Long term follow-up of frontline Dasatinib in older patients with chronic myeloid leukemia in chronic phase treated outside clinical trials: a real-life cohort observational study

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Background

A limited amount of data has been published in chronic-phase chronic myeloid leukemia (CP-CML) patients aged >75 years treated frontline with second-generation tyrosine kinase inhibitors. The clinical scenario of chronic myeloid leukemia (CML) has significantly changed since the introduction of tyrosine kinase inhibitors (TKIs). In most cases, long-term treatment and molecular monitoring are required with life expectancy approaching that of the general population [1] and allowing to achieve a deep molecular response (DMR) in a substantial number of patients [2]. However, despite these outstanding results, few data are yet available regarding older patients with chronic phase CML (CP-CML) outside clinical trials that usually fix very strict inclusion criteria, linked to age limit per se or comorbidities. A limited amount of data has been published in chronic-phase chronic myeloid leukemia patients aged >75 years treated frontline with Dasatinib (DAS). Dasatinib might be effective in older patients (aged 75 years) affected by CP-CML with acceptable toxicity. These findings, although evaluated in a limited and selected cohort of patients, suggest that DAS could be effective in older patients (aged >75 years) affected by CP-CML with acceptable toxicity.

ABSTRACT

Background: A limited amount of data has been published in chronic-phase chronic myeloid leukemia (CP-CML) patients aged >75 years treated frontline with second-generation tyrosine kinase inhibitors.

Aims: To address this issue in a clinical ‘real-life’ setting, we retrospectively analyzed 45 CP-CML patients (pts) followed in 20 Italian Centers and treated frontline with dasatinib (DAS).

Patients and methods: Median age was 78.4 years (range 75–89.2 years). DAS starting dose was 100 mg QD in 35 pts (77.7%), 80 mg QD in 1 pts (2.2%) and 50 mg QD in 9 pts (20.1%), respectively. The median follow-up was 42.6 months (IQR 20.4 – 63.3).

Results: Grade 3 and 4 side effects, both hematological and non-hematological, were detected in 6 (13.3%) and 12 (26.6%) pts, respectively. Pleural effusions of all grades occurred in 13 pts (28.8%) after a median period of DAS exposure of 14.7 months (IQR 3.0 – 33.1). The rates of DAS dose reduction and permanent drug discontinuation were 53.3% and 20.0%, respectively. The best response, 42/45 patients (93.3%) achieved a complete cytogenetic response (CCyR), 35/45 (77.7%) a major molecular response (MMR) and 24/45 (53.3%) a deep molecular response (both MR 4.0 and MR 4.5). Only 1 patient (2.2%) progressed to the blast phase after 13 months of therapy; 8 deaths were observed (1 CML-related and 7 CML-unrelated). Cumulative event-free survival and overall survival at 36 months were 64.7% (95%, CI 49.4–80.0) and 82.3% (95%, CI 70.3–94.3), respectively.

Conclusion: These findings, although evaluated in a limited and selected cohort of patients, suggest that DAS might be effective in older patients (aged >75 years) affected by CP-CML with acceptable toxicity.
Clinical evidence has shown that, although the median age of patients at CML diagnosis ranged between 55 and 60 years [2,7,8] the introduction of several frontline TKIs treatment seems to have overcome the negative prognostic impact of older age [9,10]. Nevertheless, older patients with CML are largely represented in daily real-life management. As already reported, CML patients aged over 70 years represented 47.1% of the CML population included within the Swedish Cancer Registry between 1973 and 2013 [1]. The Simplicity study, an observational study including CP-CML patients receiving IM, DAS or NIL as frontline treatment in the United States (US) and across six European countries, registered that 30.6% of the enrolled population aged over 65 years [11]. Another real-world study, performed in the US by using health care claims from Commercial and Medicare systems, reported that 23% of patients with newly diagnosed CML aged over 65 years [12]. Therefore, whatever the exact percentage, all these data confirm that the older cohort with CML consists, at least, of about 20% of the whole CML population, thus representing a challenge in the choice and management of TKIs [13].

The first generation TKI Imatinib (IM) has been generally reported as a relatively safe drug with a favorable toxicity profile and a low rate of severe adverse events. For these reasons, it is commonly used in the subset of older patients regardless of the associated comorbidities and performance status [14]. However, persistent low-grade adverse events have been also associated with long-term IM treatment with consequent significant impairment of quality of life [15,16], mostly concerning renal toxicity and the onset of late chronic anemia [17,18].

The second-generation TKIs nilotinib (NIL) and dasatinib (DAS) were first introduced as the second line in IM-resistant or intolerant CML patients and then approved as first-line treatment. In this latter setting, limited data are available for older CML patients. Efficacy and safety issues of frontline NIL in the cohort of old (>75 years) CML patients have been recently investigated in 52 subjects from the Evaluating Nilotinib Efficacy and Safety in Clinical Trials as First-Line Treatment (ENEST1st) [19]. The study results outlined that age had not a major impact on both NIL efficacy and NIL-induced molecular responses. However, this study was not a real-life investigation having also strict inclusion criteria.

Therefore, to address this issue also for DAS treatment, we focused on a real-life cohort of CP-CML patients older than 75 years treated frontline with DAS with a relatively long follow-up.

**Patients and methods**

**Patients’ characteristics and inclusion criteria**

From June 2012 and October 2018, we retrospectively identified a cohort of 45 CP-CML patients followed in 20 Italian Centers. All patients gave written informed consent and all procedures were performed in accordance with the ethical standards of each institutional research committee and with the Declaration of Helsinki and its later amendments. Patients with CML, were considered eligible for this analysis if in the presence of all the following criteria: i) newly diagnosed CP-CML; ii) age ≥75 years at diagnosis; iii) no prior treatment apart from hydroxyurea given for less than three months; iv) DAS treatment frontline.

The choice of DAS treatment as frontline therapy was made by every responsible physician and was based on a combined evaluation of both CML disease and patients’ characteristics. The risk of progression was evaluated according to the Sokal score since it is still the most commonly employed risk stratification system and it was available for all of the patients.

**Cytogenetic and molecular evaluation**

Conventional chromosome banding analyses (CBA) were performed on bone marrow (BM) samples by standard G or Q banding techniques on at least 20 cell metaphases from direct or short-term (24–48 h) cultures. Fluorescence–in situ hybridization (FISH) on BM interphase cells was used if less than 20 metaphases were evaluable and were performed with BCR-ABL1 non-signal, dual-color, dual-fusion probes. Real-time quantitative polymerase chain reaction (RT-QPCR) to assess BCR-ABL1 transcript levels was performed according to suggested procedures and recommendations, and results were expressed as BCR-ABL1/ABL ratio normalized according to International Scale (IS) [20].

**Response definitions**

The chronic phase of the disease as well as patients monitoring and treatment responses, both hematologic and cytogenetic, were also categorized according to European LeukemiaNet (ELN) criteria [2]. Major molecular response (MMR or MR3) was defined as BCR-ABL1/ABL ratio <0.1%; deep molecular response (DMR) was defined as a BCR-ABL1/ ABL ratio <0.01% (MR4) or <0.0032% (MR4.5) [20]. For those patients who had been evaluated with molecular RT-QPCR only when the cytogenetic analysis was unavailable (often due to insufficient material, technical failure or patient’s refusal to undergo a BM aspirate) BCR–ABL1/ABL ratios ≤1% were considered equivalent to a complete cytogenetic response (CCyR) as previously reported [21].

Haematological and non-haematological toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0–27 November 2017); for the purpose of the present study, we graded toxicities as ‘low’ (grade 1 and 2) and ‘high’ (grade 3 and 4) and as ‘early’ and ‘late’ if they occurred before or after 6 months from DAS treatment start, respectively.

**Statistical analysis**

Data were expressed as mean ± standard deviation (SD) (normally distributed data), median and interquartile range (IQR) (non-normally distributed data), or as percentage frequencies, and within-patient comparisons were made by unpaired t-test and χ² test, as appropriate, at significance levels of p < 0.05. All the endpoints of treatment efficacy (CHR, CCyR,
and MMR) were calculated as the best response rate at any time. Overall survival (OS) was calculated from the date of DAS treatment start to death related to any cause. Event-free survival (EFS) was calculated from the date of DAS start to any of the following events: primary hematologic or cytogenetic resistance to DAS, permanent DAS discontinuation due to toxicity or any other unrelated cause (excluding discontinuation for a treatment-free remission), secondary hematologic or cytogenetic resistance, CML-related (progression to blast phase or any other cause directly related to CML) and unrelated death (concomitant diseases or any other cause not directly related to CML). Cumulative incidence of progression was calculated from the date of DAS start to any of the following events: primary resistance, secondary resistance, evolution in accelerated/blast phase. Further, DAS discontinuation for toxicity and deaths for unrelated causes were considered as competing events. Survival probabilities were calculated using the Kaplan–Meier method. Survival comparisons were made by the log-rank test. All calculations were made using a standard statistical package (SPSS for Windows Version 15.0; Chicago, IL).

Results

**Patient disposition and treatment details**

Overall, 45 newly diagnosed patients with CP-CML, aged >75 years and treated frontline with DAS were evaluated. They were collected in 20 Italian Centers and the territorial distribution of the participating Centers was nationwide. Patient characteristics are summarized in Table 1. Twenty-four patients were male (53.3%) and twenty-one females (46.6%), median age at diagnosis of CP-CML was 78.4 years (range 75–89.2 years; IQR: 76.7–80.6 years) and median follow-up was 42.6 months (IQR: 20.4–63.3 months). As expected in a relatively aged population, intermediate (66.6%) and high (33.4%) Sokal scores were frequent. Most of the patients (29 pts; 64.4%) had ≥2 comorbidities requiring concomitant therapies; performance status at baseline, according to ECOG scale, was 0–1 in forty patients (88.9%) and grade 2 or more in five patients (11.1%). The median interval from diagnosis of CML to DAS therapy was 26 d (IQR 14–42 d). Daily DAS starting dose was 100 mg QD in 35 patients (77.7%), 80 mg QD in 1 patient (2.2%) and 50 mg QD in 9 patients (20.1%), respectively. The choice of daily dose less than 100 mg was made by the responsible physician because of age >80 years (5 cases) and concomitant diseases (5 cases). All patients were evaluated for efficacy and toxicity.

### Table 1. Patients’ characteristics at diagnosis.

<table>
<thead>
<tr>
<th>No of patients</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, N (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (53.3)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (46.6)</td>
</tr>
<tr>
<td>Median age, years (interquartile range)</td>
<td>78.4 (76.7–80.6)</td>
</tr>
<tr>
<td>Median Hb value, g/dl (interquartile range)</td>
<td>12.3 (11.1–13.6)</td>
</tr>
<tr>
<td>Median WBC value, × 10^3/L (interquartile range)</td>
<td>50.8 (31.6–104.5)</td>
</tr>
<tr>
<td>Median PLT value, × 10^3/L (interquartile range)</td>
<td>357 (225–725)</td>
</tr>
<tr>
<td>Sokal risk: N (%)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>28 (66.6)</td>
</tr>
<tr>
<td>High</td>
<td>14 (33.4)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3</td>
</tr>
<tr>
<td>Performance Status (ECOG), N (%)</td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>18 (40.0)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>22 (48.9)</td>
</tr>
<tr>
<td>Grade ≥2</td>
<td>5 (11.1)</td>
</tr>
<tr>
<td>Comorbidities requiring treatment, N (%)</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>16 (35.6)</td>
</tr>
<tr>
<td>≥2</td>
<td>29 (64.4)</td>
</tr>
<tr>
<td>Main comorbidities, N (%):</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (66.6)</td>
</tr>
<tr>
<td>Ischemic cardiopathy</td>
<td>7 (15.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (17.7)</td>
</tr>
<tr>
<td>Lung disease</td>
<td>6 (13.3)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>1 (2.2)</td>
</tr>
<tr>
<td>Previous neoplasia</td>
<td>10 (22.2)</td>
</tr>
</tbody>
</table>

Toxicity and DAS dose reductions

Grade 3 and 4 side effects (supplementary Table 2, and stratified according to age), both hematological (anemia, thrombocytopenia, neutropenia) and non-hematological (effusions, congestive heart failure, cutaneous rash, persistent chronic myalgia, and others), were detected in 6 (13.3%) and 12 (26.6%) patients respectively. Pleural effusions occurred in 13 patients (28.8%). According to CTCAE classification, the effusion was of grade 1–2 in 9 cases (69.2%) while 4 cases (30.8%) were of grade 3–4. The median interval between DAS treatment and the occurrence of the effusion was 14.7 months (IQR: 3.0–33.1 months). Further, in 5 out of 13 patients (38.4%) pleural effusion occurred early during the first six months of treatment and recurred at least once after initial resolution in 7 patients (53.8%). According to the DAS starting dose, the incidence of pleural effusions was 11/35 (31.4%) in patients treated with 100 mg daily as compared to 2/10 (20%) in those patients treated with less than 100 mg daily (p = 0.494). Only 1 out of 6 patients with a concomitant lung disease developed pleural effusion. One patient showed a concomitant pericardial effusion. Concomitant lymphocytosis (peripheral absolute lymphocyte count > 4.0 × 10^3/L) was observed in 1 patient. Overall, 6 patients (46.1%) of all those patients showing pleural effusion, which represented 13.3% of the whole CML cohort) permanently discontinued DAS because of pleural effusion.

Dasatinib dose at different time points is reported in Figure 1. During treatment, 24 patients (53.3%) needed a dose reduction due to toxicity. In particular, dose reduction was required in 22/35 patients starting DAS 100 mg QD (62.8%) and in 2/10 patients starting DAS less than 100 mg QD (20.0%). DAS therapy was permanently discontinued in 9 patients (20.0%) because of toxicity (3 patients during the first 12-month period of treatment and 6 beyond). Apart from the 6 patients who discontinued because of pleural effusions, 1 patient discontinued for hematological toxicity, 1 patient for congestive heart failure and 1 patient for persistent chronic myalgia.

Dasatinib efficacy and overall response rate

All patients achieved a CHR (100%). Overall, 42/45 patients (93.3%) achieved (at any time) a CCyR, 35 out of 45 (77.7%)
gained MMR and 24/45 (53.3%) DMR (MR4 or MR4.5). Two patients showed primary resistance to DAS and 1 patient discontinued treatment (<3 months) due to toxicity (anemia, grade 3). The cytogenetic and molecular actual responses at different time points are depicted in supplementary Table 3. One-year and 2-year cumulative incidence of DMR was 38.4% (95%CI 24.1–52.7) and 55.6% (95%CI 39.9–71.3), respectively (Figure 2). After a median observation period of 42.6 months (IQR 20.4–63.3 months), only 1 patient (2.2%) progressed into a blast phase after 13 months from DAS therapy. Eight patients died (1 because of progression to blast phase and 7 from CML-unrelated reasons). Cumulative EFS and OS at 36 months were 64.7% (95%CI 49.4–80.0) and 82.3% (95%CI 70.3–94.3), respectively (Figures 3 and 4).

**Discussion**

Imatinib therapy is widely used in the frontline management of older CML patients because it is usually considered the safest treatment regarding patients’ performance status, comorbidities and associated medications [9,10,14,15,22–24]. However, second-generation TKIs can be also selected as frontline treatment strategies according to the patients’ baseline characteristics. Recently, a sub-analysis of the Evaluating Nilotinib Efficacy and Safety in Clinical Trials as First-Line Treatment (ENEST1st) trial investigated Nilotinib efficacy and safety in a group of older patients (n = 52) aged ≥75 years [19]. This study showed that advanced age was not relevant as a prognostic factor in the achievement of clinical responses, and safety issues were comparable to those observed in younger people with the exception of cardiovascular events. Similarly, since few data are available in CML patients aged > 75 years and treated frontline with DAS, we performed this retrospective ‘real-life’ analysis of DAS treatment in CML-CP patients outside clinical trials. It is likely that our study was limited by the number of only 45 CP-CML patients and by the retrospective and observational nature, but we believe that our findings can allow clinicians to understand how investigational results might be translated into real-life patients’ management.

We are also aware that our cohort of patients might represent a selected population of older CML patients with good features at CML onset. However, it is worthy of note that a recent analysis on the choice of frontline TKI, in more than 1700 patients with CML in Italy, detected 26 patients.
(8.6%) among 300 very elderly subjects treated frontline with DAS [25].

Our study showed that DAS therapy might be effective also in older people with CML. In our series, DAS treatment revealed CCyR rates of 93.3%, MR3 rate of 77.7% and DMR of 53.3% as cumulative incidence. In addition, DAS-related grade 3/4 events, both hematological and non-hematological, were detected in 6 (13.3%) and 12 (26.6%) patients, respectively, and were quite comparable to those reported in the DASISION trial (where the median age of the enrolled patients was 49 years and cases aged >65 years represented only 8%) [4] as well as in another previous real-life study in patients aged > 65 years [26].

Furthermore, the present data were also compared with those achieved in patients > 60 years and treated with DAS in second or subsequent lines of therapy [27]: while clinical efficacy was superior in our cohort (as expected in a setting with less advanced disease) toxicities were similar.

We also reported a higher total incidence of DAS-related pleural effusions (28.8%) and 9 patients discontinued due to effusions. This finding was not unexpected since age has been already reported to be the only variable retaining a negative predictive role in multivariate analysis [28].

Overall, in our experience, DAS frontline therapy was permanently discontinued in 20% of the patients and we proceeded with a lower dose in half of the cases. In particular, DAS reduction was required in 62.8% of the patients starting DAS 100 mg daily whereas DAS therapy was reduced only in 20.0% of those patients starting with less than 100 mg daily. Therefore, our efficacy data seem to support the concept that lower doses of DAS might be as effective as standard doses in the setting of older CML people, having also a better safety profile [29], giving a higher pros/cons ratio and helping to maintain a good quality of life (QOL). In this view, clinical benefits were reported also for DAS dosage as low as 20 mg daily [30,31] and it might be speculated that lower
doses might become the initial drug approach for elderly patients, at least for those with a non-high-risk score.

In addition, a recent evidence-based study compared health-related quality of life (HRQOL) in newly diagnosed CML patients treated with either IM- or DAS-therapy, reporting only negligible differences between DAS and IM in the cohort of patients aged over 60 years [32]. Therefore, older patients with CML seem to have similar HRQOL profiles when treated with these two TKIs.

Moreover, we are aware that treatment-free remission (TFR) may not be the main goal for these aged CML patients. However, since evidence has shown that the use of second-generation TKIs may increase the proportion of potential candidates eligible for TKI discontinuation [33,34], frontline DAS therapy might be useful for selected older patients with CML, who, after achieving a sustained DMR, might be considered for a TFR opportunity or a possible treatment-free interval [35]. With this view, age older than 65 years has been recently identified as a prognostic factor in predicting a successful TFR [36].

In conclusion, our findings, even if limited by the observational and retrospective nature of the study, suggest that DAS therapy could have an important role also in the treatment-free remission setting, as compared to younger subjects, with an acceptable safety profile and with a possible opportunity of therapy discontinuation.

Disclosure statement

These Authors declare the following conflict of interest: FS: honoraria by Bristol Myers-Squibb, Incyte, Novartis, Pfizer; FDR: honoraria by Amgen, Bristol Myers-Squibb, Celgene, Incyte, Novartis, Pfizer. MB: honoraria by Novartis, Pfizer, Incyte, BMS/Celgene, AbbVie; MB0: honoraria by Amgen, Bristol Myers Squibb/Celgene, Incyte, Novartis, Pfizer, GC: honoraria by Novartis, Incyte, Pfizer; GR honoraria by Bristol Myers Squibb/Celgene, Novartis, Incyte, Pfizer; EA: honoraria by Bristol Myers Squibb/Celgene, Novartis, Incyte, Pfizer; Al honoraria by Novartis, Bristol Myers Squibb/ Celgene, Pfizer, Incyte; MT: honoraria by Bristol Myers Squibb/Celgene, Novartis, Pfizer, Incyte. MC: honoraria by Novartis. All other authors have no potential conflict of interests regarding the article.

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