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Comparison of long-term outcome of early versus late chronic phase imatinib receivers

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Abstract

The introduction of imatinib mesylate made a remarkable contribution to the management of patients with chronic myeloid leukemia. In this study, we assessed the long-term efficacy of imatinib exposure in patients with CML in chronic phase according to European recommendations which consists both early and late chronic phase patients. This is a retrospective study including 101 chronic phase CML patients from a single center. The patient outcomes were analyzed according to initial treatment with imatinib either as firstline or secondline option following prior interferon. Kaplan-Meier curves were constructed to estimate probability and differences between subgroups were analyzed by the log-rank test. Forty-three percent of the patients had a prior history of interferon therapy. Of the 101 patients included, complete cytogenetic responses were achieved in 43.6 % of patients; major cytogenetic response in 55.4%; major molecular response in 36.6%. Totally, 21.3% had cytogenetic failure and 5.3% without any hematological response. Response rates were lower in late chronic phase patients compared to early chronic phase patients. This study justified the significance of ELN criteria and once again approved the high efficacy of imatinib treatment in chronic phase CML patients.

Key words

CML, Imatinib mesylate, ELN recommendation, Late chronic phase

1 Introduction

Imatinib at a standard dose of 400 mg daily is the standard of care for initial treatment of chronic phase (CP) CML [¹]. Results of International Randomized Study of Interferon versus STI571 (IRIS) for previously untreated CP CML patients fundamentally altered the management of CML during the last decade [²]. Even the possibility of cure by use of imatinib as a single agent in some patients with CML has risen. The achievement of complete cytogenetic response (CCyR) has been accepted as the major objective for a prolonged survival while on imatinib therapy [³]. Updated results from IRIS demonstrated that patients within the imatinib arm had a 7-year overall survival (OS) rate of 86%, and freedom from progression was 93% [⁴]. However, despite this remarkable success in CML therapy, access to imatinib treatment became available in a delayed manner in many parts of the world as well as in our region generally due to economic reasons. Therefore, a considerable number of patients were late chronic phase (LCP) patients in real life clinical practices during the last decade. Cases where imatinib was administered after prior treatment, mainly IFN-α, which had failed to achieve or
maintain a hematologic and/or a cytogenetic response, or not tolerated later on, are defined as LCP patients [5]. The response rates in LCP patients seem to be lower compared to early chronic phase (ECP) patients [5]. Additionally, in the previous trials a trend toward better duration of CCyR when obtained early has also been observed [6].

In the current report we analyzed the outcome of CP CML patients who began treatment with imatinib either as a first- or second-line option following prior interferon. An important proportion of our patients were actually LCP patients who were resistant to interferon therapy and these patients had their disease for a certain period of time before the introduction of imatinib. The long-term outcome of the patients treated with second-line imatinib has been analysed. In addition outcomes of patients according to recent European Leukemia Net recommendations were reviewed.

2 Patients and methods
Between June 1995 and May 2011, 101 adult patients with CML in chronic phase received treatment with imatinib either after interferon therapy (n=43) or as initial therapy (n=58). The definitions of optimal response and failure were those derived from the 2009 European LeukemiaNet recommendations [7]. We performed quantitative PCR testing every 3 months and bone marrow cytogenetics at diagnosis and 6 month intervals for the first year, every 12-18 months following achievement of of a CCyR. Measurement of Bcr-Abl transcripts was carried out using quantitative real-time PCR (Lightcycler® 480 System, Roche Diagnostics, Mannheim, Germany). In most of our cases, regular cytogenetic data were not available and response criteria were evaluated predominantly depending on Bcr-Abl/G6PD transcript ratios until 2006 and Bcr-Abl/Abl later on. While interpreting the data, conversions of bcr-abl transcript level ratio to the control gene were performed accordingly. If there were any evidence for resistance or progression we performed bone marrow cytogenetic investigation. Risk classification was done according to Sokal scoring system at diagnosis. Dose escalation/modification of imatinib treatment was done according to IRIS protocol criteria in early 2000s and as evolving data became available ELN recommendations were referred [2, 7, 8]. Few patients received imatinib through Glivec International Patient Assistance Program (GIPAP) in our center until 2003 when it was licensed in our country. All the patients received Gleevec® (imatinib mesylate, Novartis Pharmaceuticals Corporation, USA). The results were calculated as median±SEM. The student test and Mann-Whitney test was used for comparison of means for paired parameters and non-parametric data, respectively. Chi-square test was used for the comparison of categorical variables. Kaplan-Meier curves were constructed to estimate probability and differences between subgroups were analyzed by the log-rank test. Overall survival (OS) was calculated for all patients from the date of diagnosis to the date of last follow-up or death from any cause. Progression free survival (PFS) was calculated for all patients from the time of first commencement of treatment to the date of last follow-up or to the date of relapse, progression, or death because of leukemia. Patients who had stem cell transplantation were censored at the time of transplant. Event-free survival (EFS) was measured from start of imatinib until loss of a CHR or a major cytogenetic response (MCyR), progression, or death from any cause during treatment. The statistical software package SPSS 16.0 (SPSS, Inc., Chicago, Ill., USA) was used and \( P \leq 0.05 \) was considered significant.

3 Results
Patient characteristics are shown in Table 1. The median age of patients was 42 years (range, 20-78 years); 49 (48.5%) patients were female. The distribution of patients according to Sokal scores at diagnosis were as follows; 16 (15.8%) were low risk, 42 (41.6%) intermediate risk and 28 (27.7%) were high risk patients. Sokal scores were missing in 15 (14.9%) of the patients.

For patients who had prior treatment with interferon the median duration until imatinib intake was 31 months (range, 3-97 months); for the rest median interval was 2 months (range, 0-75 months). The median follow-up duration within the whole group was 65.5 months, (range, 2-204 months). The median duration of imatinib therapy was 47 months (range, 3-100 months). During follow up, CCyR was obtained in 43.6%; MCyR in 55.4%; major molecular response (MMR) in 36.6%
of the patients according to 2009 ELN recommendations. Totally 71.3% (72) of all patients were still on imatinib at the time of last follow up; 3 patients were on 600 mg (dosage modification because of loss of hematologic response-LHR); 3 patients on 800 mg (LHR) and 4 patients (dosage modification because of grade 3-4 cytopenias) were on 300 mg. The rest of the patients were still on 400 mg per day. Sixteen (15.8%) of the patients were receiving nilotinib 800 mg daily and 9 (8.9%) of the patients were on dasatinib 100-140 mg daily. One of these patients was imatinib-intolerant, 4 had blast transformation and the remaining patients were receiving either nilotinib or dasatinib for LHR. Two patients had undergone HLA-matched sibling HSCT; one of them had extramedullary leukemic involvement while on imatinib 400 mg daily; the other patient preferred transplantation while in chronic phase. A total of 29 (28.7%) patients discontinued imatinib therapy either because of intolerance, resistance or progression. The option of mutational analysis for those who have loss of response or no response at the appropriate time points was not available for our patients.

Table 1. Patient characteristics according to complete cytogenetic response at 12 months of imatinib

|                          | Non-CCyR (n=43) | CCyR (n=44) | p   |
|--------------------------|-----------------|-------------|-----|
| Age, yrs                 | 41 (21-69)      | 42 (20-78)  | 0.9 |
| Gender (F:M)             | 21/22           | 22/22       | 0.5 |
| Hb (g/dL)                | 10.8±0.3        | 11.5±0.4    | 0.09|
| WBC (×10^9/µL)           | 136.7±15        | 105.2±34    | 0.7 |
| PLT (×10^9/µL)           | 353±34          | 392±46      | 0.7 |
| LDH (IU)                 | 1362±123        | 1551±151    | 0.6 |
| Median duration of CP before STI (mo) | 31 (1-132) | 3 (1-97) | 0.00 |
| Imatinib resistance      | 24              | 7           | 0.00|
| F/U duration (mo)        | 86 (10-204)     | 48 (8-204)  | 0.00|
| Imatinib dose escalation from |               |             |     |
| 400 to 600               | 15              | 2           |     |
| 400 to 800               | 2               | 1           |     |
| 600 to 800               | 5               | 1           |     |
| Second gen TKI           |                 |             |     |
| Nilotinib                | 10              | 4           |     |
| Dasatinib                | 2               | 1           |     |
| Median follow-up from imatinib escalation/second TKI, mo | 52 (2-148) | 36 (8-151) | 0.8 |
| Time to drug modification| 30(3-76)        | 39 (12-91)  | 0.1 |
| Disease group at imatinib dose escalation |               |             |     |
| Hematologic relapse      |                 |             |     |
| Hematologic resistance   | 22              | 6           |     |
| Cytogenetic relapse      |                 |             |     |
| Loss of CCyR but still in MCyR | 17 | 5 |     |
| Cytogetic resistance     |                 |             |     |
| Resistance with no cytogenetic response | 9 | 4 |     |
| MCyR with no CCyR        | 7               | 4           |     |
| Death during treatment   | 8               | 5           | 0.3 |
| Prior interferon therapy | 27              | 15          | 0.01|
| Median STI duration, mo  | 60(8-96)        | 41(3-100)   | 0.07|
| Early vs. late imatinib treatment | 19/24 | 36/7 | 0.00 |
| Sokal score (low/int/high) | 5/18/14 | 8/22/10 | 0.4 |
| MMR@18                   | 9               | 28          | 0.01|

CCyR: complete cytogenetic response; MMR: major molecular response.

Median time interval until dose escalation or second generation tyrosine kinase inhibitor initiation for resistant or progressive disease while on imatinib was 32 months (range, 4-91 months) in 31 patients. At the end of follow up, with a
median interval of 48 months (range, 0-96 months) after imatinib introduction, 68.3% of the patients (69) were in CCyR and 46.5% (47) were in MMR. There were no significant difference in prior interferon intake history of the patients who were still in CCyR and MMR ($P >0.05$). The improvement in cytogenetic and molecular responses at the end of follow-up was most likely due to early introduction of alternative therapies. The incidence of adverse effects was 6.9% within the whole group including mostly cutaneous and hematologic side effects.

We analyzed outcomes for 101 patients with CP CML treated in a single institution according to recent European Leukemia Net recommendations. In addition, we assessed the long-term efficacy of imatinib therapy in patients who received imatinib either after interferon or as initial therapy. Ten of (9.9%) patients who started with 400 mg were reduced to 300 mg within 3 months of imatinib therapy due to side effects (grade 3/4 neutropenia). At 6, 12 and 18 months of treatment 10 (9.9%), 9 (8.9%) and 4 (4%) of the patients were still receiving 300 mg imatinib per day, respectively. Those patients who reached CCyR at 12 months did not differ in their Sokal risk score at diagnosis ($P=0.4$). The difference in median survival time was significant according to Sokal risk groups ($P=0.006$). There was a trend toward a better outcome in the lower Sokal risk patients in terms of PFS ($P=0.05$). When all patients including those on nilotinib/dasatinib are considered, at a median of 6 years 74% of the patients were still in CCyR.

The CCyR rates at 12 months were 62%, 55%, and 42% for low-, intermediate-, and high-risk patients, respectively, according to Sokal ($P=0.4$). The 5-year OS, PFS, and EFS rates were 100%,86%, and 83%, for low-risk patients; 90%, 86%, and 77% for intermediate-risk patients; and 78%, 70%, and 49% for high-risk patients, respectively. The differences were significant ($P=0.006; P=0.05; P=0.02$, respectively).

### 3.1 Prognostic significance of complete cytogenetic response at 12 months of imatinib therapy

![Figure 1](https://example.com/figure1.png)

Figure 1. Probability of overall (A) and progression free survival (B) according to complete cytogenetic response (CCyR) at 12 months

Forty-four (43.6%) of the patients achieved CCyR at 12 months of imatinib therapy. Prognostic significance of Sokal score was once again confirmed when patients with a CCyR at 12 months are compared with those of non-CCyR patients. Sokal score at diagnosis was similar in responders and non-responders ($P=0.05$). Time from diagnosis until imatinib intake was significantly shorter in patients who had CCyR ($P<0.05$, Table 1). Prior interferon intake seem to have a negative effect on cytogenetic response at 12 months ($P = 0.01$, Table 1). Early access to imatinib within 12 months of diagnosis was significantly higher in responders compared to non-responders ($P<0.05$, Table 1). The probabilities of OS and PFS for responders and nonresponders were not different (Figure 1A-1B, $P>0.05$). However, at a median of 67 months, the probability of PFS in the CCyR group was significantly longer than the non-CCyR group in patients who had imatinib
treatment within 12 months of diagnosis (early receivers) (78% vs. 30.5%, \( P = 0.001 \), Figure 2A) compared to those who had later introduction of imatinib i.e. after 12 months of diagnosis (late receivers) (41.7% vs. 50.4%, \( P = 0.9 \), Figure 2B). As most of the late receivers had resistant/progressive disease while on interferon, introduction of imatinib treatment following interferon therapy did not seem to compensate for the unstable disease.

**Figure 2.** Probability of PFS according to CCyR at 12 months in patients who had imatinib treatment within (A) and after (B) 12 months of initial diagnosis

Totally drug modification for any reason in the non-CCyR group was significantly higher compared to CCyR group (\( P < 0.05 \)), a finding which might be considered as an indirect evidence of more resistant disease phenotype in the non-CCyR group (Table 1).

### 3.2 Prognostic significance of major molecular response at 18 months of imatinib therapy

**Figure 3.** Probability of overall survival (A) and PFS (B) according to major molecular response (MMR) at 18 months
Thirty-seven (36.6%) of the patients achieved MMR at 18 months of imatinib therapy. Patients who had MMR at 18 months had a lower Sokal risk score compared to non-responders (non-MMR) \( (P=0.03, \text{ Table 2}) \). Time from diagnosis until imatinib intake was significantly shorter in patients who had MMR \( (P<0.05) \). Earlier use of imatinib within 12 months of diagnosis caused a statistically significant molecular response \( (P=0.001) \). Although the probability of OS was not significantly different when both groups are compared (Figure 3A, \( P>0.05 \)), the probability of PFS for major molecular responders was significantly longer in responders (Figure 3B, \( P=0.006 \)). At a median of 75 months, the probability of PFS in the MMR group was significantly longer than the non-MMR group in patients who had imatinib treatment within 12 months of diagnosis (87.5% vs. 22.7%, \( P=0.005 \)) compared to those who had later introduction of imatinib i.e. after 12 months of diagnosis (50% vs. 33.3%, \( P>0.05 \)).

**Table 2.** Patient characteristics according to major molecular response at 18 months of imatinib

|                      | MMR (n=37) | Non-MMR (n=34) | \( p \) |
|----------------------|------------|----------------|------|
| Age, yrs             | 39±2.2     | 41.5±2.1       | 0.7  |
| Hb (g/dL)            | 11.5±0.3   | 10.3±0.3       | 0.04 |
| WBC \( (\times10^9/\mu L) \) | 119±17     | 144±14         | 0.6  |
| PLT \( (\times10^9/\mu L) \) | 341±33     | 389±52         | 0.4  |
| LDH (IU)             | 1551±146   | 1358±194       | 0.7  |
| Sokal                | 7/19/6     | 4/11/15        | 0.03 |
| Time until imatinib  | 3 (1-97)   | 35 (1-132)     | 0.00 |
| Early vs. Late imatinib | 28        | 12             | 0.001|
| Median F/U (months)  | 60 (8-204) | 87(14-204)     | 0.004|
| Prior IFN            | 14         | 26             | 0.001|
| Median imatinib duration | 58 (3-100) | 60 (12-89)     | 0.8  |

Patients in CCyR who had also achieved MMR at 12 and 18 months did not have PFS or OS advantage. This difference did not reach to a statistically significant level most likely due to small number of patients in each of the groups.

### 3.3 Comparison of response criteria in early versus late chronic phase patients

**Table 3.** Comparison of prognostic parameters in ECP vs. LCP patients

|                      | ECP (n=58) | LCP (n=43) | \( P \) |
|----------------------|------------|------------|------|
| Age, yrs             | 41(20-78)  | 42(21-69)  | 0.8  |
| Gender (F:M)         | 27/31      | 22/21      | 0.6  |
| Hb (g/dL)            | 11.1±0.2   | 10.8±0.3   | 0.6  |
| WBC \( (\times10^9/\mu L) \) | 109±28     | 100±13     | 0.6  |
| Median duration of CP before imatinib (mo) | 2 (0-77)   | 31 (3-97)  | 0.00 |
| Time to drug modification | 35 (4-64) | 31(3-91) | 0.9  |
| Imatinib resistance  | 9          | 22         | 0.01 |
| Median imatinib duration | 26 (0-77) | 63 (18-100)| 0.00 |
| F/U duration (mo)    | 32 (2-204) | 96 (21-204)| 0.00 |
| Sokal                | 5/18/12    | 11/24/16   | 0.6  |
| CCyR@12 mo           | 29         | 15         | 0.01 |
| MMR@18 mo            | 23         | 14         | 0.002|

Early chronic phase (ECP) patients defined as those who had imatinib therapy upfront and late chronic phase patients (LCP) as those who received imatinib after prior treatment namely, IFN-\( \alpha \) which ended up with failure, loss of response or
intolerance are compared (Table 3). Fifty-eight (57.4%) of the patients were within the ECP group. Our data demonstrated that frontline imatinib was effective and early administration was significantly advantageous for CCyR and MMR. Progression free survival at 12 and 18 months of imatinib treatment was significantly longer in patients who achieved optimal response and received imatinib within 12 months of diagnosis as demonstrated above (Figure 2). In the ECP group the 5-year OS (69.2% vs. 33.1%), PFS (58% vs. 35.6%) and EFS (48.5% vs. 17%) rates were superior compared to those of LCP patients ($P=0.01$, 0.006 and 0.003, respectively). At a median of 40 months, 71.5% of ECP patients were in CCyR compared to 64% of LCP patients with imatinib treatment only ($P=0.5$). When second generation TKIs were introduced after any failure following imatinib treatment, 72.3% of ECP patients remained in CCyR compared to 84.3% of LCP patients at a median of 5 years ($P=0.1$).

3.4 Prognostic significance of leukemianet criteria for failure and suboptimal response

Totally 5, 14, 27 and 21 of the patients were classified as failure at 3, 6, 12 and 18 months of imatinib therapy, respectively. The definition of failure was sustained in all the patients except 6 who were classified as failure at 12 months; two died due to blastic transformation and one had allogeneic stem cell transplantation before 18 months and 3 were reclassified as suboptimal responder at 18 months. Outcome of non-failure (optimal responder) patients compared to failure patients were significantly better at various time points, i.e. 3, 12 and 18 months in terms of PFS and this advantage remained at 18 months survival analysis (Table 4). For example, the probability of progression free survival of failure patients compared with non-failure patients at 3 months was significantly shorter in the former (Table 4, $P=0.012$). A total of 4, 6, 12 and 12 patients were classified as suboptimal responders at 3, 6, 12 and 18 months, respectively. Prognostic significance of LeukemiaNet criteria for suboptimal response was insignificant compared to failing patients (Table 4).

Table 4. The probability of five-year OS and PFS according to ELN failure and suboptimal response criteria

|                      | N   | PFS,% | OS,%  |
|----------------------|-----|-------|-------|
| Failure at 3 mo      |     |       |       |
| Yes                  | 5   | 60    | 100   |
| No                   | 76  | 85.1  | 93.6  |
| Failure at 6 mo      |     |       |       |
| Yes                  | 14  | 64.3  | 92.9  |
| No                   | 50  | 86.8  | 91.5  |
| Failure at 12 mo     |     |       |       |
| Yes                  | 44  | 69.1  | 83.3  |
| No                   | 27  | 92.9  | 97.4  |
| Failure at 18 mo     |     |       |       |
| Yes                  | 36  | 61.5  | 84.7  |
| No                   | 21  | 100   | 100   |
| Suboptimal at 3 mo   |     |       |       |
| Yes                  | 4   | 50    | 50    |
| No                   | 81  | 85.1  | 93.6  |
| Suboptimal at 6 mo   |     |       |       |
| Yes                  | 6   | 100   | 100   |
| No                   | 48  | 86.8  | 91.5  |
| Suboptimal at 12 mo  |     |       |       |
| Yes                  | 12  | 100   | 100   |
| No                   | 43  | 92.9  | 97.4  |
| Suboptimal at 18 mo  |     |       |       |
| Yes                  | 12  | 91.7  | 92.3  |
| No                   | 36  | 93.3  | 93.3  |
When we pooled failure patients and suboptimal responders as non-responders and compared these patients with responders, we found that at 18 months responding patients had a better five-year PFS compared to non-responders (93.3% vs. 69.3%, \( P = 0.006 \)). Similar advantage was also observed at 3 months (85.1% vs. 53.3%, \( P = 0.022 \)). There were no difference in the probability of PFS at 6, 12 months (86.8% vs. 73.7%, \( P = 0.1 \); 92.9% vs. 77.4%, \( P = 0.1 \)) and OS at 3 (93.6% vs. 77.8%, \( P = 0.06 \)), 6 (91.5% vs. 94.7%, \( P = 0.547 \)), 12 (91.3% vs. 89.8%, \( P = 0.8 \)) and 18 months (100% vs. 87.4%, \( P = 0.1 \)) respectively.

4 Discussion

Imatinib was approved for adults with newly diagnosed chronic phase CML in 2001 when the pivotal trial IRIS had been completed with a substantial survival advantage. However, access to imatinib in many developing countries occurred in a delayed manner. In this study, an overview of CML treatment in clinical practice in southern region of our country which also included an analysis comparing the efficacy of treatment between ECP and LCP patients has been performed.

All of our patients had received imatinib at some point since diagnosis. This proportion is high when compared with developed countries while in the same period. For example, a retrospective study from Northern France conducted between 1985 and 2004 revealed that 38% of 783 patients were treated with imatinib \[9\]. In another analysis reflecting a subset of patients from France from the European UNIC study which recruited patients between September 2006 and March 2007, 96% of the patients had imatinib at some point from diagnosis \[10\]. In general, imatinib was tolerated well in our patient cohort. The incidence and the severity of the adverse effects were comparable with the previous reports in literature \[11, 12\].

One of the aims of this study was to assess the outcome actual treatment practices in our center. First of all, Sokal’s prognostic risk system seemed predictive in the imatinib era. Keeping in mind the prospective design of IRIS and IRIS-like trials, the OS, PFS and EFS rates in our cohort at a median of 65 months was 89%, 79% and 74% respectively which was comparable to those in the literature though was lower than the original IRIS trial \[2\]. In the IRIS trial, the estimated 8-year OS, EFS and PFS were 85%, 81% and 92%, respectively. At 8 years, 55% of the 553 imatinib treated patients remain on study imatinib, with discontinuation due to intolerance (6%), resistance (16%), stem cell transplant (3%), death (3%) or other reasons (17%) \[13\]. Results from a German trial reported a 5-year OS of 94% and a 2-year EFS of 80%, \[7, 14\]. In a similar study from UK, at 5-year follow-up of 204 newly diagnosed CP CML patients treated, the cumulative incidences of CCyR and MMR were 83.2% and 82.7 % respectively and a total of 26% patients discontinued therapy after a median of 15.5 months \[15\]. In the UK study, patients defined as “failure” at 12 months showed significantly worse 5-year survival (87.1% vs. 95.1%, \( P < 0.0001 \)). Similar to a population-based small study which reported 41% CCyR \[16\], in our cohort we had a lower efficacy with a 43.6% CCyR rate at one year with imatinib only. We agree with Lucas and colleagues that imatinib in CML might have a lower efficacy than in clinical trials \[16\].

The level of response to treatment at earlier time points in CML correlates with a low risk of progression and better outcomes \[17-20\]. MDACC single arm studies demonstrated that early CCyR and MMR may protect against progression \[20\]. In the previous trials a trend toward a better duration of CCyR when obtained early has been observed \[6\]. As already mentioned, in our center, we had patients who could be described as early or late CP patients according to their firstline or response to treatment so that a retrospective analysis was doable. Response rates were lower in LCP patients compared to ECP patients. In ECP patients, OS, PFS and EFS rates were superior to those of LCP patients. A similar benefit has been observed in terms of PFS and OS in a GIMEMA trial in ECP patients \[5\]. The pattern of response to imatinib was poorer in LCP patients to that observed in ECP patients in our study. The MCyR, CCyR and MMR rates were 57.1%, 35.7% and 35%, respectively in LCP patients in our analysis which was lower than the reported rates in similar but prospective trials \[5, 21-23\]. These rates range between 60-73% for MCyR; 41-63% for CCyR and 60-74% for MMR. Although direct comparison is not possible with the results from such randomised controlled trials our data suggest that prior treatment history is an important prognostic marker for response to treatment with imatinib. In this study we found that PFS and OS become superior in cytogenetic and molecular responders when imatinib treatment is introduced early. Moreover, we
show that the disadvantage of later introduction of imatinib in LCP patients might be overcome by the introduction of newer tyrosine kinase inhibitors. However, despite that the length of observation time is quite long in this analysis, still a longer follow up is needed in order to understand whether this benefit would be durable or not.

European LeukemiaNet recommendations were designed to help clinicians identify responses of CML-CP patients on standard dose imatinib based on response to treatment at various time points using specific hematologic, cytogenetic, and molecular criteria [3, 7]. However, different methods of disease monitoring are used less often in clinical practice than according to recommendations. We are aware of the fact that ELN recommendations were published and updated not before 2006 so that making clinical decisions based on these before this date may seem inapplicable. Despite that the availability of testing facilities was not always optimal in our center, it was important to observe that the predictive value of European LeukemiaNet recommendations be validated with our data. Classification of patients based on “failure” criteria was helpful in identifying patients responding poorly. The criteria for “suboptimal response” were not useful. It is of note that there was small number of patients for evaluation. On the other hand pooling patients classified as failure and suboptimal response may lead to a more accurate prediction of the poor-risk patients using failure only. Although there was a trend toward a longer PFS in patients with CCyR at 12 months and MMR at 18 months, the difference was not significant in our cohort. However, the prognostic significance of achieving CCyR at 12 months or MMR at 18 months was clear in our study in terms of PFS in ECP patients. In this analysis, as well as in many major trials in the literature including IRIS, patients in CCyR who had also achieved MMR at 12 and 18 months did not seem to have PFS or OS advantage indicating lack of prognostic impact of molecular responses [3, 15, 20]. We agree with Marin and his colleagues that this might be most probably due to early intervention of CCyR loss with more effective therapy [3]. Given the availability of newer tyrosine kinases revision of recommendations for the definition of “suboptimal response” criteria might be considered. The significance of suboptimal response is heterogenous in previous studies [24]. In a recent report from MDACC, a group of suboptimal responders had an outcome similar to failed patients and also another proportion of patients had similar responses as those of optimal responders [24]. ELN recommendations must be improved for every day clinical practice to optimize response analysis and patient prognosis. Starting resistant patients more potent agents relatively early after the development of resistance is highly effective in terms of prognosis. The fate of LCP patients who do not respond to imatinib but other tyrosine kinases either dasatinib or nilotinib would be informative in order to make decisions since a notable proportion of patients do not respond imatinib adequately also do not have durable responses.

In conclusion, early introduction of tyrosine kinase inhibitors either imatinib as firstline or nilotinib/dasatinib as secondline treatment is an important prognostic parameter in terms of survival. Finally, our study confirmed the utility of European recommendations retrospectively.

References

[1] Kantarjian HM, Larson RA, Guilhot F, O'Brien SG, Mone M, Rudoltz M, et al. Efficacy of imatinib dose escalation in patients with chronic myeloid leukemia in chronic phase. Cancer. 2009; 115: 551-60. PMid:19117345 http://dx.doi.org/10.1182/blood-2008-04-154344
[2] Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med. 2001; 344: 1031-7. PMid:11287972 http://dx.doi.org/10.1056/nejm200104053441401
[3] Marin D, Bazeos A, Mahon FX, Eliasson L, Milojkovic D, Bua M, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol. 2010; 28: 2381-8. PMid:20385986 http://dx.doi.org/10.1200/JCO.2009.26.3087
[4] O'Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, Radich JP, et al. International Randomized Study of Interferon Versus STI571 (IRIS) 7-year follow-up: sustained survival, low rate of transformation and increased rate of major molecular response in patients with newly diagnosed chronic myeloid leukemia in chronic phase treated with imatinib. [abstract]. Blood. 2008; 112S: 186.
[5] Palandri F, Iacobucci I, Martinelli G, Amabile M, Poerio A, Testoni N, et al. GIMEMA Working Party on CML. Long-term outcome of complete cytogenetic responders after imatinib 400 mg in late chronic phase, philadelphia-positive chronic myeloid leukemia: the GIMEMA Working Party on CML. J Clin Oncol. 2008; 26: 106-11. PMid:18165644 http://dx.doi.org/10.1200/JCO.2007.13.2373
[6] Guilhot F, Larson RA, O’Brien SG, Gathmann I, Druker BJ. Time to Complete Cytogenetic Response (CCyR) Does Not Affect Long-Term Outcomes for patients on Imatinib Therapy [abstract]. Blood. 2007; 110: 27.

[7] Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009; 27: 6041-51. PMid:19884523 http://dx.doi.org/10.1200/JCO.2009.25.0779

[8] Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F, et al. Evolving concepts in the management of chronic myeloid leukemia: Recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2006; 108: 1809-20. PMid:16709930 http://dx.doi.org/10.1182/blood-2006-02-005686

[9] Corm S, Leroyer A, Wemeau M, Bregman B, Oukessou A, Hemels M, et al. A retrospective 20-year survey of the incidence of chronic myeloid leukemia in the Northern France region. [abstract]. Blood. 2006; 108: 4800.

[10] Michallet M, Tulliez M, Corm S, Gardembas M, Huguet F, Oukessou A, et al. Management of chronic myeloid leukaemia in clinical practice in France: results of the French subset of patients from the UNIC study. Curr Med Res Opin. 2010; 26: 307-17. PMid:19961284 http://dx.doi.org/abs/10.1185/03007990903479299

[11] Quintás-Cardama A, Cortés JE, Kantarjian H. Practical management of toxicities associated with tyrosine kinase inhibitors in chronic myeloid leukemia. Clin Lymphoma Myeloma. 2008; Suppl 3: S82-S88. PMid:19254885

[12] Branford S, Hughes T, Milner A, Koelmeyer R, Schwerar A, Arthur C, et al. Efficacy and safety of imatinib in patients with chronic myeloid leukemia and complete or near-complete cytogenetic response to interferon-alpha. Cancer. 2007; 110: 801-8. PMid:18754032 http://dx.doi.org/10.1038/leu.2008.221

[13] Deininger M, O'Brien SG, Guilhot F, Goldman JM, Hochhaus A, Hughes TP, et al. International Randomized Study of Interferon Vs STI571 (IRIS) 8-Year Follow up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with imatinib. [abstract]. Blood. 2009; 114: 1126.

[14] Hehlmann R, Sauselle S, Lauseker M, Proetel U, Kovalevskaya E, Leitner A, et al. Randomized comparison of imatinib 400 mg vs.imatinib IFN vs. imatinib aracC vs. imatinib after IFN vs. imatinib 800 mg: Optimized treatment and survival-Designed first interim analysis of the German CML Study IV. [abstract]. Blood. 2008; 112: 184.

[15] de Lavallade H, Apperley JF, Khorashad JS, Milojkovic D, Reid AG, Bua M, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol. 2008; 26: 3358-63. PMid:18519952 http://dx.doi.org/10.1200/JCO.2007.15.8154

[16] Lucas CM, Wang L, Austin GM, Knight K, Watmough SJ, Shwe KH, et al. A population study of imatinib in chronic myeloid leukemia demonstrates lower efficacy than in clinical trials. Leukemia. 2008; 22: 1963-6. PMid:18754023 http://dx.doi.org/10.1038/leu.2008.225

[17] Pavlovsky C, Kantarjian H, Cortes JE. First-line therapy for chronic myeloid leukemia: past, present, and future. Am J Hematol. 2009; 84: 287-93. PMid:19306355 http://dx.doi.org/10.1002/ajh.21380

[18] Druker BJ, Guilhot F, O'Brien SG, Gathmann I, Kantarjian H, Gattermann N, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006; 355: 2408-17. PMid:17151364 http://dx.doi.org/10.1056/NEJMoa062867

[19] Branford S, Rudzki Z, Harper A, Grigg A, Taylor K, Durrant S, et al. Imatinib produces significantly superior molecular responses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Leukemia. 2003; 17: 2401-9. PMid:14523461 http://dx.doi.org/10.1038/sj.leu.2403158

[20] Kantarjian H, O'Brien S, Shan J, Huang X, Garcia-Manero G, Faderl S, et al. Cyto genetic and molecular responses and outcome in chronic myelogenous leukemia: Need for new response definitions? Cancer. 2008; 112: 837-5. PMid:18085610 http://dx.doi.org/10.1002/cncr.23238

[21] Kantarjian HM, Cortes J, O'Brien S, Giles FJ, Albitar M, Rios MB, et al. Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood. 2002; 99: 3547-3553. PMid:11986206 http://dx.doi.org/10.1182/blood.V99.10.3547

[22] Cervantes F, Hernández-Boluda JC, Steegmann JL, Conde E, Alvarez-Larrán A, et al. Imatinib mesylate therapy of chronic phase chronic myeloid leukemia resistant or intolerable to interferon: Results and prognostic factors for response and progression-free survival in 150 patients. Haematologica. 2003; 88: 1117-22. PMid:14555307 http://dx.doi.org/10.1182/hematol.2003-07-2575

[23] Alvarado Y, Kantarjian H, O'Brien S, Faderl S, Borthakur G, Burger J, et al. Significance of suboptimal response to imatinib, as defined by the EuropeanLeukemiaNet, in the long-term outcome of patients with early chronic myeloid leukemia in chronic phase. Cancer. 2009; 115: 3709-18. PMid:19517462 http://dx.doi.org/10.1002/cncr.24418