4 Imatinib: The First-Line CML Therapy

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4.1 Introduction

Imatinib, the first TKI (tyrosine kinase inhibitor) of BCR-ABL1 introduced for the therapy of CML (chronic myelogenous leukemia), has profoundly changed the outcome perspectives of a disease previously fatal in the vast majority of the patients and which now shows an overall survival similar to that of a control population without leukemia. However, in addition to those who cannot tolerate the drug (approximately 10–15% of the total), 20–25% of the imatinib patients treated with the usual dosage of 400 mg do not reach an optimal response criteria according to the ELN (European Leukemia Net) recommendations. This has led to the exploration, as front-line therapy for CML, of second-generation tyrosine kinase inhibitors like nilotinib, dasatinib, and bosutinib, more powerful TKIs with respect to imatinib and initially registered as second-line therapy for the CML cases intolerant or resistant to imatinib. The clinical trials comparing imatinib versus the second generation TKIs have shown that the latter are able to induce faster and deeper molecular responses with respect to 400 mg imatinib, but these advantages are counterbalanced by a higher degree of immediate and long-term toxicities and by no improvement in the overall survival (OS) and progression-free survival (PFS) rates. In addition, more recently studies testing higher dosages of imatinib (800 mg per day) compared to standard dose imatinib or dose-adapted imatinib or imatinib plus interferon have been reported to be able to induce better cytogenetic and molecular responses, including the achievement of deep molecular responses like MR4 and MR4,5 which are needed to attempt treatment-free remission (TFR). Therefore, considering that imatinib has become a generic drug and that this has considerably lowered its cost allowing its use in patients all over the world, it is easy to understand why imatinib still represents the first-line therapy of choice for the majority of CML patients.

4.2 Imatinib and Response to Therapy

Imatinib was the first tyrosine kinase inhibitor (TKI) introduced in the therapy of chronic myeloid leukemia (CML), and it is still the standard of care and the most widely used frontline therapy for CML patients in chronic phase [1]. Indeed, the long-term overall survival (OS) observed in patients treated first line with imatinib has been matched but never overcome by other TKIs [2–4]. The most relevant data of the 8-year follow-up of the IRIS study that have also been confirmed by other studies and by

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https://doi.org/10.1007/978-3-030-71913-5_4

independent retrospective analysis performed on patients outside clinical trials show a cumulative CCyR rate around 83–85% and an estimated OS rate of approximately 82–84% at 10 years, which is far better from what was observed before the introduction of this drug [5, 6]. This result may be ascribed to a substantial decrease in the number of the progressions to accelerated phase or blast crisis observed in patients treated with imatinib. Many records indeed suggest that progressions to a more advanced phase of the disease still represent a major cause of death for CML patients, still being incurable in most cases even in the tyrosine kinase inhibitor (TKI) era [7]. With imatinib therapy, the occurrence of progression drops from an expected rate of approximately 15% per year to a rate of 2–3% per year, and only for the first 2–3 years of treatment as during the subsequent years events of progression are really occasional [6]. This is certainly due to the great reduction of the leukemic mass observed in most of the imatinib-treated patients, which in few cases can also result in an apparent disappearance of the leukemic clone, but also to the fact that imatinib, inhibiting the BCR-ABL tyrosine kinase (TK) activity that plays a major role in determining the genomic instability of the leukemic cells, may per se be able to slow the propensity to progress [8].

It has been demonstrated that the patients who benefit from TKI therapy with imatinib are those who achieve and maintain CCyR for at least 2 years, as in these cases, the OS is similar to that of a control population without leukemia [9]. On the other side, various analyses have shown that patients who do not achieve good cytogenetic or molecular responses to imatinib at defined time points have a worse outcome, characterized by an increased risk of relapse, progression, and death [10, 11].

Based on these principles, a panel of CML experts from the European Leukemia Net (ELN) and members of the National Comprehensive Cancer Network (NCCN) have previously established and, more recently, revised treatment milestones to be achieved during CML treatment with TKIs [12, 13]. This obviously implies that to optimize CML treatment with TKIs an appropriate and timely follow-up with cytogenetic and standardized molecular methods of adequate reliability is needed. In particular, molecular monitoring of BCR-ABL transcript levels by real-time quantitative PCR (RQ PCR) has become the most useful and precise way to monitor CML patients, almost replacing the cytogenetic analysis during follow-up, although not at diagnosis as stated in the ELN 2020 recommendations [14–17]. Indeed, with respect to conventional cytogenetic analysis, RQ PCR not only allows monitoring the first steps of reduction of the leukemic burden occurring within the first months of TKI therapy but may also allow estimating the amount of the residual disease once CCyR is achieved, as the sensitivity that can be reached with the present RQ PCR procedures in a sample of good quality is in most cases between $10^{-4}/10^{-5}$, which corresponds to an amount between 2 and 3 logs below the threshold of the achievement of CCyR [14]. According to the established international scale (IS), the relevant BCR-ABL1% to be achieved are 1% (2-log reduction with respect to the median BCR-ABL1 amount present at diagnosis and that roughly corresponds to the threshold of CCyR), and 0.10% BCR-ABL1 (major molecular response (MMR)) and 0.01–0.0032% BCR-ABL1 corresponding, respectively, to MR4 (4-log reduction) and MR4.5 (4.5-log reduction) [18].

The attainment of CCyR or 1% BCR-ABL1 can still be considered the most significant response to target, as this goal has been demonstrated to be associated to the highest probability of long-term survival for CML patients [19–21]. On the other side, some data support the notion that deeper responses, as the achievement of level of $\text{BCR-ABL}^{\text{IS}} \leq 0.1\%$ (MMR), may indeed improve OS relative to achieve CCyR without MMR [21]. Indeed a 4-year landmark analysis performed within the context of the German CML-study IV suggests that patients who after 4 years were able to achieve a stable MR4.5 molecular response showed at 8 years a statistically significant better survival with respect to those patients who have simply achieved CCyR but not MMR [21]. If these results are confirmed, MR4.5 will represent a new molecular predictor

of long-term outcome. In any case, it has been clearly established by several clinical studies that a stable deep molecular response (at least MR4 or even better MR4.5) is required to obtain long-lasting treatment-free remission (TFR) that is progressively becoming the new treatment goal for CML patients [22–25]. Thus, the achievements of MMR and of MR4.5 in addition to CCyR and MMR are appealing targets to pursue, as they predict more durable and stable responses and can also open up the possibility to try stopping therapy.

It is noteworthy that many studies, particularly in more recent years, have indicated that early cytogenetic and molecular responses within the first year of therapy represent the strongest prognostic parameters not only in terms of OS, progression-free survival (PFS) or event-free survival (EFS) but also in terms of possibility of achieving deeper molecular responses and, therefore, the possibility of discontinuing treatment without molecular relapse (TFR) [26–28]. Based on these observations, some recent treatment recommendations as those of the GIMEMA group have been modified with respect to the past the time points at which the expected response goals should be met to match the criteria for optimal response and have also introduced MR4 (0.01% BCR-ABL1) in the optimal response requirements within the first 24 months of therapy [25].

Based on these parameters, it appears that approximately one third of CML patients do not show an optimal response to imatinib therapy, and they, therefore, face a statistically significantly higher risk of an inferior outcome in terms of EFS, PFS, and also OS (approximately 80% at 5 years with respect to >95% of those below 10% BCR-ABL at 3 months) [20, 27, 28]. Actually, it is true that with imatinib most of these patients will only show a delayed response and will not progress or die, but it should also be considered that approximately 15–20% of them in a short time will die and many of them because of CML and progression [20, 27, 28]. In addition to the cases of failure, progression, and death, the reasons for discontinuation also include 10–12% of patients who show adverse events (AEs) and are intolerant to imatinib treatment and should be moved to treatment with another TKI.

It is also noteworthy that the percentage of the patients who do not respond optimally to imatinib may vary according to the initial clinical and hematological features that determine their initial risk category, as established by Sokal and also by the more recent ELTS (EUTOS Long Term Survival) score, which appears to be even more precise than Sokal scores in predicting the outcome of the CML patients in terms of death by CML [29]. In the IRIS study, patients with low-, intermediate-, or high-risk Sokal scores showed significantly different response rates as 5-year CCyR (89, 82, and 69%, respectively: $P < 0.001$) and progression to advanced disease (3, 8, and 17%, respectively: $P = 0.002$).

Based on all these considerations, several clinical trials aiming to improve the first-line treatment of patients with chronic phase CML have been performed. These therapeutic strategies that have been tested include the first-line administration of the second-generation TKIs (originally used as second-line therapy) or higher dosages of imatinib from the start. Also combinations of imatinib with other drugs, namely interferon-alpha (IFN-α), have been tested and trials are still ongoing, but for the moment these therapeutic options remain investigational and are not used in normal clinical practice.

4.3 Imatinib Versus Second-Generation TKIs as First-Line Treatment

At present, the use of three second-generation TKIs (nilotinib at the dosage of 300 mg BID, dasatinib 100 mg OD and bosutinib at the dosage of 400 mg OD) has been approved and registered as first-line therapy [2, 3, 30]. As patients with CP CML have very long survival and very long follow-ups are, consequently, required before the efficacy of these alternative treatment options could be measured in terms of OS, important surrogate markers as the rates of CCyR, MMR, MR4, and MR4.5 achieved at relevant time-points and progression-free survival (PFS)

parameters have been frequently used as a way to evaluate the relative responses and to compare results. However, it is important to consider that the methods to assess and to report the rate of responses can sometimes vary and that also the definitions of the EFS and PFS may change according to the protocol in different trials and may, therefore, introduce bias in the comparative evaluation of the results obtained in different clinical studies.

The rationale to test the second-generation TKIs (i.e., nilotinib, dasatinib, and bosutinib) against imatinib as first-line therapy was due to the fact that they were more potent than imatinib in inhibiting BCR-ABL1 TK activity, and they were already approved as second-line therapy for imatinib-intolerant or imatinib-resistant patients, being able to induce a CCyR rate of approximately 40–50% in these patients also when the resistance was due to the presence of clones with BCR-ABL1 mutations (with the notable exception of the T315I mutation) poorly responsive to imatinib therapy [31–34].

The efficacy and the toxicity of nilotinib and dasatinib as first-line therapy were initially assessed in phase 2 studies [35–37]. The results obtained in 73 newly diagnosed CP-CML patients treated with nilotinib 400 mg twice a day by the GIMEMA CML working party showed CCyR achievement at 3 months in 78% of the patients and in 96% at 6 months, whereas the MMR rates observed were 52% and 66%, respectively, at the same time points and 85% at 12 months [35]. Similarly, results of 100 newly diagnosed CML patients treated at the MD Anderson Cancer Center with nilotinib 400 mg twice daily (BID) showed, with a median follow-up of 29 months (range 1–73), a cumulative CCyR rate of 93%, MMR rate of 73% and CMR rate (defined according to the previous ELN criteria as undetectable hybrid transcripts with a sensitivity of at least $10^{-4}/^{-5}$) of 33% [36]. At the same institution, 86 newly diagnosed patients were treated with dasatinib 50 mg twice daily (BID) or 100 mg QD [37]. With a median follow-up of 24 months, most patients achieved a rapid CCyR (94% at 6 months) with a cumulative CCyR ratio of 98%. After 12 and 18 months, MMR was achieved by 71 and 79% of patients. The toxicity profile with dasatinib was also favorable with a better tolerability with dasatinib QD vs. BID dosing.

ENESTnd is a phase 3, randomized, open-label, multicenter study comparing the efficacy and safety of nilotinib with imatinib in patients with newly diagnosed CML that has now completed the tenth year of follow-up [2, 38]. The trial included 846 patients randomly assigned 1:1:1 to nilotinib 300 mg BID (n = 282), nilotinib 400 mg BID (n = 281), or imatinib 400 mg/day (n = 283). MMR at 12 months was the primary endpoint. Patients were also stratified by Sokal risk score, which resulted in equal distributions of low-, intermediate-, and high risk Sokal scores in each arm of the trial. Efficacy results were presented in the intent-to-treat (ITT) population. The MMR rate at 12 months was significantly higher for nilotinib 300 mg BID (44%, $P < 0.0001$) and nilotinib 400 mg BID (43%, $P < 0.0001$) than for imatinib (22%). As this was the primary endpoint of the study, nilotinib 300 mg BID was approved by FDA and EMA and registered as the first-line therapy. Responses were rapidly achieved with nilotinib, with 6-month MMR rates of 33%, 30%, and 12% for nilotinib 300 mg BID, nilotinib 400 mg BID, and imatinib, respectively. These higher responses were also associated with fewer progressions to AP/BC with nilotinib than with imatinib as already observed during the follow-up at 5 years of the study [39]. Cumulative 10-year MMR rates of patients assigned to nilotinib 300, nilotinib 400, and imatinib are 82.6%, 80.4%, and 69.6% and cumulative MR4.5 rates are 63.8%, 61.6%, and 45.2%, respectively. The difference between MR4.5 rates achieved with nilotinib vs. imatinib by 10 years was similar to that observed after 5 years of treatment study [38, 39].

However, as already observed in the results of the 5-year follow-up, the occurrence of cardiovascular events (CVEs) was much more frequent with nilotinib than with imatinib and was dose dependent, being more frequent in the nilotinib 400 mg BID arm that in the nilotinib 300 mg BID [39]. They in addition continue to increase at similar rates during the subsequent 5 years [38]. Finally the observed 10-year OS rates are similar

between nilotinib and imatinib and in conclusion, the 10-year follow-up data confirm the sustained efficacy of frontline nilotinib in achieving earlier and deeper molecular responses but also underline the high risk of developing CVEs with prolonged nilotinib therapy.

Dasision is a phase 3, randomized, open-label, multicenter study comparing the efficacy and safety of dasatinib 100 mg OD as the first-line therapy with respect to that of imatinib [3, 40]. This study achieved a minimum follow-up of 5 years and was subsequently terminated [40]. Patients with newly diagnosed CML-CP were stratified according to the Euro Risk Score and randomly assigned to dasatinib 100 mg/day or imatinib 400 mg/day. Confirmed CCyR by 12 months was the primary endpoint of the study and by 12 months was significantly higher for dasatinib (83%, $P < 0.001$) than for imatinib (72%), allowing this drug also to be approved as the first-line therapy by FDA and EMA. The best cumulative MMR rate by 12 months was also significantly higher for dasatinib (46%, $P < 0.0001$) than for imatinib (28%) [40]. After 5 years, molecular response rates continue to be higher for dasatinib compared with imatinib (rates of MMR 76% vs. 64%, $P = 0.002$ and rates ofMR4.5 42% vs. 33%, $P = 0.025$). Transformations to AP/BC on study or after discontinuation were lower with dasatinib ($n = 12/259$; 4.6%) compared with imatinib ($n = 19/260$; 7.3%). However, 5-year PFS and OS rates were similar across treatment arms (PFS 85% dasatinib, 86% imatinib; OS 91% dasatinib, 90% imatinib) [40]. A higher proportion of patients on dasatinib achieved BCR-ABL ≤10% at 3 months (84%) compared with those on imatinib (64%). Patients who achieved BCR-ABL ≤10% versus >10% at 3 months showed improved PFS and OS and lower rates of transformation to AP/BP (PFS 89 vs. 72%, $P = 0.0014$; OS 94 vs. 81%, $P = 0.0028$; transformation $n = 6/198$ [3%] vs. $n = 5/37$ [14%]) than imatinib (PFS 93 vs. 72%, $P < 0.0001$; OS 95% vs. 81%, $P = 0.0003$; transformation $n = 5/154$ 3% vs. $n = 13/85$,15%) [28]. Concerning the AEs of dasatinib, the total incidence of pleural effusion after 5 years is 29%, but most cases were grade 1 or 2 (67 out of 74), and discontinuation of dasatinib due to pleural effusion occurred in only 15 patients (6% overall and 20% of patients who experienced a pleural effusion). Arterial ischemic events were not common, occurring in 12 patients (5%) on dasatinib and 6 patients (2%) on imatinib [40]. More recently, however, one investigator-initiated study comparing dasatinib 100 mg OD vs. imatinib 400 mg OD, although showing that the proportion of patients achieving CCyR was superior with dasatinib (84% vs. 69%) as well as the 12-month molecular responses (MMR 53 vs. 35%, $P = 0.049$; MR4 25 vs. 10%, $P = 0.038$), did not show any advantage in terms PFS as well as in terms of OS [41].

BELA is a phase 3 multicenter study comparing the efficacy and safety of bosutinib 500 mg OD with that of imatinib 400 mg OD [42]. In this study, CCyR by 12 months that was the primary endpoint of the study did not result to be significantly higher for bosutinib (70%), compared with imatinib (68%), and initially this did not allow bosutinib to be approved as the first-line therapy. These results have been jeopardized by the high rate of discontinuation mainly due to nonhematologic drug-related AEs that occurred in the bosutinib arm (19% rate of discontinuation in the bosutinib arm with respect to 5% in the imatinib arm) and, in particular, the high rates of discontinuation due to diarrhea on bosutinib. However, MMR rates by 12 months were significantly higher for bosutinib (39% bosutinib versus 26% imatinib, $P = 0.002$), and there were numerically fewer progressions to AP/BC with bosutinib (2%) than with imatinib (4%) [42].

Subsequently, bosutinib at a lower dosage of 400 mg OD was again tested vs. imatinib in the BFORE study, which showed a MMR rate at 12 months, the primary end-point significantly higher with bosutinib vs. imatinib (47.2% vs. 36.9%, respectively; $P = 0.02$) [30]. Also the complete cytogenetic response (CCyR) rate by 12 months (77.2% vs. 66.4%, respectively; $P = 0.0075$) was significantly higher with bosutinib. Disease progression to accelerated/blast phase was observed in four patients receiving bosutinib and in six patients receiving imatinib. Grade 3 diarrhea was observed in this trial in 7.8% of the cases treated with bosutinib, at a

lower incidence with respect to what was observed in the BELA trial. The results of this trial finally led to the registration of bosutinib as an additional option for first-line treatment.

In conclusion, because of their higher inhibition capacity of the BCR-ABL1 TK, second-generation TKIs demonstrate the achievement of faster molecular responses with respect to imatinib 400 mg, with more patients achieving BCR-ABL1 $\leq$ 10% at 3 months and higher rates of MMR and of deep molecular responses (DMR) like MR4 and MR4.5. Another clinical advantage of their use as front-line therapy could be represented by a trend toward a lower rate of transformation. On a longer run the advantage could be represented by a faster achievement of conditions allowing to try to discontinue the therapy. However, 5- and 10-year OS are not statistically different with respect to imatinib and some observed long-term toxicity effects, like a higher rate of cardiovascular events, could raise concerns for their use, particularly in some categories of patients.

4.4 High-Dose Imatinib

Current treatment guidelines for CML recommend first-line therapy with imatinib at a dose of 400 mg/day. However this dosage may not be optimal for patients characterized by a genetic predisposition to a lower efficiency of the OCT-1 transporter, a pump regulating the intracellular influx and concentration of imatinib, which, on the contrary, could significantly benefit from higher initial imatinib dose [43]. Furthermore, phase 1 dose-finding trials demonstrated no dose-limiting toxicities at imatinib doses up to 1000 mg/day, and a dose–response relationship was observed. The best results with imatinib 400 mg were obtained when imatinib plasma concentration was at least 1000 μM/L. This explains also why responses to imatinib are also dependent on a perfect adherence to dosage and to scheduled treatment [44].

Based on these considerations, shortly after the approval of imatinib, a number of studies were started to assess the efficacy and the safety of higher-dose imatinib (800 mg) administration [45–48]. The results of these studies generally showed that patients treated with 800 mg achieved more rapid cytogenetic and molecular responses, but no significant differences were reported in EFS, PFS, or OS. The lack of OS benefit with the higher dose could be due to the frequent dose reductions and treatment interruptions caused by a poor tolerance of 800 mg imatinib dosage.

This problem, as shown in the Study IV of the German CML Study Group, can be overcome by the use of a dose of imatinib adapted to allow a good tolerability by the individual patients. Comparing imatinib 400 mg/day with 800 mg/day alone, the rate of MMR at 12 months was 59% vs. 44% ($P < 0.001$) in favor of the arm in which the patients were starting with 800 mg per day but were allowed to adapt the dose. Indeed the median dose in the 800 mg arm was 628 mg/day, suggesting that treatment of early-phase CML with imatinib can be optimized and that early high-dose therapy followed by rapid adaptation to good tolerability can increase the rate of MMR at 12 months.

These data have been confirmed by a randomized study comparing the rates of molecular, hematological, and cytogenetic responses to imatinib 400 vs. imatinib 400 mg twice daily (imatinib 800) in which dose adjustments were allowed to maximize retention on study [49]. Molecular response at 12 months was deeper in the imatinib 800 arm (4-log reduction of BCR-ABL1 mRNA 25 vs. 10% of patients, $P = 0.038$; 3-log reduction 53% vs. 35%, $P = 0.049$). Furthermore, in both arms, few patients relapsed, progressed, or died, but both PFS ($P = 0.048$) and RFS (relapse-free survival) ($P = 0.031$) were superior for imatinib 800 [49].

Furthermore the 10-year follow-up of the German CML Study IV shows that very deep molecular responses can be obtained with prolonged imatinib therapy in the majority of CML patients [6, 21, 50]. Indeed after 10 years, 92% of patients in MMR reached $MR^{4.5}$, 88% in MR^4 reached MR^5, and, therefore, most imatinib-treated patients could become candidates for treatment discontinuation without the need to

switch to a second-generation TKI. These results were obtained by also continuing imatinib therapy in patients in CCyR but not in MMR and switching only the patients falling in the failure category according to the ELN recommendations. The switch occurred in 26.5% of the total population for resistance or intolerance, and the switched patients did worse than the rest and represented a poorer risk group [6].

4.5 Combination Therapy: Imatinib Plus Interferon-Alpha

Because of the established clinical benefit of IFN in CML treatment, combination therapy between this drug and imatinib always appeared appealing and it is under investigation in a number of clinical trials. In a phase 2 GIMEMA study of imatinib 400 mg/day plus pegylated interferon alpha (PEG–IFNα2a) 50–150 μg/week, CCyR and MMR rates were 70% and 47% at 12 months, with a probability of maintaining CCyR at 5 years in responding patients of 94% [51]. However, compliance to IFN was poor with 87% of patients discontinuing IFN within 2 years.

Some large randomized phase 3 trials are comparing imatinib monotherapy with combination treatment. In the open-label French SPIRIT trial, patients were randomized 1:1:1:1 to receive imatinib 400 mg/day, imatinib 600 mg/day, imatinib 400 mg/day plus cytarabine, or imatinib 400 mg/day plus PEG–IFNα2a [52]. A potential advantage for imatinib/IFN treatment was first observed in 18-month MMR (41 vs. 52 vs. 53 vs. 62%; $P = 0.0001$) along with deep molecular response (4-log reduction of BCR-ABL transcripts, CMR4) (4 vs. 7 vs. 5 vs. 15%; $P = 0.0013$) rates and reconfirmed at later times. However, further follow-up of SPIRIT is needed to establish whether these early differences confer a long-term survival advantage. Grade 3–4 neutropenia with or without thrombocytopenia during the first year was higher for combination arms (imatinib/cytarabine 41%, imatinib/IFN 40%) than in monotherapy arms (400 mg 8%, 600 mg 14%). Overall, 45% of the patients discontinued IFN during the first 12 months. Interestingly, the duration of treatment with IFN had an impact on responses: in patients who have been treated for less than 4 months as compared to more than 12 months, rate of MMR, optimal molecular response MR4, and undetectable minimal residual disease increased from 48% to 82%, 23% to 49%, and 8% to 20%, respectively. A rather similar comparison has been performed within the German CML Study Group (Study IV), with an arm in which patients were receiving imatinib 400 mg/day in combination with unpegylated IFNα2beta [53]. With respect to imatinib 400 mg/day alone, 12-month CCyR rates were similar, 52% for imatinib and 51% for imatinib plus IFN, and 12-month MMR rates were 30% and 35%, respectively. After 5 years of follow-up, no difference was reported between arms in progression-free survival (PFS) or overall survival (OS) [53]. In a third trial performed by the Nordic CML study group, newly diagnosed chronic-phase CML patients with a low or intermediate Sokal risk score and in imatinib-induced complete hematologic remission were randomized either to continue imatinib 400 mg/day or to receive a combination of PEG-IFN-α2b 50 μg weekly and imatinib 400 mg/day [54]. In the combination arm, 34 patients (61%) discontinued PEG-IFN-α2b, most because of toxicity. The MMR rate at 12 months was significantly higher in the imatinib plus PEG-IFN-α2b arm (82%) compared with the imatinib monotherapy arm (54%; intention-to-treat, $P = 0.002$), and the MMR rate increased with the duration of PEG-IFN-α2b treatment (<12-week MMR rate 67%, >12-week MMR rate 91%) [54]. Finally, to determine whether adding PEG-IFN-α2b and GM-CSF to high-dose imatinib may further improve the cytogenetic and molecular response rates in CML patients, 94 patients were treated with imatinib 800 mg/day for the first 6 months and then randomized to continue high-dose imatinib alone or in combination with PEG-IFN-α2b at the dosage of 0.5 μg/kg per week and GM-CSF 125 mg/m2 three times weekly [55]. With a median follow-up of 54 months, no differences in the CCyR, MMR, and CMR rates were observed. However, the potential benefit of adding

PEG-IFN-α2b and GM-CSF to imatinib may have been limited by the fact that, due to adverse events, all patients enrolled in the PEG-IFN-α2b arm discontinued this drug.

Reasons for these different findings between the French SPIRIT trial and the Nordic trial on one side and the German CML Study IV and the MD Anderson trial on the other side are not clear at the moment; however, multiple differences present in the protocols (i.e., the type of IFN used, patient populations, and trial designs) need to be considered.

In conclusion, although literature data are still rather controversial on the real efficacy of the association of imatinib plus IFN and higher rates of discontinuation are recorded due to IFN toxicity, the association of IFN and TKIs still appears particularly appealing for many investigators in view of the potential long-term effect on the higher rate of TFR [56].

4.6 Conclusions

The choice of the best first-line treatment of CML in chronic phase, in particular if imatinib or second-generation TKIs, has been a frequently discussed and controversial issue even among specialists. On the second-generation side there were mainly the rapidity and the depth of the response observed, whereas on the imatinib side there was the long-term safety and the cost. Now this equilibrium has been changed by two factors: (a) imatinib has become a generic drug and its cost is really affordable in most countries of the world and (b) the German CML study IV has demonstrated that over a period of 10 years the molecular responses that can be obtained by imatinib, in particular if dose adapted, are similar to those that can be obtained by second-generation TKIs and with less toxicity. So, with the exception of specific cases in which the achievement of a very rapid deep response is desired, imatinib can still represent the first choice for the vast majority of the patients.

In addition, the cost and the safety profile of imatinib make this drug the ideal partner of other drugs able to inhibit BCR-ABL1 TK activity, like the recently developed asciminib, a highly specific inhibitor of the BCR-ABL1 TK of the new category STAMP (Selectively Targeting the ABL Myristilation Pocket) compounds [57].

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