Chapter 5
Chronic Myelogeneous Leukemia

Andreas Hochhaus and Susanne Saussele

Abstract The impact of age as a poor prognostic factor in chronic myeloid leukemia (CML) has been well described. In the interferon era, elderly patients diagnosed with CML in chronic phase had shorter survival compared to younger patients. With the advent of targeted therapy with imatinib, studies described consistently improved responses in elderly late chronic phase patients treated with imatinib after IFN failure, with similar overall survival compared to the younger population.

Imatinib in newly diagnosed older patients showed similar rate of cytogenetic and molecular responses compared to younger patients. Few data are available relating elderly CML patients subset treated with 2nd-generation TKIs after resistance/intolerance to imatinib: both nilotinib and dasatinib have demonstrated efficacy and limited toxicity profile as in younger patients. The aim of this review is to highlight the fact that elderly CML patients can benefit from targeted therapy with limited adverse events.

Keywords Chronic myelogeneous leukemia • Tyrosine kinase inhibitors • Imatinib • Nilotinib • Dasatinib

Introduction

Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder originating from the translocation t(9;22)(q34;q11) with the resulting Philadelphia chromosome (Ph) 22q-. Juxtaposition of the ABL gene on chromosome 9 with the BCR

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Prof. Dr. A. Hochhaus (✉)
Abteilung Hämatologie/Onkologie, Klinik für Innere Medizin II,
Universitätsklinikum Jena, Erlanger Allee 101, Jena 07740, Germany
e-mail: andreas.hochhaus@med.uni-jena.de

S. Saussele, MD
III. Medizinische Universitätsklinik, Medizinische Fakultät Mannheim,
der Universität Heidelberg, Mannheim, Germany

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gene on chromosome 22 leads to a fusion gene, which is translated to a novel protein with abnormal tyrosine kinase activity. The incidence rate of CML varies from 0.6 to 2 cases per 100,000 people/year and increases with age, with a male prevalence. Median age at presentation is estimated around 65 years, but age figures differ between cancer registries and clinical trials by 10–20 years. Most clinical trials underestimate the real age of CML patients in the whole population and elderly patients are underrepresented in most studies. As a prominent example, the IRIS trial, which led to approval of imatinib for chronic phase CML, excluded patients >70 years of age [1]. A German study, aimed to determine population-based age and gender-specific incidence of CML, reported a median age of CML patients of 60.3 years, with a male/female ratio of 1.66. The crude incidence for CML was 0.79, whereas age-specific incidence was 0.57 for patients aged less than 65 years, and 1.91 for patients aged >65 years. Overall, only 64 % of patients were included in clinical trials: differences between patients who participated to trials vs patients who did not were in age (10.7 years younger), low prognostic score and management in hospital. Elderly patients had a 3.8-times lower probability to be enrolled in a clinical trial [2].

Epidemiology

The increasing age of patients is considered an important factor influencing decisions in daily clinical practice. Although there is, in principle, equal access for medical care for all patients across Europe, patients' age seems to be used as a selection criterion for treatment management [3]: An epidemiological survey in the southeast of Germany observed that only 59 % of the CML patients (median age of 64 years, no inclusion in investigational studies) received imatinib alone, 10.2 % received imatinib in combination with hydroxyurea or interferon alpha, 25.8 % were treated with hydroxyurea and 7.6 % received interferon alpha. This study, conducted in 2006, had used the database of the Bavarian association of statutory health-insurance-accredited physicians, covering 83.5 % of all patients treated outside a clinic's care in Bavaria with 10.4 million people [3]. The use of pre-imatinib-era treatment strategies such as hydroxyurea, ara-C, or interferon alpha by some physicians as salvage treatment after imatinib failure and unsuitability of stem cell transplantation (SCT) still occurs despite the growing availability of newer tyrosine kinase inhibitors (TKIs). Age is no longer a risk factor for worse outcome since the introduction of imatinib as targeted therapy [4, 5]. With imatinib therapy, older age appears to have lost much of its prognostic relevance suggesting that poor prognosis previously observed with older age was rather related to treatment-associated factors than to disease biology of CML in older patients [4]. As the long-term outcome is similar to that of younger patients [5], there is no reason to deprive older patients of the treatment with TKIs.

Furthermore, patient management by a hospital is also a significant positive factor for participation in clinical trials, as the result from epidemiological observations

suggests [2]. CML patients treated in hospitals have a six-fold higher chance of being included in clinical trials than patients outside a hospital. Younger CML patients are more likely treated in university hospitals or specialized cancer treatment centers where study infrastructure for patient safety and data management are easily available. This patient group has, in general, a good prognosis and is likely to be a candidate for participation in clinical trials. In contrast, elderly patients are mainly cared for in general hospitals or in speciality practices with a reduced access to investigational therapies [6]. Reasons for non-inclusion of elderly patients in trials might also be, in some cases, immobility and comorbidities and, in others, the reluctance of physicians to admit elderly patients [2].

Current Treatment Standards

The European LeukemiaNet (ELN) has developed recommendations for medical management of patients of all ages with CML in daily clinical practice [7]. Thus, CML patients should be treated under the guidance of an experienced physician affiliated to a center with appropriate facilities for cytogenetic and molecular monitoring. Furthermore, the centers should offer and ask patients to be registered in clinical studies.

It is recommended that in practice, outside of clinical trials, the first-line treatment of chronic phase CML can be any of the three TKIs that have been approved for this indication and are available almost worldwide, namely imatinib (400 mg QD), nilotinib (300 mg BID), and dasatinib (100 mg QD). These three TKIs can be used also in second or subsequent lines, at the standard, or at a higher dose (400 mg BID for imatinib, 400 mg BID for nilotinib, and 70 mg BID or 140 mg QD for dasatinib). Bosutinib (500 mg QD) has been approved for patients resistant or intolerant to prior therapy. Ponatinib (45 mg QD) has also been approved for patients resistant or intolerant to prior TKI therapy, in particular patients with the T315I BCR-ABL mutation. Allogeneic SCT will continue to be an important treatment for patients who fail to respond durably to TKIs and are eligible for SCT. It seems reasonable that for patients in CP, transplant should be reserved for those who are resistant or intolerant to at least one 2nd generation TKI. The nature of conditioning therapy is controversial because in chronic phase there is no evidence at present that myeloablative conditioning offers any advantage over reduced intensity preparative regimens.

Current Diagnostic Approaches

A careful and close monitoring of treatment response and of prognostic factors is required to identify development of resistance to therapy, intolerance or noncompliance or progression to advanced-phase disease. Monitoring can be performed

using molecular or cytogenetic tests, or both, depending on local facilities and on the degree of molecular standardization of the local laboratory.

Molecular testing should be performed by RQ-PCR to measure the BCR-ABL transcript level, that is reported on the international scale (IS). RQ-PCR should be repeated every 3 months until major molecular response (MMR, BCR-ABL IS $\leq$0.1 %) is achieved, then every 3–6 months. If transcript levels have increased >5 times in a single follow-up sample and MMR was lost, the test should be repeated in a shorter time interval, and patients should be questioned carefully about compliance. If cytogenetics is used, it must be performed by banding analysis of at least 20 bone marrow cell metaphases, at 3, 6, 12 months, until a CCyR is achieved.

Clonal chromosome abnormalities in Ph negative cells, which may develop in up to 10 % of responders and are more frequent in older patients, are a warning only in case of chromosome 7 involvement [7].

In routine clinical practive, however, a survey of 956 physicians in the US and in Europe suggests that treatment practices in some areas of CML management are not in line with the international recommendations [8]. Problematic areas were suboptimal timing of treatment decisions during monitoring, and unawareness of new molecular monitoring techniques and of the potential benefit of new treatment options.

Prognostic Scores

Older age was referred to be a poor prognostic variable: a negative effect on survival was reported when patients were treated with therapeutic strategies including conservative drugs (busulfan, hydroxyurea, interferon alpha) or transplant procedures. Thus, age was an important factor in the calculation of the Sokal and Euro (Hasford) scores. In the IFN era, older age was a consistently poor prognostic factor, probably related to inadequate drug delivery and treatment toxicity experienced in this setting. In the era of TKI, the outcome of elderly patients was extensively investigated. Most of the literature regarding efficacy and safety of imatinib revealed that this drug eliminated the negative effect of age on response rate and survival. Therefore, a new prognostic score was proposed (EUTOS score), based on 2,060 patients treated front-line with imatinib. A multivariate analysis was performed to identify prognostic factors at baseline with impact on the CCyR status at 18 months. The best proposed model included only basophils and spleen size. Age, as other candidate variables, such as blasts, lost their significance. The simple formula proposed was:

$$\text{EUTOS score} = \left(7 * \text{basophils in \%}\right) + \left(4 * \text{spleen size in cm below costal margin}\right)$$

with indication of high risk by a score >87 and low risk by a score $\leq$87. Indirectly, the analysis proved that advanced age did not represent an adverse prognostic factor in the TKI era [9].

Interferon Alpha in Elderly Patients

To assess the long-term outcome of older patients with BCR-ABL positive CML, 199 patients aged ≥60 years representing 23 % of 856 patients enrolled in the German randomized CML-studies I (interferon alpha (IFN) vs hydroxyurea (HU) vs busulfan and II (IFN + HU vs HU alone) were analyzed after a median observation time of 7 years. The 5-year survival was 38 % in older and 47 % in younger patients ($P < 0.001$). Adverse effects of IFN were similar in both age groups, but IFN dosage to achieve treatment goals was lower in older patients [10].

The MD Anderson Cancer Center (MDACC) reported the experience of IFN therapy in CML patients ≥60 years. Patients were treated with IFN at a median dose of $5*10^6/m^2$ MU as single agent or in association with other substances. Older patients represented 13 % of an overall population of 274 newly diagnosed patients enrolled in trials. With IFN therapy, 51 % had a cytogenetic response with 20 % of CCyR. These results were not different from those reported in the younger population. The most frequent side effect reported was neurotoxicity in 31 % of patients [11]. In 1998, the Austrian group reported efficacy and safety data relating 41 elderly patients treated with IFN at daily dose of 3.5 MU, alone or in combination with low dose cytarabine [12]. Slight difference was reported between elderly and younger patients in terms of CCyR (10 % vs 13 %), but this was not statistically significant.

The Effect of Imatinib in Older Late Chronic Phase Patients

The first extended analysis on efficacy and safety of imatinib in older patients aged >60 years was reported by Cortes et al. of the MDACC [4]; 187 patients with newly diagnosed CML treated with imatinib first line, of whom 49 (26 %) were in the older age, were compared with 351 patients in late chronic phase after IFN failure, of whom 120 (34 %) were older than 60 years. The cut-off of 60 years was chosen because this limit was identified to be of prognostic relevance in previous multivariate analysis performed in CML cases, but also because patients aged more than 60 years were usually ineligible for transplant procedures and had also poor tolerance to IFN therapy. In early chronic phase, cytogenetic responses were similar to those of younger patients. Only two of the elderly patients were reported to suffer from transformation to advanced phases of disease compared to 5 in the younger subset. In late chronic phase patients, 120 were older (34 %), with a lower incidence of additional chromosome abnormalities compared to younger subjects, more frequent leukocytosis and bone marrow basophilia. 44 % of older patients achieved a CCyR compared to 56 % in younger patients. In multivariate analysis for predicting factors for survival, older age was in chronic and advanced disease not associated to poor outcome.

Rosti et al. reported for the GIMEMA group on 284 patients in late chronic phase CML treated with imatinib 400 mg/day. CCyR rates were lower in older patients (≥65 years) than in younger patients (<65 years) with more adverse events in older patients, but nevertheless overall survival was the same in both age groups [5]. The MDACC and the GIMEMA reports both demonstrated that the poor prognostic impact of older age was minimized by imatinib [13].

Imatinib in Newly Diagnosed Untreated Elderly Patients

Gugliotta et al. reported similar rates of CCyR and MMR in 115 patients ≥65 years among 559 patients in early CP treated with imatinib 400 or 800 mg/day. No relevant differences were observed between older and younger patients except for hemoglobin level, WBC count (median 42/nl in elderly vs 61/nl in younger) and spleen size [14].

In a multicenter study of high-dose imatinib in 115 newly diagnosed patients in chronic phase Cortes et al. reported a similar dose-intensity and no difference in adverse events at any severity for patients <65 and ≥65 years. MMR was achieved by 79 % of patients who received at least 90 % dose-intensity (RIGHT study, [15]). Latagliata et al. analyzed 117 patients in early chronic phase CML under imatinib treatment with 300–800 mg/day. No significant difference in the rate of CCyR was reported in older (≥65 years) compared to younger (<65 years) patients. Adverse events (WHO grades 3–4) were more frequent and rates of dose reduction and discontinuation of imatinib were higher in older patients [16]. Recently, the Spanish group reported the results of the observational ELDERGLI study [17]: patients age was >70 years with newly diagnosed chronic phase CML or >65 years in late chronic phase. Thirty-six patients were included with a median age of 76.6 years and a female predominance. Most frequent comorbidities reported were cardiovascular events and type II diabetes mellitus. After a median follow up of 24 months, increasing response rates were observed, with 83 % CCyR and 69 % MMR after 18 months. Only one patient progressed to blast crisis. Hematological toxicity recorded was moderate with overall 8 % anemia and thrombocytopenia and 11 % neutropenia of all grades. Most frequent non-hematological side effects were superficial edema that accounted for 44 % (grade 1/2), diarrhea (27.7 %), and infections (25 %), which caused death in two patients. The group considered imatinib a safe and effective drug also for older patients.

Strategies to Overcome Resistance in Older Patients

Few data were reported for older patients rescued with nilotinib or dasatinib after resistance or intolerance to imatinib. A subanalysis of a phase II trial with nilotinib at the dose of 400 mg BID reported on 98 patients out of 321 enrolled older patients >65 years with 8 % of these patients being >80 years of age. Baseline features were

similar between younger and older patients. The rate of discontinuation was 18 %, whereas the CCyR rate was 38 % compared to 44 % in younger patients. One-year estimated overall survival was 91 % for older versus 97 % for younger patients. Similar frequencies of side effects were reported in older and younger patients: in particular, as regards biochemical abnormalities, 23 % of older patients experienced lipase elevation compared to 14 % of younger patients, while 3 % of older patients experienced total bilirubin increase compared to 9 % for younger patients. No particular differences were revealed between the age groups in terms of hematological side effects and in terms of pleuro/pericardial effusions or bleeding events. 4 % of older patients had a myocardial infarction compared to 1 % in younger patients. For the QT interval according to Fridericia formula (QTcF), prolongation higher than 500 ms was recorded in 2 % of older compared to 1 % in younger patients [18].

The expanding nilotinib access study (ENACT, [19]) enrolled 1,422 CP-CML imatinib resistant and/or intolerant patients, of whom 452 patients were aged >60 years and 165 of these were >70 years old. A higher proportion of patients aged >65 years enrolled had a longer median duration of CML and most of them were enrolled for intolerance. The results showed that about 50 % of patients aged >65 years experienced nilotinib dose interruptions and reductions due to side effects lasting more than 5 days. In this trial, 41 % of older patients achieved MCyR with 31 % achieving CCyR (33 % of elderly >70 years). In terms of safety, 56 % of older patients experienced grade 3/4 toxicity, most frequently hematological (thrombocytopenia 24 % and neutropenia 14 %). Patients who had experienced pleural effusion during dasatinib treatment did not have a recurrence of the same effect during nilotinib treatment.

Recently, a retrospective Italian analysis on 125 CP-CML patients resistant to imatinib aged >60 years was published [20]. Median age at the start of dasatinib treatment was 69 years, with a high rate of intermediate and high Sokal risk strata. Fifty-seven patients were pretreated and resistant to IFN before imatinib. Fifty-eight patients had received high-dose imatinib for resistance to the standard dose. Thirteen patients were treated with dasatinib for intolerance and 112 for resistance. The starting daily dose of dasatinib was 140 mg in 52 patients, 100 mg in 56 patients, and <100 mg in 17 patients. As to efficacy, 60 reached CCyR as best response. Four-year OS was 84.2 %. Thirty-one percent of patients experienced grade 3/4 hematological toxicity, mostly in the group of patients treated with 140 mg/day. Twenty-seven percent of patients experienced nonhematological toxicity, with no difference in the rate of events between patients treated with different dosage and schedule. Forty-one patients experienced pleuro/pericardial effusion that was of grade 3/4 in 8 % of patients, with higher frequency in the group of patients treated with 140 mg/day. Due to toxicity, 67 patients required a dose reduction and 19 patients needed permanent discontinuation. This real-life experience showed that dasatinib could be safely used in older patients.

A subanalysis of 119 patients aged >65 years treated with bosutinib was presented in 2012 and a comparison was made with 451 younger patients [21]. Bosutinib was administered at a dose of 500 mg/day. Bosutinib was discontinued in 80 % of patients over 65 years of age compared to 67 % of younger patients, in 32 % of cases being due to adverse events, mostly thrombocytopenia. Rate of

treatment transformation, incidence of hematological side effects and the incidence of diarrhea were similar between patients older or younger than 65 years.

Recently, a 3rd-generation inhibitor was tested in resistant CML patients: ponatinib is a potent, oral inhibitor able to block native and mutated BCR-ABL, including T315I mutation, which are resistant to dasatinib and nilotinib. The phase II "Ponatinib Ph+ALL and CML Evaluation" (PACE) trial tested ponatinib 45 mg QD in 449 patients (median age 59 years; range 18–94) resistant or intolerant to dasatinib or nilotinib or with the T315I mutation in different phases of disease. In chronic phase patients, 46 % achieved a CCyR and 32 % MMR with 12 % $MR^{4.5}$ (BCR-ABL IS $\leq$0.0032 %). Similar responses were obtained in patients with or without mutations, with a higher rate in patients with the T315I mutation. However, 20 % of arterial and venous thrombotic events prompted a revision of the treatment recommendations with a lower dose recommended in good responders and precautions regarding vascular events [22].

Second Generation TKIs in First Line Use in Older Patients

The DASISION trial (Dasatinib versus Imatinib Study in Treatment-Naïve CP-CML patients) was a large phase III trial comparing dasatinib 100 mg BID versus imatinib 400 mg QD in newly diagnosed patients. A subanalysis of the study showed efficacy and safety results according to baseline comorbidity and age. In the dasatinib arm, CCyR rates were 88 % for patients aged <46 years, 78 % for those aged 46–65 years, and 85 % for those aged >65 years; the corresponding MMR rates were 45, 47, and 50 %, respectively. In the imatinib arm, CCyR rates of 70, 70, and 83 % were reported for patients <46 years, 46–65 years, and >65 years, respectively; MMR rates were 26, 30, and 29 %, respectively. Safety profiles were similar across all age groups in both treatment arms, except for fluid retention rates observed in the dasatinib arm (13, 25, and 35 %) compared to the imatinib arm (34, 45, and 67 %) for patients aged <46, 46–65, and >65 years, respectively [23].

The ENESTnd trial (Evaluating Nilotinib Efficacy and Safety in Clinical Trials of Newly Diagnosed Ph+CML Patients) is a phase III trial testing two different doses of nilotinib (300 and 400 mg BID) versus the standard dose of imatinib (400 mg QD). In this trial, 36 patients (13 %) and 28 patients (10 %) were >65 years old in the 300 and 400 mg BID nilotinib arms, respectively. Efficacy was maintained in older patients, with an MMR rate of 78 % in the nilotinib 300 mg BID arm and a $MR^{4.5}$ rate of 31 %. CCyR rates by 24 months were 83 and 68 % among older patients treated with nilotinib 300 and 400 mg, respectively, compared to 87 % in younger patients in either of the nilotinib arms. 72 and 61 % of older patients achieved MMR, respectively, whereas in younger patients, the respective rates were 71 and 67 %. As regards safety, no patients had grade 3/4 neutropenia and only one older patient reported grade 3/4 thrombocytopenia in each nilotinib arm. Transient, asymptomatic lipase elevations occurred in 11 and 16 % of older patients treated with nilotinib 300 and 400 mg, and in 7 % of younger patients in each arm.

Hyperglycemia occurred in 23 and 16 % of patients aged over 65 years on nilotinib 300 and 400 mg, respectively, and in 4 % of younger patients in either arm. Overall, the primary endpoint (MMR within 12 months) was maintained in the nilotinib 300 mg BID arm at 4-year follow-up with an MMR rate of 76 versus 56 % for imatinib; the MR^4 rates were 56 and 32 % and the $MR^{4.5}$ rates were 40 and 23 %. Statistically significant reduction of progression rate was observed in the nilotinib 300 mg BID arm (0.7 %) as compared to imatinib (4.2 %) [24].

Bosutinib was tested in a phase III randomized trial in first line versus imatinib standard dose (BELA trial). A subanalysis in older patients enrolled in the BELA trial was presented: 30 patients were treated with bosutinib and 27 with imatinib. None of the patients aged >65 years treated with bosutinib progressed. Among patients aged >65 years, grade 3/4 events were more frequently recorded (gastrointestinal events, elevated transaminases, pyrexia); 64 % of this subset required dose reduction, and 39 % required treatment discontinuation due to side effects [25]. Overall, the study did not achieve the primary endpoint (rate of CCyR) because at 12 months there was no difference between the two arms (70 % for bosutinib vs 68 % for imatinib). Despite these results, the MMR rate improved in the bosutinib arm (41 vs 21 % for imatinib arm) and responses were achieved faster with this inhibitor. Consequently, only 2 % of patients progressed to advanced phases of disease as compared to 4 % in the imatinib arm.

All studies clearly showed that efficacy was similar for the three different inhibitors tested as frontline treatment, even in patients aged >65 years, but with a specific safety profile for each one which should be carefully evaluated according to the presence of concomitant comorbidities [26].

Pharmacokinetics

For all patients, potential drug-drug interactions are a concern when multiple medications are taken, and elderly patients are more likely than younger patients to be on a multiple medication regimen. For patients aged >65 years, 90 % are taking at least one prescription drug, and 65 % are taking at least 3 prescription drugs, compared with 65 and 34 % of patients aged 45 to 64 years, respectively. All TKIs are metabolized in a similar fashion, primarily by cytochrome P450 (CYP) 3A4 (CYP3A4), a liver enzyme that is active in the metabolism of many other drugs. Other CYP enzymes and UDP-glucuronosyltransferase appear to play a minor role. Clinical recommendations for the use of TKIs with other medications, therefore, largely involve concomitant use of agents (including food, vitamins, or supplements) that are strong inducers or inhibitors of CYP3A4 or are substrates of CYP3A4. Further, the prescribing information for TKIs provides guidance for the concomitant use of antiarrhythmics or agents that prolong QTc and for the concomitant use of cumulative high-dose anthracyclines [27].

The first analysis of the effect of different imatinib dose regimens in older vs. younger patients with CML was performed using data from the German CML-

Study IV [28]. The most important finding of this analysis is that older patients on Imatinib 800 mg (IM800) had no delay in reaching MMR and MR^4 as this was the fact with standard dose imatinib where MMR and MR^4 were achieved significantly later than in younger patients. Superiority of the response rates to IM800 was more pronounced in the older than in the younger group. This effect is remarkable as the median dose for older patients on IM800 was lower than that of younger patients and only moderately higher than in older patients on Imatinib 400 mg (IM400). The result is in line with observations within this study that superior cytogenetic and molecular remission rates were reached in patients with IM800. To avoid severe adverse events on IM800, imatinib was adapted to tolerability in both age groups. Dose reductions were higher in older patients, although adverse events occurred not more frequently than in younger patients. A similar dose-intensity and no difference in adverse events was reported in high-dose imatinib therapy for patients <65 years and ≥65 years by Cortes et al. [4]. Most non-hematologic adverse events occurred more often in the IM800 arm, independent of age, but since grades 3 and 4 adverse events were similar between IM400 and IM800, this appears tolerable with regard to a potentially better outcome. The baseline characteristics beyond age seem to have no influence, but the proportion of patients with lower Karnofsky index was significantly higher in older patients. To compare survival between age groups, the German population adjusted for age and sex was taken into account. Overall survival was reduced in older compared to younger patients due to a generally reduced life expectancy of older people, whereas the five-year relative survival of older patients was comparable with that of younger patients. Nevertheless, it is important to note that a bias in favour of the study patients is likely. The relative survival estimates may be too optimistic, since the exclusion criteria of CML-Study IV prevented the participation of some of the frailest patients, e.g. those with other neoplasias in need of treatment or with conditions preventing study compliance and thus, with a supposedly reduced life expectancy. This would explain the better survival in older patients on IM800 (100.8 % at five years) than in the general population.

Comorbidities and TKI Treatment

Individual TKIs have different patterns of side-effects, and this should be considered when choosing amongst these drugs. Side effects can be divided into three general categories. The first includes major, grade 3/4, side effects that typically occur during the first phase of treatment, are manageable, but require temporary treatment discontinuation and dose reduction, and can lead to treatment discontinuation in about 10 % of patients. The second category includes minor side effects that begin early during treatment and can persist forever. They are also manageable, and tolerable, but affect negatively the quality of life, and are a cause of decreased compliance, that is a major cause of failure. Many of these side effects are common to all TKIs, with some differences in frequency and severity, so that several patients

can benefit from changing the TKI. The third category includes late, "off-target" complications, that can affect the cardiovascular system, heart and blood vessels, the respiratory system, liver, pancreas, the immune defense, secondary malignancies, calcium, glucose and lipid metabolism, etc. All TKIs can be toxic to the heart and should be used with great caution in patients with heart failure. Nilotinib has been reported to be associated particularly with arterial pathology, peripheral and coronary. Dasatinib has been reported to be associated particularly with pleura effusions and lung complications. Overall, the long term off-target complications of 2nd generation TKIs are not yet fully understood. Since they are a potential cause of morbidity and mortality, continued clinical monitoring of all patients is required.

The onset of peripheral arterial occlusive disease (PAOD) was reported in selected cohorts of patients treated with nilotinib, outside clinical trials. In particular, le Coutre and colleagues [29] reported 175 patients treated with nilotinib second line and PAOD was recorded in 11 patients (6 %), of which 7 were more than 60 years old with pre-existing risk factors, such as smoking, obesity, diabetes, hypertension, and hypercholesterolemia.

Recently, the same group recommended the use of the ankle-brachial index (ABI) and duplex ultrasonography as tools to identify patients at risk of PAOD during treatment with TKIs and revealed a significantly higher frequency of this side effect in patients treated with nilotinib, although with unknown mechanisms. The coexistence of comorbidities and older age did not preclude possible treatment with this drug, but suggests that patients older than 65 years be closely monitored for early identification of this side effect. Cardiovascular morbidity and the risk for the development of PAOD should be considered in CML patients. Other potential manifestations of atherosclerosis, including fatal myocardial infarction, have been attributed to imatinib, nilotinib, and dasatinib. The authors strongly suggest to capture baseline ABI, biochemical risk factors and to monitor these parameters regularly throughout TKI therapy of CML [30].

Comorbidities are common among the elderly patients, but specific studies of TKI therapy in older patients with coexisting illnesses have not been conducted. A subanalysis of the DASISION trial of front-line dasatinib use in patients with CML-CP demonstrated no differ- ence in the outcomes for the cohort with any of the allowed comorbidities (ie, allergic, dermatologic, diabetic, endocrine, metabolic, gastrointestinal, hematologic-lymphatic, hepatobiliary, hyperlipidemic, musculoskeletal, renal, and respiratory) vs. those without comorbidities. Findings from a subanalysis of the ENESTnd trial that examined front-line nilotinib treatment in patients with preexisting type 2 diabetes suggested that the efficacy and safety of nilotinib in patients with diabetes were similar to those seen in the overall patient population. These preliminary results support the safety and efficacy of TKI therapy in patients with many comorbidities. However, patients with preexisting cardiovascular disease have been excluded from studies with nilotinib and dasatinib. The use of these agents in patients with preexisting cardiovascular disease needs to be better understood, both in the general CML population and among elderly patients with CML. The currently reported data lend further urgency to the conduct of appropriate

TKI cessation studies in patients with CML-CP who have a (yet to be defined) adequate molecular response to initial TKI therapy [31].

Lataglia et al. investigated the safety and tolerability of imatinib in very elderly CML patients in chronic phase, 211 chronic-phase CML patients aged >75 years were retrospectively analyzed using data collected from 31 institutions in Italy. Results from this large cohort of patients show that no upper age limit should be applied for the administration of imatinib to patients with chronic phase CML; the very elderly, including those with concomitant severe diseases, should be offered this treatment. The role of a reduced starting dose of imatinib warrants further studies [32].

Conclusions

Before the advent of TKIs, studies have shown that advanced age may be a negative independent factor for response in the category of elderly patients due to concomitant comorbidities and consequent increased toxicity of available agents, like interferon alpha. Any preference to avoid such therapies in elderly patients rose from lack of data due to exclusion of frail elderly patients from major clinical trials testing interferon. CML management has dramatically improved after the introduction of imatinib: in fact, this drug completely changed the way to treat and the outcome of elderly patients. It has been reported that imatinib use did not vary by race/ethnicity, socioeconomic status, geographic residence or insurance status, even after these analyses were adjusted for age at diagnosis. Imatinib has yielded promising results when used in older patients as 2nd line after IFN therapy failure or as frontline therapy; efficacy in terms of cytogenetic and molecular responses was reported similar to that described in younger patients. Imatinib has a favourable safety profile also in elderly patients, but with overall more frequent toxicity leading to high rate of discontinuation and dose reduction, probably related to the presence of concomitant comorbidities. All publications agreeing that, in the TKI era, it would be reasonable to define an elderly patient according to reproducible tools of fragility (such as comorbidity indexes) rather than simply according to years of age and physician's perception. Limited data are available for 2nd generation TKIs in older subset of patients after resistance or intolerance to imatinib: for nilotinib, no data were reported outside clinical trials, whereas for dasatinib, all data available were published in "real life" clinical practice. Few data were available for dasatinib and nilotinib in newly diagnosed elderly patients enrolled in randomized phase III trials, which selectively included only patients with limited spectrum of comorbidities. In conclusion, although lack of data exists for elderly CML subset, all published data showed that response to TKIs was not affected by age.

Several strategies have been developed to overcome the problem of imatinib resistance, including dose escalation of imatinib, combination treatments, or novel targeted agents: no different strategies were specifically applied in patients aged >65 years. This subset can be treated the same as younger patients with choice of

therapy and careful monitoring in patients with specific preexisting comorbidities. Higher doses of imatinib seem to be effective in specific categories, such as resistant patients with previous cytogenetic response and no mutations, but not in patients with primary resistance or hematological failure. Trials with 2nd-generation TKIs after imatinib resistance have been shown to rescue about 50 % of resistant patients, regardless of the type of mutations and age at the time of the switch. Monitoring patients, regardless of age, according to ELN recommendations and early identification of patients with failure or suboptimal response with prompt switching to 2nd-generation TKIs could improve the outcome of patients treated with imatinib. The results of randomized trials testing safety and efficacy of 2nd-generation TKIs in first line reported a rapid reduction of leukemic burden, which translates into a reduced incidence of resistance. Even in older patients, all agents tested were effective and induced a rapid reduction of leukemic burden with limited toxicity, but until now, no clear correlation between greater molecular responses obtained with 2nd-generation TKIs and overall survival has been apparent. Longer follow-up is needed to verify whether a higher rate of deep molecular response is sustained and if a possible discontinuation of therapy, regardless of age, may be planned [26].

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