Assessment at 6 months may be warranted for patients with chronic myeloid leukemia with no major cytogenetic response at 3 months

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ABSTRACT

Response to tyrosine kinase inhibitors at three months is a predictor for long-term outcome in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors. We analyzed 456 newly diagnosed chronic myeloid leukemia patients treated with tyrosine kinase inhibitors to determine their outcome based on their response at six months. Forty-four (10%) patients did not achieve major cytogenetic response at three months: 18 of 67 (27%) patients treated with imatinib 400; 18 of 196 (9%) with imatinib 800; and 8 of 193 (4%) with 2nd generation tyrosine kinase inhibitors. Among them, 19 (43%) achieved major cytogenetic response at six months and subsequently had an overall outcome similar to the patients who achieved a major cytogenetic response at three months. In conclusion, the response to tyrosine kinase inhibitors at three months is a static, one-time measure. Assessing the response at six months of patients with poor response at three months may provide a better predictor for long-term outcome.

Introduction

Despite the excellent response to front-line therapy with imatinib and 2nd generation tyrosine kinase inhibitors (TKIs) dasatinib and nilotinib,[1-4] some patients with chronic myeloid leukemia (CML) fail to responsd to therapy and have poor long-term outcome.[5] It has been suggested that the achievement of early response to TKIs is a major determinant for long-term outcome.[6-9] The assessment of cytogenetic or molecular response at three months has been defined as a strong predictor for outcome of patients treated with front-line TKIs.[6,8-12] Patients who do not achieve a major cytogenetic response (MCyR) or BCR-ABL transcript level less than 10% at three months have inferior event free survival (EFS) and perhaps overall survival (OS).[10-12] It is still a question of debate as to whether this finding is enough to justify a change in therapy for such patients.

The purpose of this analysis is to define whether additional assessment at six months may improve the ability to identify those patients destined to have a poor long-term outcome among those with a poor response at three months.

Methods

Patients

Between July 2000 and June 2011, a total of 456 newly diagnosed CML patients in chronic phase (CP) were treated at the MD Anderson Cancer Center with: imatinib 400 mg daily (n=67), imatinib 800 mg daily (n=196), or 2nd generation TKIs (2nd GTKIs, dasatinib and nilotinib; n=193) in consecutive or parallel trials. All trials were approved by the institutional review board (IRB) and all patients signed informed consent in accordance with the Declaration of Helsinki. Cytogentic and molecular responses were generally evaluated at baseline and every three months for the first year and then every six months. Cytogenetic responses were defined as described previously.[13]

Statistical analysis

Differences among variables were evaluated by Fisher's exact test for categorical and Mann-Whitney U test for continuous variables. Time-to-event analyses were performed by the Kaplan-Meier method, and survival curves were compared with the log rank test. All P values were two-sided. $P>0.05$ was considered significant.

Results and Discussion

Among 456 patients treated, 44 (10%) did not achieve MCyR at 3 months: 18 of 67 (27%) treated with imatinib 400; 18 of 196 (9%) with imatinib 800; and 8 of 193 (4%) with 2nd GTKI. Compared to patients who achieved MCyR at three months, these patients were younger, had a higher Sokal score, lower hemoglobin, higher white blood cell count, higher peripheral blood blast percentage, larger spleen, and were mainly treated with imatinib 400 mg daily (Table 1). Since some patients (mostly treated with imatinib 400) started treatment with imatinib in 2000 when early molecular monitoring was not done routinely, 24 (54%) patients had no BCR-ABL transcript level at three months, thus we focused on cytogenetic response.

Among these 44 patients, at six months, 19 (43%) achieved MCyR: 8 (18%) complete cytogenetic response (CCyR) and 11 (25%) partial cytogenetic response (PCyR. In addition, 17 (38%) continued to have no MCyR, 2 (5%) had inevaluable cytogenetic analysis, and 6 (14%) were off study: one trans-

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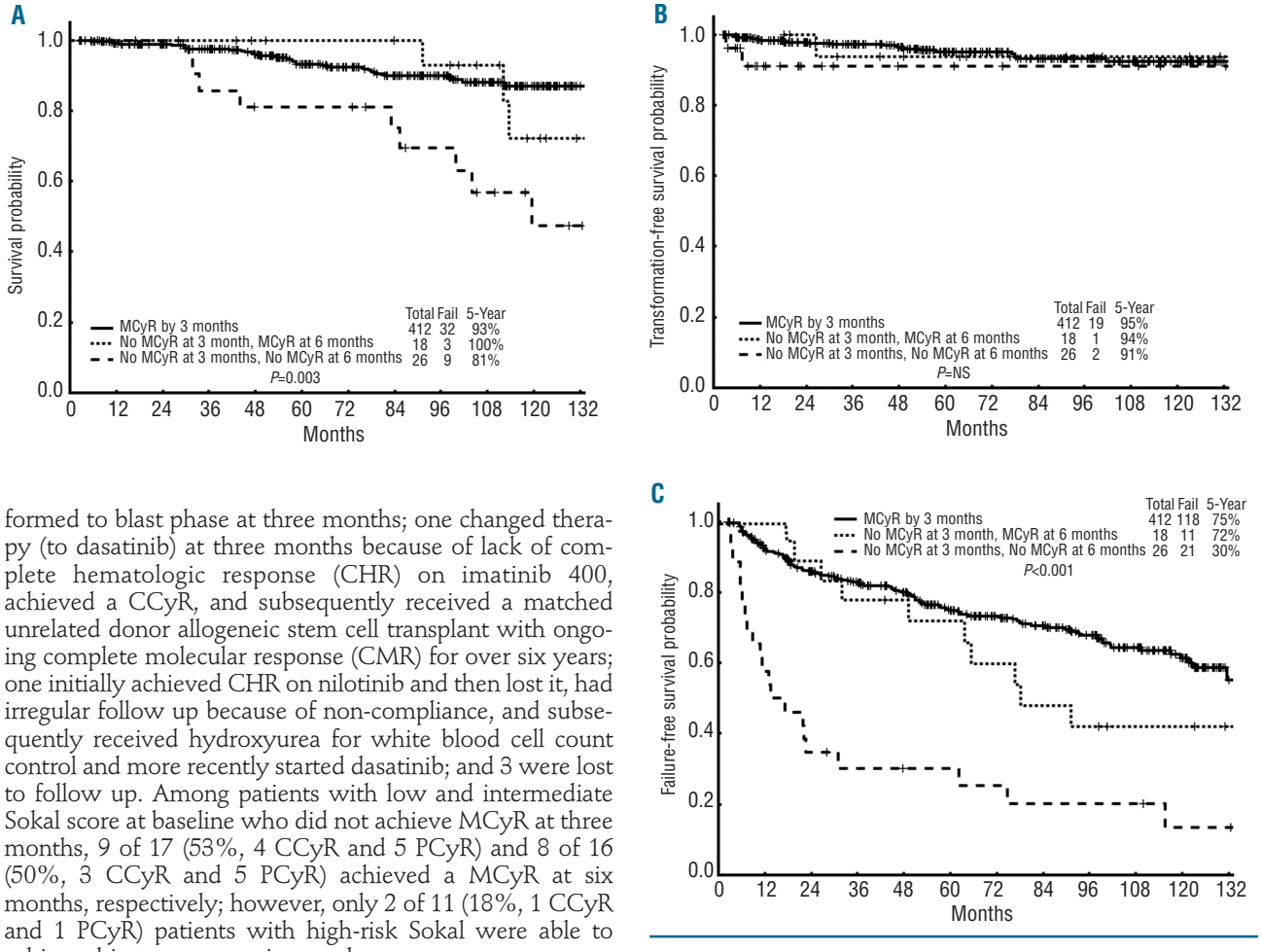
Table 1. Patients' characteristics in patients who achieved MCyR *vs.* N. (%) MCyR at 3 months.

Characteristics	N. %		*P* Value
	No MCyR at 3 months	MCyR at 3 months	
Number	44	412	
Median age, years (range)	43 (17-79)	49 (14-86)	0.007
Gender: male	26 (59)	241 (58)	0.93
Sokal risk group			<0.001
Low	17 (39)	255 (62)	
Intermediate	16 (36)	123 (30)	
High	11 (25)	34 (8)	
Median Hgb g/dl (range)	11.6 (6.2-14.9)	12.4 (6.7-16.7)	0.003
Median WBC x10^9/L (range)	45.6 (2.2-283)	27.5 (0.8-342.5)	0.042
Median platelets x10 /μL (range)	320 (103-1731)	343 (58-2928)	0.58
Median PB blasts %, (range)	1 (0-12)	0 (0-10)	<0.001
Median basophils in PB %, (range)	3 (0-16)	3 (0-19)	0.81
Median spleen size at diagnosis, cm (range)	5 (0-30)	0 (0-22)	<0.001
Philadelphia chromosome variant	2 (5)	21 (5)	0.87
Treatment group			<0.001
Imatinib 400	18 (27)	49 (73)	
Imatinib 800	18 (9)	178 (91)	
2nd GTKIs	8 (4)	185 (96)	

MCyR: major cytogenetic response; Hgb: hemoglobin; WBC: white blood cell; PB: peripheral blood; 2nd GTKIs: second generation tyrosine kinase inhibitors.



formed to blast phase at three months; one changed therapy (to dasatinib) at three months because of lack of complete hematologic response (CHR) on imatinib 400, achieved a CCyR, and subsequently received a matched unrelated donor allogeneic stem cell transplant with ongoing complete molecular response (CMR) for over six years; one initially achieved CHR on nilotinib and then lost it, had irregular follow up because of non-compliance, and subsequently received hydroxyurea for white blood cell count control and more recently started dasatinib; and 3 were lost to follow up. Among patients with low and intermediate Sokal score at baseline who did not achieve MCyR at three months, 9 of 17 (53%, 4 CCyR and 5 PCyR) and 8 of 16 (50%, 3 CCyR and 5 PCyR) achieved a MCyR at six months, respectively; however, only 2 of 11 (18%, 1 CCyR and 1 PCyR) patients with high-risk Sokal were able to achieve this response at six months.

During the first six months of therapy, 23 (52%) of the 44 patients required dose interruption of their initial therapy due to side effects (4 on imatinib 400, 14 imatinib 800, and

Figure 1. (A) Overall survival, (B) transformation free survival and (C) failure free survival among patients who did not achieve MCyR at 3 months and subsequently achieved MCyR at 6 months compared to patients who never achieved any MCyR by 6 months.

5 2nd GTKI). Among them, 11 (48%) patients required dose interruption in the first three months, 6 (26%) between 3-6 months, and 6 (26%) in both periods. Median duration of interruption was 19 days (range 1-59). Thirteen (30%) patients required dose reduction of their original dose during the first six months, 8 (62%) during the first three months, 4 (31%) between 3-6 months, and one (7%) in both periods.

With a median follow up of 95 months, the OS, failure free survival (FFS) and transformation free survival (TFS) for patients who did not achieve MCyR at three months and subsequently achieved a MCyR at six months were very similar to those of patients who achieved a MCyR at three months, and superior to that of patients still with no MCyR at six months (Figure1).

The identification of the prognostic significance of response to TKI three months after the start of therapy has triggered a controversy as to the optimal management of these patients. There are no currently available data from prospective studies suggesting change of therapy among these patients alters the outcome. The NCCN has recommended that these patients should be offered a change of therapy, with no option for continuation of therapy. However, only approximately 20% of those who have a poor response at three months have a poor outcome (i.e. an 'event') and up to 10% of those with a good outcome at three months still have a poor long-term outcome. Thus, a change for all would be aimed at helping only 10-15% of patients. In this analysis, we attempted to determine whether an additional observation at six months might better discriminate those patients destined to have a poor outcome. Indeed, those who still have not achieved a MCyR (currently considered suboptimal response by ELN)[13] have a poor outcome, whereas those who by then have achieved MCyR have an excellent outcome. In our series, only one patient progressed to blast phase and this occurred at three months, with no transformations occurring between 3-6 months. Our patient population had a higher percentage of patients with a low risk Sokal score at baseline than that reported in other series. This score seems to be a good surrogate to predict the response at three and six months. Patients with high-risk Sokal score at baseline had a higher chance of failing to achieve MCyR at three months. Moreover, among patients with a high-risk score who achieve MCyR at three months, only 18% of them may subsequently achieve this response at six months suggesting that Sokal score may be helpful to identify those patients with the worse outcome that may need a different approach. In contrast to our data, a recent series suggested that waiting for six months does not offer additional discrimination,[14] although the cutoff sought at six months was different (BCR-ABL 1%, grossly equivalent to CCyR).[15] The differences between these two analyses can only be sorted by prospective studies that investigate these options and the long-term value of change of therapy *versus* continuation for patients with poor response at three months. Until such studies are available, it appears sensible to monitor patients closely and continue therapy for at least three more months.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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