinib therapy using data from the 6-year update of the dose optimization study CA180-034 (Figure S5). Similar to the frontline therapy analyses, we used conditional survival to calculate PFS and OS at random time-points using random *BCR-ABL1* transcript levels. For example, the probability that a patient with CML-CP treated with dasatinib for 15.6 months, who achieved a *BCR-*

ABL1/ABL1 transcript ratio of 0.09%, and has not yet progressed or died be free from progression 2 or 5 years later was 86.9% and 60.8% and that of being alive at the same time-points was 91.7% and 77.7%, respectively (Figure 3). This particular patient, with *BCR-ABL1* transcript levels of 0.09% at 15.6 months, is predicted to be at the 74 percentile in terms of molecular response for the entire population. Such patient, therefore, is estimated to have a molecular response at this time-point that is deeper than that of approximately 3 quarters of the patients at that specific time-point.

Impact of age in outcome prediction

Given that age is an independent risk factor for future survival, we next analyzed the outcomes of patients in the study CA180-034 adjusted by age. To that end, we divided patients in 3 age groups: <40, 40–60, and >60 years. While patients older than 60 years of age had a significantly shorter survival, those with ages <40 and those aged 40 to 60 had similar survival rates (Figure S6). For that reason, the latter 2 groups were combined for the rest of the analyses. In order to assess the impact of age on future survival, we then analyzed the outcomes of 4 specific hypothetical patients that were alive after 15.6 months of therapy: (i) *BCR-ABL1/ABL1*=0.02%, age 40; (ii) *BCR-ABL1/ABL1*=17%, age 40; (iii) *BCR-ABL1/ABL1*=0.02%, age 60; and (iv) *BCR-ABL1/ABL1*=17%, age 60. Figures 4A and S7 depict the predicted future PFS and OS for those 4 patients, and illustrates the impact of age in patients with similar *BCR-ABL1/ABL1* ratios. Expectedly, for patients of similar age, those with the lowest *BCR-ABL1/ABL1* ratios had predicted improved future survival, which was most noticeable in the short-term, during the first few years of follow-up (Figure 4B). Therefore, any analysis of future probability of survival must take into account the age of the patient being examined.

Nomograms for predicting future survival

Next, we designed nomograms to calculate patients' outcomes at any time-point during the course of therapy. By using the principle of conditional survival, we can plot nomograms for predicting the future survival of patients at the time-points specified by current monitoring recommendations (3, 6, 9, and 12 months) from the start of treatment (Figure S8). However, the statistical principle of conditional survival can be applied for predicting future outcomes at any time-point during treatment. We generated nomograms to predict overall future PFS as well as for predicting the 10% quantile of future PFS for patients who have lived any given length of time without progression on second line therapy. Figure 5A plots the median future PFS. The horizontal axis represents the time at which the prediction is made and the vertical axis represents the median future PFS. Figure 5B represents the 10% quantile for survival, which is the time that will elapse between the time-point at which the prediction is being made (i.e. a clinical assessment) and the time when 10% of patients who were free from progression at the time of prediction will have progressed. As an example, for an imaginary patient evaluated 9.5 months after having started second line dasatinib therapy with a *BCR-ABL1* transcript level of 0.1%, 10% of patients with similar RT-PCR ratio at the same time-point will have progressed in the subsequent 6.2 months. This type of nomogram provides invaluable information about the worst outcomes that can befall patients with the same PCR as the one being evaluated. So, in essence, at any given time and for any RT-PCR value, we can predict how much time will it take for any given fraction of the patient cohort

with the same transcript levels who are alive or without progression at that time to die or to progress. The quantification of these risks may then be used for more rationally considering a change on therapy if the future risk is deemed excessive with the current treatment.

Discussion

Recommendations for monitoring patients with CML define an optimal response to imatinib therapy as the achievement of certain leukemic burden reduction at specific time-points.^{1,2} However, the latter only provide recommendations at 3, 6, 12, and 18 months after the start of imatinib therapy, which is a clear limitation when evaluating clinical response to TKI therapy at time-points different from those pre-specified. In addition, robust recommendations to predict outcomes for patients receiving second line TKI therapy are lacking. Thus, tools that can predict outcomes at any time-point during the course of therapy, both for patients receiving frontline as well as second line TKIs are warranted. The definitions of optimal and suboptimal response, as well as failure to TKI therapy are linked to PFS and OS rates observed in TKI clinical trials. However, such survival statistics are static and anchored to the time of a therapeutic intervention, thus neglecting the fact that with every passing fraction of time a patient remaining alive and without experiencing an event, such patient will be improving his or her probabilities of favorable future outcomes.

However, the hazard of mortality or that of progressing or having an event changes with every fraction of time that elapses since the start of TKI therapy. Therefore, as time from CML diagnosis elapses, the prognostication of future outcomes (i.e. PFS or OS) can be further refined. To our knowledge, this is the first analysis of conditional survival in patients with CML. Information derived from this analysis will be very relevant for patients with CML who have returning to clinic after having survived or remained free from progression or events on TKI therapy so as to provide a more accurate risk assessment, therefore accounting for the change in risk profile over time. It must be however emphasized that the probability that a given patient reaches any given time-point during the course of therapy alive or without experiencing an event depends on the patient's baseline prognosis at the start of therapy (e.g. Sokal score). Importantly, conditional survival calculators have been devised for other cancers.^{11–16}

By utilizing serial *BCR-ABL1* transcript level measurements from the DASISION trial in combination with conditional survival calculations, we constructed a nomogram to calculate future outcomes in patients with CML receiving either frontline or second line therapy by means of conditional survival calculations. This tool is user friendly and can be used in real time to inform patients about their future outcomes in a more accurate and dynamic way compared to conventional survival statistics calculated from TKI start. Given the fact that patients with CML have improved dramatically their survival probability with the introduction of TKI therapy, the use of statistical tools that account for the time already survived have important implications to determine more realistic expectations and to manage uncertainty regarding long term outcomes.

A potential limitation of our analysis is the fact that as more time elapses from the time of initiation of TKI therapy, the number of patients available for predicting outcomes

diminishes as more patients die or experience events, which hinders the precision of the calculation of future outcomes. An obvious means to overcome this shortcoming is the use of an even larger cohort of patients, which could be accomplished by combining datasets of patients treated with different TKIs. In addition, the relatively short follow-up of the datasets used for these analyses prevents calculations of outcomes in the distant future. As previously shown by our group, patients achieving similar reductions in the proportion of metaphases carrying the Philadelphia chromosome or reductions in *BCR-ABL1* transcripts at a specific time-point exhibit similar long-term outcomes regardless of the TKI utilized (i.e. imatinib, high-dose imatinib, nilotinib, dasatinib) to reach such level of response.¹⁷ Similar results were obtained in the current analyses when we compared the outcomes of patients with newly diagnosed with CML receiving treatment with either imatinib or dasatinib as frontline therapy in the DASISION study at multiple random time-points. This is in line with a recent analysis of the DASISION trial evaluating the outcomes of patients at 3 and 6 months after starting imatinib or dasatinib therapy. The difference may be in the probability of reaching the deepest molecular responses, which, as demonstrated in DASISION for dasatinib and in ENESTnd for nilotinib, is greater with second generated TKI compared to imatinib.^{6,17,18} Regardless, this result is interesting as it might be expected that a patient achieving a given *BCR-ABL1* transcript level on a less potent TKI would have a more favorable outcome, reflecting perhaps a more benign biology.

In conclusion, we have devised a nomogram that predicts the future outcomes of patients treated in the frontline and second line settings according to their *BCR-ABL1/ABL1* ratios, independent from the time at which these ratios are obtained. This prognostic tool could be made readily available for clinical purposes, which could greatly facilitate monitoring and prognostication in CML at any time-point during the course of therapy in a more accurate and dynamic fashion than available options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Future progression-free survival of a patient with *BCR-ABL1/ABL1* ratio of 0.17% after 3 months on dasatinib (a) or imatinib (b) as initial therapy for CML CP.

Figure 2. Future progression-free survival of a patient with *BCR-ABL1/ABL1* ratio of 0.17% after 8.7 months on dasatinib (a) or imatinib (b) as initial therapy for CML CP.

Figure 3. Future progression-free survival and overall survival of a patient with *BCR-ABL1/ABL1* ratio of 0.09% after 15.6 months on dasatinib after imatinib failure.

(a)

(b)

Figure 4.

Prediction of future progression-free survival according to age. (a) Future progression-free survival for patients with different depths of molecular response at 15.6 months after having started dasatinib (after imatinib failure) according to age. (b) Future progression-free survival for patients older than 60 years who are free from progression at 6, 12, 18, and 24 months according to the depth of molecular response.

Figure 5. Nomograms to predict future progression-free survival (PFS) using the medians (a), and the 10% quantiles (b), for patients living any given length of time without progression on dasatinib as second line therapy.