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ORIGINAL ARTICLE

# Outcome of very elderly chronic myeloid leukaemia patients treated with imatinib frontline

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## Abstract

Very elderly (> 75 years) chronic myeloid leukaemia (CML) patients at diagnosis are sometimes treated with different doses of imatinib (IM) based on concomitant diseases and physicians' judgement. However, data on long-term follow-up of these patients are still lacking. To investigate treatment response and outcome, we retrospectively revised an Italian database of 263 very elderly CML patients receiving IM from the time of diagnosis. Median age at diagnosis was 78.5 years and 56% of patients had 2 or 3 comorbidities. A complete haematological and cytogenetic response were achieved in 244 (92.8%) and 184 (69.9%) patients, respectively. In 148 cases (56.2%), a major molecular response was observed, which was deep in 63 cases (24%). A blastic phase occurred in 11 patients (4.2%). After a median follow-up of 45.0 months, 93 patients have died (9 from disease progression) and 104 (39.5%) are still in treatment with IM. Incidence of grades 3–4 haematological and non-haematological toxicity was similar to those reported in younger patients. Five-year event-free survival was 54.5% and 45.2% in patients ≤ 80 years and > 80 years, respectively ($p = 0.098$). Five years OS was 75.7% and 61.6% in patients ≤80 years and > 80 years, respectively ($p = 0.003$). These findings show that IM plays an important role in frontline treatment of very elderly CML patients without increased toxicity and any effort to treat these patients with standard doses should be made in order to achieve responses as in younger subjects.

**Keywords** Chronic myeloid leukaemia · Elderly · Outcome · Tyrosine kinase inhibitor

## Introduction

Chronic myeloid leukaemia (CML) is a relatively rare disease, with a median age at diagnosis of 66 years in European countries [1–3]. This means that nowadays, up to 50% of CML patients are older than 60 years and that many more will be over 60 in the future.

Prior to the tyrosine kinase inhibitors (TKI) introduction, older age was considered an adverse prognostic factor and was included in two of the most used scoring systems, the Sokal score [4] and the Hasford score [5]. After the introduction of TKI in the treatment of CML, age lost most of its prognostic impact: several studies on efficacy and safety of imatinib showed that this drug overcame the negative effect of age on response rates [6–8].

More recently, the EUTOS long-term survival score (ELTS) provided a superior prognostic discrimination of the probabilities of CML-related death and overall survival compared with the Sokal, the Euro, or the EUTOS score [9];

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nevertheless, patient age is still included among the relevant variables.

All patients with CML, irrespective of their age, should be treated with TKI as first-line therapy. Despite this, management of elderly patients with CML is complex: progressive deterioration of performance status, presence of comorbidities, higher number of concomitant medications, worst tolerance to TKI treatment, and impaired physical functions are all reasons for fewer opportunities to be included in clinical trials. It is worth of note that the median age in population-based registries is significantly higher than that reported in clinical trials [3].

In particular, so called very elderly patients (older than 75 years) are rarely included in both company-sponsored and investigator-initiated clinical trials [10–13]. On the other hand, in the current clinical practice, imatinib is widely used also in very elderly patients, as yet [14]; however, data on depth of response and long-term follow-up based on "real-life" evaluations are still lacking.

To highlight these issues, we analysed data from a large cohort of CML patients aged 75 years old or more and treated with imatinib frontline.

## Patients and methods

### Patient and study design

Thirty-four Italian centres have collected retrospective data regarding 263 patients older than 75 years with newly diagnosed CML in chronic phase who were treated with imatinib between February 2002 and January 2016. Imatinib starting dose was not pre-defined, but based on physician's choice. Inclusion criteria were as follows:

- Confirmed diagnosis of Ph + CML in CP
- Age ≥ 75 years old
- Frontline treatment with imatinib at 400 mg or less initial dose: short time cytoreduction with hydroxyurea was allowed.

To reduce selection bias, all centres were asked to report all patients with inclusion criteria observed in the time period considered.

### Clinical parameters and toxicities

The following clinical features were recorded at diagnosis: age, gender, peripheral blood cell counts, spleen and liver enlargement, smoking habit, and number and type of concomitant diseases and drugs. Risk of progression was calculated according to the Sokal score because it was the most consolidate one and it was available for all patients [4].

Any clinical condition requiring a specific treatment was considered as a concomitant disease.

Haematologic and non-haematological toxicities were graded according to the WHO scale; for the purpose of the present study, we graded toxicities as "low" (1, 2) and "high" (3, 4) and as "early" and "late" if they occurred less or more than 6 months from imatinib start, respectively.

### Cytogenetic and molecular evaluation

Cytogenetic analyses to detect Philadelphia chromosome were performed on bone marrow (BM) aspirates 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 bone marrow interphase cells was used if less than 20 metaphases were evaluable and was performed with BCR-ABL1 non-signal, dual-colour, dual-fusion probes.

Real-time quantitative polymerase chain reaction (RT-Q-PCR) 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 Recommendation.

### Response definitions

Haematological and cytogenetic responses were categorized according to standard criteria [15]. As to molecular responses, major molecular response (MMR) 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) IS [16]. Those patients who were evaluated only with molecular analysis and had a BCR-ABL1/ABL1 ratio < 1% were considered as in complete cytogenetic response (CCyR) also.

Primary haematologic resistance was defined as failure to achieve a complete haematologic response (CHR) after 3 months of treatment; primary cytogenetic resistance was defined as failure to achieve CCyR after 12 months of treatment. Secondary resistance was defined as the loss of a previously achieved CHR, CCyR, or MMR at any time. Progression was defined as transformation into blastic or accelerated phases.

### Statistical analysis

Data were expressed as mean ± standard deviation (SD) (normally distributed data), median and interquartile range (IR) (non-normally distributed data), or as percentage frequencies, and within-patient comparisons were made by unpaired $t$ test and $\chi^2$ test, as appropriate, at significance levels of $p < 0.05$. All the endpoints of treatment efficacy (CHR, CCyR, and MMR) were calculated as incidence at any time.

Overall survival (OS) was calculated from the date of imatinib start to death due to any cause. Event-free survival (EFS) was calculated from the date of imatinib start to any of the following events: primary haematologic or cytogenetic resistance to imatinib, permanent imatinib discontinuation due to toxicity or any other unrelated cause (excluding discontinuation for a DMR), secondary haematologic or cytogenetic resistance to imatinib, death due to any cause. Cumulative incidence of progression was calculated from the date of imatinib start to any of the following events: primary resistance, secondary resistance, evolution in accelerated/blastic phase, considering imatinib discontinuation for toxicity and deaths for unrelated causes as competing events. Survival probabilities were calculated using the Kaplan–Meier method. Survival comparisons were made by the log-rank test. A multivariate Cox analysis was used to assess the relationship between variables of interest and outcome.

All calculations were made using a standard statistical package (SPSS for Windows Version 15.0; Chicago, IL).

## Results

### Patient characteristics

A total of 263 very elderly patients (median age 78.5, range 75.0–93.5) were evaluated; ninety-six patients (36.5%) were older than 80 years and 21 (7.9%) were older than 85 years. Table 1 describes the main clinical features at diagnosis in the whole cohort of patients.

The most common concomitant diseases at diagnosis are reported in Table 2. A previous neoplastic disease (with the exclusion of squamous cell carcinoma) was recorded in fifty-nine cases (22.4%): different types of tumours are listed in Table 2.

Intake of concomitant drugs is summarized in Table 1. The median number of concomitant drugs was 4 (range 1–12) and only 14 patients (5.3%) did not take any medication. Anticoagulant or antiplatelet therapy was taken in 151 patients (57.4%), while 115 patients (43.7%) were taking proton pump inhibitors.

Median time between diagnosis of CML and imatinib initiation was 0.8 months (range 0.3–1.6). In 184 patients (69.9%) hydroxyurea was administered as pre-treatment cytoreduction before imatinib. The initial dose initial of imatinib was 400 mg/day in 180 patients (68.4%), 300 mg/day in 67 patients (25.5%), and < 300 mg/day in 16 (6.1%).

Among patients aged ≥ 80 years, the rate of subjects who received ≤ 300 mg as initial dose was significantly higher than among patients aged < 80 years (58/96 (60.4%) vs 46/167 (27.5%), $p > 0.001$).

**Table 1** Clinical features at diagnosis

| | |
|---|---|
| No. of patients | 263 |
| Male/female, *n* (%) | 128/135 (48.7/51.3) |
| Median age, years (range) | 78.5 (75.0–93.5) |
| Sokal risk, *n* (%) | |
| Low | 1 (0.4) |
| Intermediate | 171 (68.4) |
| High | 78 (31.2) |
| Not evaluable | 13 |
| Median Hb, g/dl (range) | 12.3 (6.0–15.7) |
| Median WBC, $\times 10^9$/L (range) | 66.4 (5.3–354.0) |
| Median PLTs, $\times 10^9$/L (range) | 496 (140–2,081) |
| Spleen enlargement, cm below costal margin (%) | |
| Not palpable | 170 (66.6) |
| 1–5 | 74 (29.1) |
| > 5 | 11 (4.3) |
| Not evaluable | 8 |
| Smokers, *n* (%) | |
| Yes | 11 (4.7) |
| Ex | 61 (26.5) |
| No | 159 (68.8) |
| Not evaluable | 32 |
| Comorbidities at diagnosis, *n* (%) | |
| 0–1 | 63 (23.9) |
| 2–3 | 147 (55.8) |
| ≥ 4 | 53 (20.3) |
| Concomitant drug intake, *n* (%) | |
| No drugs | 14 (5.3) |
| 1–3 | 104 (39.5) |
| 4–5 | 80 (30.4) |
| 6–12 | 65 (24.7) |

### Toxicity and dose modification

Haematological and non-haematological toxicities are described in the Table 3. Grades 3–4 haematological toxicity was reported in 57 patients (21.6%): anaemia in 6.8%, neutropenia in 9.8%, and thrombocytopenia in 7.2%.

Non-haematological toxicities of all grades were recorded in 164 patients (62.3%): the most common were fluid retention (31.1%), cutaneous side effects (15.9%), and musculoskeletal pain (15.5%). Grades 3–4 non-haematological toxicities were reported in 51 patients (19.4%), the most common being fluid retention and cutaneous side effects (3.4% each), followed by pleural effusion and cardiovascular events (2.2% each).

According to age at diagnosis, there was no difference in the rates of both haematological (all grades 74/167 (44.3%) vs 45/96 (46.8%), $p = 0.688$; grades 3–4 34/167 (20.3%) vs 23/96 (23.9%), $p = 0.495$) and non-haematological toxicities (all

**Table 2** Most common comorbidities, *n* (%)

| | |
|---|---|
| Arterial hypertension | 150 (61.9) |
| Arrythmias | 41 (15.5) |
| Dyslipidemia | 28 (10.6) |
| Cardiovascular disease | 85 (32.3) |
| Diabetes | 50 (19.7) |
| Previous neoplasm | 59 (22.4) |
| Gastro intestinal | 18 (30.5) |
| Prostatic | 14 (23.7) |
| Breast | 11 (18.6) |
| Genitourinary | 6 (10.1) |
| Lung | 5 (8.4) |
| Non-Hodgkin lymphoma | 4 (6.7) |
| Ph-neg acute lymphoblastic leukaemia | 1 (1.6) |
| Gastro intestinal disease | 59 (22.4) |
| Kidney disease | 26 (9.8) |
| Chronic bronchitis | 25 (9.5) |
| Neurologic or psychiatric disorders | 26 (9.8) |
| Thyroid dysfunction | 22 (8.3) |
| Benign prostatic hyperplasia | 22 (8.3) |
| Other | 28 (10.6) |

grades 107/167 (64.0%) vs 57/96 (59.3%), $p = 0.449$; grade 3–4 33/167 (19.7%) vs 18/96 (18.7%), $p = 0.842$) between patients aged < 80 and ≥ 80 years.

During the observation period, 98 patients (37.2%) did not require any dose reduction/discontinuation of imatinib due to toxicity. A temporary dose reduction was required in 43 patients (16.5%), while a permanent dose reduction was required in 122 patients (46.3%). In particular, permanent imatinib reduction was required in 88/180 patients (48.8%) with initial dose of 400 mg (final reduced dose of 300 mg in 63 cases, 200 mg in 22 cases, and 100 mg in 3 cases, respectively), in 18/67 patients (26.4%) with initial dose of 300 mg (final reduced dose of 200 mg in 17 cases and 100 mg in 1 case), and in 3/17 patients (17.6%) with initial dose of 200 mg.

Seventy-five patients (28.5%) needed a temporary discontinuation of treatment due to toxicity, lasting less than 6 weeks in 63 cases and more than 6 weeks in the remaining 12 cases. In 30 patients (11.4%), imatinib was permanently interrupted due to early (13 cases) or late (17 cases) toxicities.

The rates of patients who needed dose reduction, temporary discontinuation, or permanent interruption according to age at diagnosis are reported in Table 4, without differences between those aged < 80 and ≥ 80 years.

## Response to treatment

As to cumulative response, 244 patients (92.8%) achieved a CHR after a median period of 1.0 month since imatinib initiation, 13 patients (4.9%) discontinued imatinib due to early toxicity, 4 (1.5%) were primary resistant, and 2 (0.8%) died from unrelated cause early after imatinib initiation (1 from previous neoplastic disease and 1 from pre-existing cardiologic disease).

**Table 3** Haematological and non-haematological toxicities

| | All grades (*n* pts) | All grades (%) | Grades 3–4 (*n* pts) | Grades 3–4 (%) |
|---|---|---|---|---|
| Haematological toxicity | 119 | 45.2 | 57 | 21.6 |
| Anaemia | 82 | 31.1 | 18 | 6.8 |
| Neutropenia | 39 | 14.8 | 26 | 9.8 |
| Thrombocytopenia | 52 | 19.7 | 19 | 7.2 |
| Non-haematological toxicity | 164 | 62.3 | 51 | 19.4 |
| Cutaneous | 42 | 15.9 | 9 | 3.4 |
| Pleural effusion | 12 | 4.5 | 6 | 2.2 |
| Acute myocardial infarction | 5 | 1.9 | 5 | 1.9 |
| Diarrhoea | 18 | 6.8 | 5 | 1.9 |
| Nausea, vomiting, abdominal pain | 25 | 9.5 | / | / |
| Gastro intestinal haemorrhage | 3 | 1.1 | 3 | 1.1 |
| Fluid retention | 82 | 31.1 | 9 | 3.4 |
| Musculoskeletal pain | 41 | 15.5 | / | / |
| Asthenia | 13 | 4.9 | / | / |
| Pancreatic toxicity | 2 | 0.8 | 2 | 0.8 |
| Laboratory abnormalities | 13 | 4.9 | / | / |
| Cardiovascular | 15 | 5.7 | 6 | 2.2 |
| Other | 16 | 6.1 | 9 | 3.4 |

**Table 4** Dose management due to toxicity according to age at diagnosis

| | Age < 80 years | Age ≥ 80 years | *p* |
|---|---|---|---|
| Permanent dose reduction, *n* (%) | 76/167 (45.5%) | 46/96 (48%) | 0.706 |
| Temporary imatinib discontinuation, *n* (%) | 48/167 (28.7%) | 27/96 (28.1%) | 0.915 |
| Permanent imatinib interruption, *n* (%) | 20/167 (12%) | 10/96 (10.4%) | 0.702 |

Among these 244 patients in CHR, 12 refused any other cytogenetic or molecular evaluation, 30 achieved CHR only, and 202 (76.8% of all 263 patients) achieved a cytogenetic response, which was partial in 18 patients and complete in 184 for a cumulative incidence of CCyR of 69.9%. Of the 184 patients in CCyR, 148 (56.2% of all 263 patients) achieved a MMR and 63 of them (24% of all 263 patients) obtained a DMR. Different responses to treatment according to age at diagnosis are reported in the Table 5.

## Follow-up and survival

After a median follow-up of 45.0 months (range 12–173 months) (IQR 22.3–72.0) from imatinib start, 93 patients have died (9 from disease progression and 84 from unrelated causes), 26 were lost to follow-up, and 144 are still alive: 104 are still in treatment with imatinib, 8 discontinued imatinib for sustained DMR after a median time of 105.7 months (range 103–109.4), and 32 switched to 2nd generation TKI (nilotinib in 15 patients and dasatinib in 17 patients) due to toxicity or primary/secondary resistance to imatinib. No patient died of treatment-related toxicity.

Evolution to blastic phase occurred in 11 patients (4.2%) after a median interval from imatinib start of 12.9 months (range 1.0–73.9): it was myeloid in 8 patients and lymphoid in 3 patients. Only 2 out 11 patients who evolved in blastic phase have previously achieved a CCyR. Evolution to blastic phase was observed in 6 patients younger than 80 years and in 5 patients older than 80 years, without statistical difference. A secondary neoplasm occurred in 22 patients (8.4%) and 11 of them died from this cause.

Five-year cumulative incidence of progression of the whole cohort was 25.6% (CI 95% 19.3–31.9) (Fig. 1): according to age, 5-year cumulative incidence of progression was 26.8% (CI 95% 18.8–34.8) in patients < 80 years compared to 22.6% (CI 95% 13.4–31.8) in patients ≥80 years ($p = 0.961$).

Five-year EFS of the whole cohort was 51.2% (CI 95% 44.8–57.6): according to age, 5-year EFS was 54.5% (CI 95% 46.3–62.7) in patients < 80 years compared to 45.2% (CI 95% 34.0–56.4) in patients ≥ 80 years ($p = 0.098$) (Fig. 2).

Five-year OS of the whole cohort was 70.9% (CI 95% 64.6–77.2): according to age, 5-year OS was 75.7% (CI 95% 68.5–82.9) in patients < 80 years compared to 61.6% (CI 95% 50.0–73.2) in patients ≥ 80 years ($p = 0.003$) (Fig. 3).

## Discussion

Various studies have already shown that imatinib has greatly reduced the negative impact of age on response rate [6–8, 18] compared with the IFN era. The toxicity profile of imatinib appears to be very similar between younger and older patients, but some studies reported a higher incidence of grades 3–4 haematologic and non-haematologic adverse events in elderly patients [6, 7, 17], leading to a higher rate of discontinuation, dose reductions, and worst adherence to treatment. Previous data show that age is not necessarily a contraindication for TKI use. In CML, the efficacy of TKIs has been shown to be independent of age [20]. On the other hand, the role of imatinib in patients older than 75 years is still debated: in some studies, there was no evidence of longer survival compared to pre-imatinib era treatment strategies [19, 21]. As a consequence, in the current clinical practice, imatinib is used in very elderly patients with a wide range of initial doses and dose adjustments during follow-up.

We previously reported on the cytogenetic and molecular response and early toxicities in a cohort of very elderly patients treated with imatinib in 1st or 2nd line [14]: therapeutic results were encouraging with an acceptable safety profile, but the short follow-up did not allow long-term evaluations.

In the present study, only very elderly patients treated with frontline imatinib were considered for at least two main

**Table 5** Response to imatinib according to age at diagnosis

| | Age < 80 years | Age ≥ 80 years | *p* |
|---|---|---|---|
| Complete haematologic response, *n* (%) | 154 (92.2) | 90 (93.7) | 0.439 |
| Complete cytogenetic response, *n* (%) | 123 (73.6) | 61 (63.5) | 0.088 |
| Major molecular response, *n* (%) | 97 (58.0) | 51 (53.1) | 0.435 |
| Deep molecular response, *n* (%) | 40 (23.9) | 23 (24.0) | 0.852 |

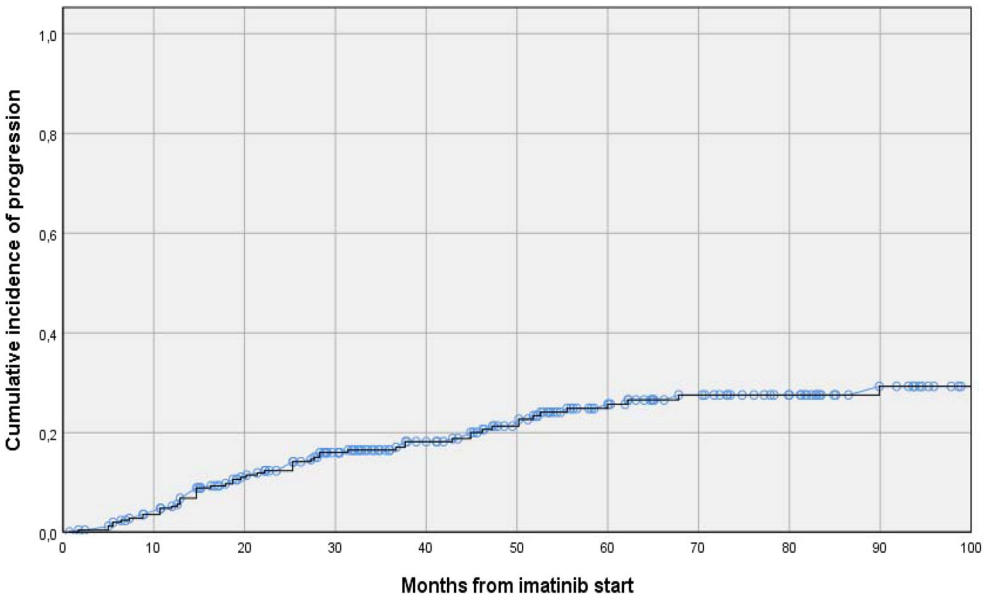


**Fig. 1** Cumulative incidence of progression of the whole cohort

reasons: to evaluate an homogeneous cohort of patients and to present data useful for clinical current practice with the treatment generally employed in this patient subgroup. In this sense, we did not consider in the present analysis those patients treated after 2010 with other TKI inhibitors (dasatinib or nilotinib), as we know that these drugs were very rarely prescribed in first-line approach of very elderly patients. Moreover, the greater number of patients and the longer

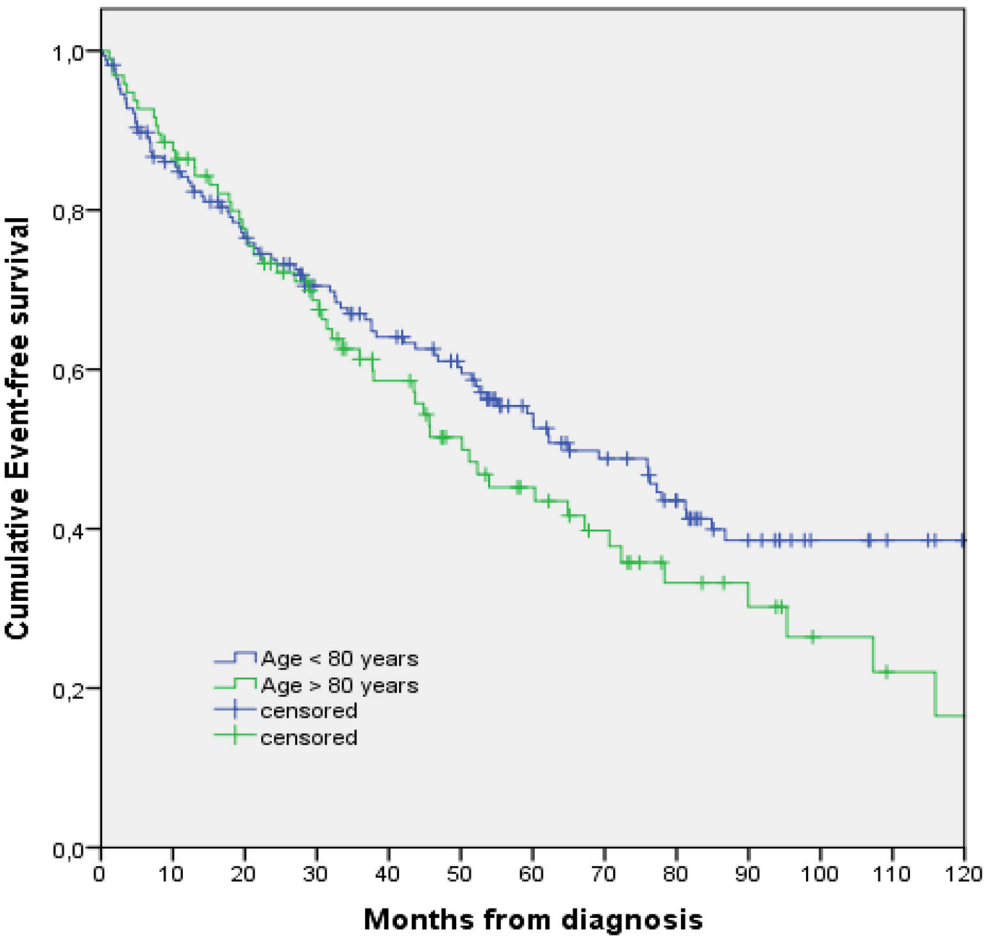


**Fig. 2** Event-free survival according to age at diagnosis

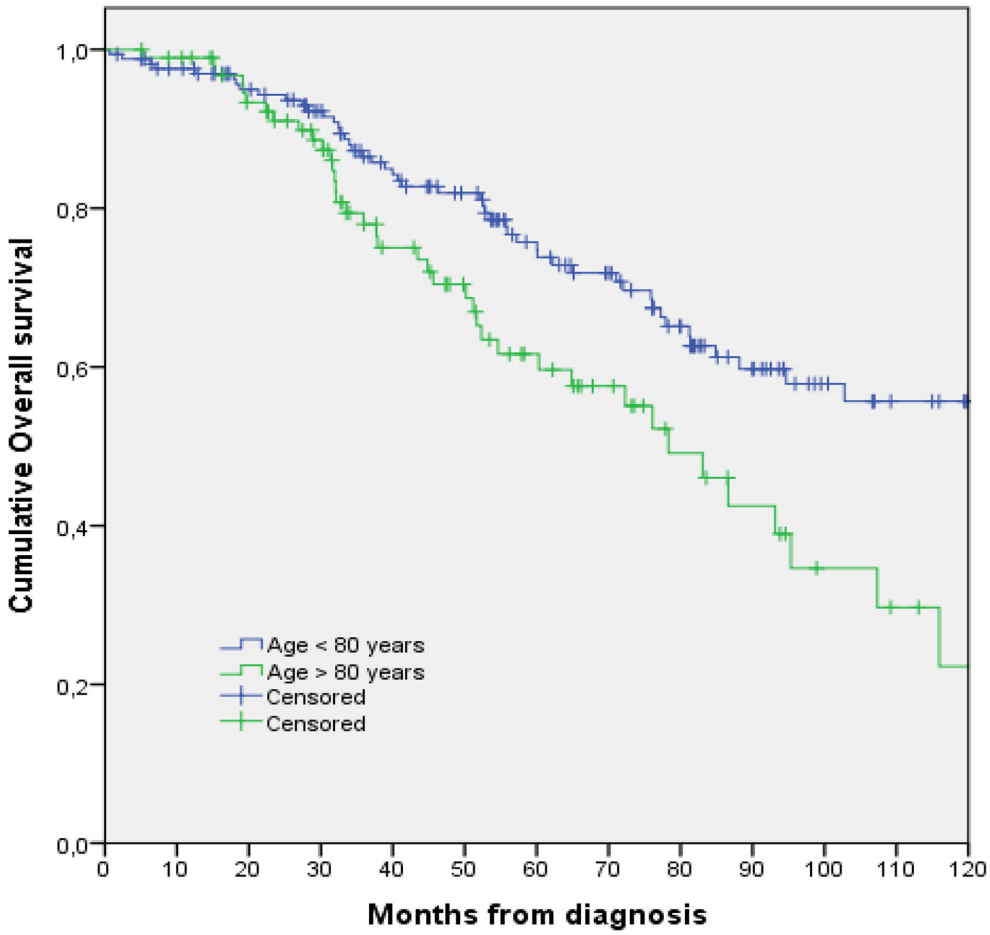


**Fig. 3** Overall survival according to age at diagnosis

period of observation compared with our previous study allowed us to evaluate long-term follow-up.

More than two-third of patients received a standard initial dose of imatinib, while only 83 patients (31.5%) of cases started therapy at less than 400 mg. Unfortunately, the database did not allow us to accurately establish the average dose of each patient or the cumulative dose during each year.

Cumulative rates of CCyR and MMR were remarkable, being 69.9% and 56.2% respectively; grades 3–4 haematological and non-haematological toxicities were relatively uncommon and their incidence was similar to those reported in younger patients.

Due to the retrospective nature of our study, a possible under-estimation of adverse events should be considered, mainly for the difficulty in accurately reporting grades 1 and 2 adverse events.

Nonetheless, the relatively long observation time from imatinib start (median follow-up of almost 4 years) allows for some considerations to be drawn. As expected [7], the rate of dose modification was higher than in younger patients: 60% of patients needed a dose reduction, which was permanent in more than half of them. However, the dose adaption was able to limit permanent imatinib discontinuation in only 11% of patients, a rate similar to those reported in clinical controlled studies involving younger cohorts.

The majority of these patients had already reached an optimal response at the time of reduction, and thus the high rate of dose reduction did not translate into a lower efficacy of imatinib in the long-term. It is worth of note that there were no differences in the toxicity profile, in the dose management, and, eventually, in the long-term outcomes between patients aged < 80 years and > 80 years.

As to CML evolution, blast crisis was reported in 4.2% of patients, without any difference between patients younger and older than 80 years; the vast majority of deaths were due to causes not related to CML, as expected in a cohort of patients aged > 75 years [18]. In addition, the achievement of a stable DMR led to a successful imatinib discontinuation in selected patients; although in a smaller percentage, these results resemble those reported in younger patients and suggest that the goal of a treatment-free remission may be achievable even in very old individuals.

Finally, the observed 5-year OS rate of 70.9% in the whole cohort was very encouraging and similar to that of a matched-age general population [22].

Data regarding quality of life and adherence to treatment were not available for this study because at the time of our data collection, physicians were not used to gathering these very important information.

## Conclusions

All the patients with CML, irrespective of their age, should be treated with TKI as first-line therapy. Imatinib should be considered the best option to manage those very elderly patients with severe comorbidities, due to the lower profile of toxicity and its efficacy; an initial dose reduction, at least in selected patients, represents a reasonable option in this setting. Specific clinical trials addressing relevant issues for clinical practice in elderly patients should be promoted.

We are aware that the present study suffers from the limitations common to any retrospective analysis but it represents a "real-life" depiction of "very elderly" patients that are underrepresented in clinical trials and in the literature.

### Compliance with ethical standards

Monica Crugnola, Fausto Castagnetti, Massimo Breccia, Elisabetta Abruzzese, Gabriele Gugliotta, and Fabio Stagno declare that they received speaker honorarium from Novartis, BMS, Incyte, Pfizer, Amgen. Massimiliano Bonifacio declares research funding from Novartis and speakers honorarium from BMS, Incyte, Pfizer. No conflict of interest has been declared from other authors. All procedure performed in this study were in accordance with ethical standards and with the Helsinki declaration. Informed consent was obtained from all individual participants included in this study.

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