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Role of High Dose Imatinib in BCR/ABL^{pos}/Ph^{pos} CML

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1. Introduction

The therapy with imatinib became the standard of care for the initial treatment of chronic myeloid leukemia (CML) regardless of age, disease status or prognostic scores. Based on the most recent update of the International Randomized Interferon versus STI571 (IRIS) study comparing imatinib 400 mg once daily with interferon alpha plus low doses of Ara C the overall survival (OS) of CML patients at 8 years has improved dramatically to 85% (Deininger et al., 2009) and the estimated median survival is estimated to improve to more than 20 years. In consequence, this will increase the prevalence of CML patients in Europe dramatically from about 70.000 to 120.000 in 2011 to 160.000 and more than 300.000 in the year 2050, assuming a stable incidence of CML between 1 to 2 per 100.000 persons. Interestingly, despite this dramatic success in the therapy of CML with imatinib 400 mg once daily the maximum tolerated dose of imatinib has not been identified in the phase I study (Druker et al., 2001). Nevertheless, there is clear evidence of a dose response relationship from pre-clinical models as well as from the phase I study (Druker et al., 2001; Druker et al., 1996; Deininger et al., 1997; Cambacorti-Passerini et al., 1997). The main reason for choosing a dose of 400mg as starting dose for subsequent clinical trials was the fact that early and significant rates of hematologic and even more important, major and complete cytogenetic responses were achieved with the 400 mg dose that were not further increased with higher doses in these early times (Druker et al., 2001). In contrast, drug related adverse events (AEs), especially WHO grade 3 or 4 AEs that were not seen with imatinib doses up to 300 mg slightly increased with higher doses ranging from 600 mg up to 1000 mg per day. In general, however, imatinib was well tolerated even at higher doses and demonstrated a clear benefit over interferon alpha plus low doses of Ara C in terms of both, efficacy and tolerability (Druker et al., 2001).

2. Phase II studies on High Dose (HD) imatinib in Chronic Phase (CP)

The rational for the use of higher imatinib doses frontline in CP CML patients is that despite the impressive results with 400 mg once daily a substantial number of patients experiences only suboptimal responses according to the criteria of the European Leukemia Net (ELN) (Baccaranai, JCO 2006, 2009) or a minority of patients even fails to reach a response. Early good responses are known to be associated with a favorable long-term outcome as shown

previously in patients from the IRIS study where none of the patients that achieved a complete cytogenetic response (CCyR) and a major molecular response (MMR) at 18 months progressed during the follow up phase (Druker et al., 2006). The first non-randomized study using high doses of imatinib front-line was performed at the M. D. Anderson Cancer Center with CML patients in chronic phase (CP) of their disease after failure to interferon alpha (IFN alpha) (Cortes et al, 2003). Cortes and colleagues treated 36 CP CML patients after failure to interferon alpha with 400 mg of imatinib twice daily (total daily dose of imatinib: 800mg) and 90% of the evaluable patients achieved a major cytogenetic response (MCyR) and 89% a CCyR. Moreover, this treatment with HD imatinib was also associated with a high rate of molecular remissions. In 50% and 56%, however, the dose of imatinib had to be reduced to 600 mg or 400 mg after 3 months and 6 months, respectively. The most common cause for dose reduction in this pre-treated patient population was myelosuppression including thrombocytopenia and neutropenia (Cortes et al, 2003). Nevertheless, 71% of the patients were at least capable to continue with an imatinib dose of ≥ 600 mg. In a subsequently performed phase II study in 114 newly diagnosed CP CML patients, high imatinib doses of 800 mg per day were capable to induce a MCyR in 96% and a CCyR in 90% of the patients. The estimated 2 year survival rate was 94% (Kantarjian et al., 2004). In terms of toxicity the higher doses of imatinib were comparable to the standard imatinib dose of 400 mg in regard to non-hematologic toxicities. Hematologic toxicities were again higher with the imatinib 800 mg dose compared to historical controls. In this trial on newly diagnosed CML patients in CP the dose of 800 mg of imatinib could be maintained in 64% of the evaluable patients at 6 months and in 66% of the evaluable patients at 12 months (Kantarjian et al., 2004). The data from both studies suggested that higher doses of imatinib were capable to induce higher rates of cytogenetic (both MCyR and CCyR) and molecular responses with the price of more frequent myelosuppression. The Italian GIMEMA CML working party prospectively investigated efficacy and tolerability of high dose imatinib (800 mg per day) in a multi-institutional trial (Castagnetti et al., 2009) focusing on a particular subgroup of newly diagnosed CML patients in CP, namely on 78 patients with intermediate SOKAL risk score. (Sokal et al., 1984). They found high rates of CCyR (88%) at 12 months and at 24 months (91%), respectively. Furthermore 56% and 73% of the patients having achieved a CCyR also achieved a major molecular remission (MMR) at 12 and 24 months. They reported on slightly more frequent non-hematologic toxicities like skin rash, myalgia, bone pain, gastrointestinal intolerance, fluid retention and asthenia compared to reported studies with standard dose imatinib. Moreover, they also found WHO grade 3 and 4 hematologic toxicities in terms of leukopenia (18%), thrombocytopenia (17%) and anemia (9%). Between month 3 and 6 (second quarter of therapy) 44% of the patients received the full scheduled dose of 400 mg twice daily (Castagnetti et al., 2009). Another multicenter phase II study, the "Rationale and Insight for Gleevec High – Dose Therapy (RIGHT) trial was conducted in 115 newly diagnosed CML patients in CP (Cortes et al., 2009). This study has again suggested that imatinib 800 mg per day leads to a more rapid reduction in tumor burden with higher rates of MCyR, CCyR and major molecular responses (MMR^{IS}) according to the international scale (IS) compared to historical controls for the price of a slightly increased toxicity including myelosuppression, rash, fatigue and musculoskeletal symptoms (Cortes et al., 2009). In this multicenter trial, 64% of the

patients attained 90% or more of the planned dose. The dose intensity was similar in patients younger than 65 years or in patients ≥ 65 years. The authors reported that the patients with ≥ 90% dose intensity had a significantly higher chance to obtain a MMR^{IS} and a complete molecular remission (CMR) at 18 months: 79% of the patients who received ≥ 90% dose intensity achieved a MMR^{IS} compared to only 42% of the patients who received < 90% dose intensity (p=0.015). Similarly, a CMR (defined as a ≥ 4.5 log reduction from a standardized baseline) was achieved at 18 months by 67% of the patients that received ≥ 90% dose intensity compared to 29% of patients that received < 90% dose intensity (p=0.029).

A slightly different approach was chosen by the Australasian Leukemia and Lymphoma group (ALLG) that conducted a "Therapeutic Intensification in DE-novo Leukemia" (TIDEL) phase II study (Hughes et al., 2008). Compared to all other phase II studies they did not start with 800 mg imatinib per day but with a slightly lower dose of imatinib with 600 mg per day in newly diagnosed CP CML patients and allowed an early dose intensification to 800 mg imatinib if specific response criteria were not met. All patients had an intense response monitoring of marrow cytogenetics and blood for RT-PCR of BCR-ABL mRNA levels every 3 months. The rationale for this design was the assumption that many patients would receive excellent responses with only 600 mg imatinib instead of 800 mg and that the 800 mg imatinib dose could be limited to those patients not achieving an optimal response with the 600 mg dose. The criteria for increasing the imatinib dose were as follows: failure to achieve a complete hematological response (CHR) at 3 months, a MCyR at 6 months, a CCyR at 9 months and a MMR^{IS} (defined as less than 0.01% BCR-ABL by RQ-PCR on the international scale) at 12 months. Within the first year a dose escalation from 600 mg to 800 mg imatinib was indicated in 17 out of 103 patients but only possible in 8 patients (47%) primarily due to ongoing toxicity or subsequent trial withdrawal. These patients failed to achieve or failed to maintain a MCyR at 6 months or a CCyR at 9 months. After the first year a dose escalation was indicated in 73 patients because these patients did not achieve MMR^{IS}. Dose escalation was possible in 62% of the cases. Using this two-step design, the rates of CCyR were 88% at 12 months and 90% at 24 months, respectively. These CCyR-rates were significantly better than those obtained in the IRIS trial (CCyR was 69% at 12 months and 80% at 24 months, respectively) where dose escalations were not allowed at early time points. Similarly were MMR^{IS} rates superior with 47% at 12 months and 73% at 24 months in patients receiving a daily average dose of 600 mg imatinib compared to the IRIS trial (40% MMR at 12 months and 55% at 24 months).

In summary, all these phase II studies suggest earlier and higher rates of cytogenetic and molecular remissions with higher imatinib doses for the price of slightly higher non-hematologic toxicities and higher rates of hematologic toxicities. There was hope and enthusiasm – based on these studies - that earlier achievement of cytogenetic remissions, especially CCyR and molecular remissions would result in lower rates of treatment failures and subsequently translate in superior overall survival rates.

3. Phase III studies on High Dose imatinib in Chronic Phase (CP)

Based on the superior rates of cytogenetic and molecular responses that occur faster with doses > 400 mg imatinib, several phase III studies were initiated on this issue (Table 1).

Study	Author	Design	Primary end point Comparison HD* vs SD**
TOPS	Cortes et al., 2010	newly diagnosed CP patients, n=476 800 mg imatinib/day vs 400 mg imatinib/day	MMR^{IS} at 12 months: 46% vs 40% p=0.2035
ELN	Baccarani et al., 2009b	newly diagnosed SOKAL high risk CP patients, n=216 800 mg imatinib/day vs 400 mg/day	CCR at 12 months: 64% vs 58% p=0.435
ISTAHIT	Petzer et al., 2010a	non-TKI pre-treated patients in late CP, n=227; 800 mg imatinib/day for 6 months, 400 mg imatinib thereafter as maintenance vs 400 mg imatinib/day	MCyR at 12 months: 64.4% vs 56.8% p=0.354
GERMAN CML SG and SAKK	Hehlmann et al., 2011	newly diagnosed CML patients, tolerability adapted 800 mg imatinib/day vs 400 imatinib mg/day	MMR^{IS} at 12 months: 59% vs 44% p<0.001

*HD: imatinib high dose (>400 mg/day)
**SD: imatinib standard dose (≤400 mg/day)

Table 1. Randomized phase III Studies comparing HD imatinib (600 mg - 800 mg per day) to SD imatinib (400 mg per day)

3.1 The tyrosine kinase inhibitor optimization and selectivity study (TOPS)

The tyrosine kinase inhibitor optimization and selectivity study (TOPS) evaluated the safety and efficacy of the initial treatment with imatinib 800 mg (400 mg twice daily) versus the regular 400 mg once daily dosing in newly diagnosed CML patients in CP (Cortes et al., 2010). In this study all CP CML patients were included regardless of their Sokal risk status (Sokal et al., 1984). In spite of the fact that molecular (MMR^{IS}) and cytogenetic responses (CCyR) occurred faster in patients assigned to the 800 mg dose these parameters were not significantly different at 12 months. This included the primary endpoint, the MMR^{IS} rate at 12 months which was only slightly, but not statistically significantly different with an MMR^{IS} rate of 46% in the 800 mg and 40% in the 400 mg group (p=0.2035), respectively. Moreover, the progression free survival (PFS) and overall survival (OS) was also only slightly, but not statistically significantly improved with a PFS of 97.4% and an OS of 98.2% at 18 months in the imatinib 800 mg arm compared to a PFS of 95.0% and an OS of 98.7% at 18 months in the 400 mg arm. Progression to AP or BC occurred in 1.9% in the 800 mg arm and in 3.2% in the 400 mg arm. Adverse events (AE) were generally reported to be mild or moderate in both arms. Rates of all-grade and WHO grade 3 or 4 AEs, however, were higher in the imatinib HD group (98.1% all grades and 63.6% WHO grade 3 or 4 AEs in the 800 mg group versus 93.6% all grades and 33.1% in the 400 mg group, respectively). Hematologic AEs including leukopenia, neutropenia, thrombocytopenia and anaemia were more

common in the 800 mg arm. Interestingly, biochemical abnormalities like hypophosphatemia, hypocalcaemia or transaminase elevations were not different between the 2 arms and were generally low except hypophosphatemia (12% in the 800 mg and 14.6% in the 400 mg imatinib arm, respectively). AEs in general led to a higher discontinuation rate of 9.4% in the imatinib HD group compared to 3.8% the 400 mg group. Half of the patients in the high dose arm required a dose reduction to < 600 mg at some point during the study. Nevertheless, the average daily doses of imatinib were 662 mg in the HD arm and 388 mg in the standard dose arm. At 12 months, 61% of the patients in the HD arm were still treated with their assigned dose and 78% of the patients in the HD arm were capable to take an imatinib dose of at least 600 mg per day.

3.2 High dose imatinib for Sokal high risk patients?

Potential candidates that were thought to benefit particularly from HD imatinib were patients with a high Sokal risk score (Sokal et al., 1984). A retrospective subgroup analysis of 115 patients in the TOPS trial, however, reveals an almost identical overall CCyR rate by 12 months for both groups (61.9% CCyR with 400mg/day and 63.0% with HD imatinib, p=1.0) and a slightly improved MMR^{IS} rate at 12 months for the HD group (26.2% MMR^{IS} with imatinib 400mg/day and 39.7% MMR^{IS} with HD imatinib, p=0.16). The number of patients in the high Sokal risk group was, however, too small to draw definitive conclusions (n=68). A study on this particular patient population (i.e. patients with high Sokal risk score) was initiated by the ELN with a prospective trial that compared imatinib 400 mg and 800 mg daily in the front-line treatment of 216 Sokal high risk CML CP patients (Baccarani et al., 2009a). This study, however, failed to demonstrate any benefit for HD imatinib over standard dose for the Sokal high risk population. The CCyR rate at 12 months (the primary endpoint of the study) was similar with 64% CCyR in the HD arm and 58% CCyR in the imatinib standard dose arm (p=0.435). CCyR rates, however, appeared to be related to the actual dose as 96% of the patients that were capable to take the intended dose of 800 mg imatinib in fact achieved a CCyR. In contrast, CCyR was lowest with 20% in patients assigned to the HD arm with an average daily dose of less than 400 mg imatinib per day. Furthermore, no significant differences could be detected in cytogenetic or molecular responses at any time and OS, PFS and event free survival (EFS) were also not different. The authors of this study therefore have suggested that HD imatinib (800 mg per day) cannot be recommended as front-line therapy in CML Sokal high risk patients (Baccarani et al., 2009a). In an additional study that compares a tolerability-adapted 800 mg imatinib dose per day with the standard 400 mg dose in newly diagnosed CML patients from the German CML study group in cooperation with the Swiss group for clinical research (SAKK) and which is described in detail below, the authors report that the rapidly occurring MMR^{IS} that they noticed with the tolerability-adapted 800 mg imatinib dose were only observed in low- and intermediate-risk but not in high-risk patients according to the Sokal and the EuroScore (Hasford et al., 1998), another prognostic score that was initially developed to predict the survival of CML patients treated with interferons. For unknown reasons high-risk patients seem to be less responsive to any therapy including HD imatinib, although nowadays even Sokal high-risk CML patients benefit significantly from imatinib therapy compared to treatments from the pre-imatinib era and the survival has improved dramatically even in this high-risk cohort.

3.3 Imatinib standard dose versus high dose induction trial ("ISTAHIT" study)

A different approach was tested by the Central European Leukemia Study Group (CELSG) in the international multicentre Imatinib STAndard dose versus High dose Induction Trial ("ISTAHIT") (Petzer et al., 2010a). Different from the other phase III trials that tested HD imatinib versus the standard dose they tested *pre-treated* CML patients in CP. These patients were - although pre-treated - tyrosine kinase inhibitor (TKI) naïve but pre-treated with drugs from the pre-imatinib era, such as hydroxyurea, interferons, busulfan or Ara-C. The medium number of pre-treatments before study entry was 2. Overall, this patient population was in later CP of their disease and subsequently at a higher risk for disease progression. In addition, HD imatinib (800 mg per day) was limited to the first 6 months of therapy and then reduced to 400 mg as "maintenance" therapy. The reasons for choosing this strategy were a "hit hard and early" concept in order to achieve rapid and deep cytogenetic and molecular responses on the one hand and concerns on reported hematotoxicity on the long term on the other hand, especially in regard to this pre-treated patient population in later chronic phase (Cortes et al, 2003). A report on a planned interim analysis (after half of the patients had been treated for 12 months) demonstrated significant improvements in the rates of MCyR and CCyR at early time points such as 3 and 6 months as well as in MMR^{IS} at 6 months in favour of HD imatinib compared to the standard dose (400 mg once daily) (Petzer et al., 2010a). As expected for this heavily pre-treated patient population, WHO grade 3 and 4 hematotoxicity was significantly increased during the first 6 months in HD imatinib arm, whereas WHO grade 3 and 4 non-hematotoxic AEs were comparable. Notably, severe infections were not improved in spite of the higher rates of leukopenias and neutropenias. In a first report on the final analyses of this study the authors have reported that in spite of the fact that significantly higher and more rapid cytogenetic responses occurred not only at early time points but even at later time points when HD imatinib was already reduced to standard dose after 6 months (e.g. CCyR at 12 months was superior with 52.9% in the experimental HD arm compared to 31.8% in standard dose imatinib arm; p=0.006; MMR^{IS} at 24 months was 42.5% compared to 26.5% in favour of the experimental HD arm; p=0.034) the strategy of using high doses of imatinib as induction therapy again did not improve OS and PFS (Petzer et al., 2010b). In general, in terms of the biologic effects (i.e. the achievement of cytogenetic and molecular responses) the data are similar to other imatinib HD trials, where imatinib was at least intended to be given throughout the entire study period.

3.4 Tolerability-adapted 800 mg imatinib: Experience form the German CML-SG and the Swiss group for clinical research (SAKK)

Another slightly different approach was chosen by the German CML study group in cooperation with the Swiss group for clinical research (SAKK) (Hehlmann et al). They tried to optimize the therapy for newly diagnosed CML patients in CP by comparing a tolerability-adapted 800 mg imatinib dose per day with the 400 mg dose in order to avoid higher grade toxicity. In the imatinib 800 mg/day arm the full 800 mg dose was given after a 6-week-run-in period with 400 mg imatinib per day to avoid excessive cytopenias. The median dose of imatinib in the tolerability-adapted 800 mg arm was 628 mg per day compared to 400 mg in the 400 mg per day arm. The highest median dose of imatinib was reached in the second 3-month period (month 3 to 6) with 737 mg per day. Thereafter, the

dosage decreased to around 600 mg/day due to adaptation of the dose to tolerability according to the protocol. Again, significantly higher rates of CCyR and MMR^{IS} were achieved with the higher imatinib dosage compared to the 400 mg per day dose at earlier time points (e.g. at 6 and 12 months, respectively) but these differences again subsequently decreased at later time points (e.g. MMR^{IS} at 36 months was 81.6% for the tolerability-adapted 800 mg imatinib dose and 79.3% for the imatinib standard dose arm with 400 mg per day). AEs were more frequent with 800mg imatinib per day, especially oedemas and gastrointestinal problems, but WHO grade 3 and 4 AEs were reported to be rare and not more frequent in the tolerability-adapted 800 mg imatinib dose arm. Although the rates of MMR^{IS} by 12 months were superior in the tolerability-adapted 800 mg imatinib dose arm and the achievement of MMR^{IS} by 12 months was directly associated with an improved survival no differences were reported by the authors for OS (2-year survival was 96.0% in the tolerability-adapted 800 mg dose arm and 96.9% in the imatinib 400mg dose arm, respectively) and PFS when comparing the 2 different treatment arms. This also includes progressions and numbers and causes of death (Hehlmann et al).

Taking all these phase III studies on early dose intensification of imatinib into consideration one has to state that so far none of these studies has demonstrated a substantial benefit over the standard dose of 400 mg/day, especially in terms of OS or PFS. This is somehow surprising as the majority of the studies showed a significantly higher rate of cytogenetic and molecular responses occurring at earlier time points. An improved early response was recently linked to a prolonged survival in CML-patients (Hughes et al.,2010; Iacobucci et al., 2006). These data were, however, collected from CP CML patients that were all treated upfront with a daily imatinib dose of 400 mg. It very much looks as if, over time, the inhibitory effect of imatinib reaches a plateau that is accomplished earlier with higher doses of imatinib and later with the standard 400 mg dose and no clear evidence has been available so far that under these circumstances these earlier responses will translate into an improved survival. Maybe a longer follow-up will give us the appropriate answer. For the moment, based on the data available so far, an initial high dose imatinib treatment with 800 mg per day cannot be recommended at the present time outside of clinical studies. A longer follow-up will show whether initial higher imatinib doses will possibly translate into improved long-term outcomes.

4. Dose escalation after imatinib failure

As outlined above, up front dose escalation with imatinib leads to improved and earlier cytogenetic and molecular responses in CML patients in CP but this has so far not led to an improved survival advantage. However, in the very beginning of the imatinib era the optimal dosing schedule has not been investigated extensively. This is reflected by the fact that the maximum tolerated dose has not been reached in the phase I trial (Druker et al., 2001) that comprised 83 patients. Beyond a dose of 300 mg per day toxicity and efficacy was not different in a subset of patients which led to the use of 400 mg imatinib per day in the following phase II studies. Among these trials the option to increase the imatinib dose to 2 x 400 mg per day after insufficient response to standard dose imatinib suggested that dose escalation might be a possible strategy in patients with imatinib resistance (Kantarjian et al., 2002).

4.1 Primary and secondary resistance to imatinib

Patients resistant to imatinib may experience primary (intrinsic) or secondary (acquired) resistance (Jabbour et al., 2009a). Primary resistance has been defined as the lack of a distinct level of response at various time points during treatment (landmark response). By the NCCN guidelines, primary resistance is defined as the failure to achieve CHR within 3 to 6 months of treatment initiation, lack of any level of cytogenetic response at 6 months or the lack of a MCyR at month 12 or a CCyR at month 18 (National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Chronic Myelogenous Leukemia. Version 2.2010. Jenkintown, Pa: NCCN; 2009. http://www.nccn.org/professionals/physician_gls/PDF/cml.pdf).

According to recommendations from the ELN treatment failure is defined as lack of CHR at 3 months, no CHR or lack of any cytogenetic response (CyR) at 6 months, less than partial CyR (PCyR) at 12 months or less than a CCyR at 18 months (Baccarani et al., 2009b).

Secondary resistance is a disease progression and the loss of any therapeutic effect during the treatment with imatinib. This occurs in approximately 24% of patients, mostly within the first three years, as has been shown in the IRIS-trial (Druker et al., 2006).

The reasons for resistance include point mutations of BCR-ABL, amplification of BCR-ABL, low Oct-1 activity resulting in low influx of imatinib, high MDR-1 activity resulting in high imatinib efflux, and additional clonal aberrations. According to the ELN-guidelines these patients might be candidates for dose escalation of imatinib. However, some point mutations like T315I, G250K, E255K, F486S and E255V cause absolute imatinib resistance and therefore are contraindications for a dose escalation strategy. With the exception of T315I the use of second generation TKIs like nilotinib or dasatinib is recommended in these cases. Patients with T315I are resistant to all currently available TKIs and should be treated within clinical trials and the option of stem cell transplantation should be evaluated. Other mutations like M315T, V299L etc., however, cause relative imatinib resistance, which makes dose escalation of imatinib feasible. A prerequisite for imatinib dose escalation is the absence of relevant side effects with the 400 mg dose once daily. Other reasons for relative imatinib resistance that potentially might be overcome by dose escalation are additional genetic abberations, a high efflux of the drug due to high MDR1-activity, low influx of the drug by low Oct-1 activity, and BCR-ABL amplification (figure 1).

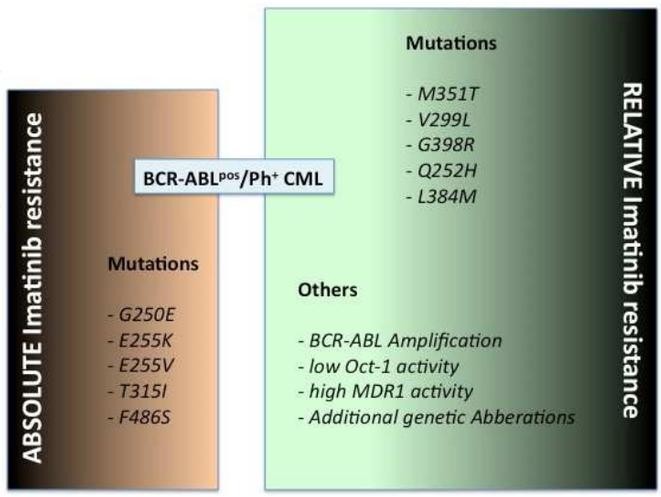


Fig. 1. Overview on causes leading to absolute or relative imatinib resistance in CML (adapted from Rudzki et al., 2011)

4.2 Clinical studies showing effect of dose escalation after imatinib failure

There are several clinical trials supporting dose escalation in patients already receiving standard dose imatinib. First, a study performed by Kantarjian et al. included patients of the phase II studies 110 and 113 and represents a single center study at the MD Anderson Cancer Center. Dose escalation was allowed from 400 to 800 mg per day if standard dose imatinib was well tolerated. If the starting dose was 300 mg or if the dose had to be decreased from 400 mg to 300 mg due to initial side effects, the dose was escalated to 600 mg per day. The indication for dose escalation was defined as not achieving a CHR (defined as haematological resistance) after 3 months, failure to achieve a MCyR at 12 months (defined as cytogenetic resistance), if CHR was lost at any time (defined as hematologic relapse) or if Ph-positive cells increased by 30% at two occasions (defined as cytogenetic relapse). From 261 included patients, 47 were escalated to 800 mg per day and 7 were escalated to 600 mg per day. Among 34 patients that were escalated due to cytogenetic resistance or relapse, 56% achieved a cytogenetic response again. CCyR, however, was only reached in 18%. Success rates were higher among patients treated for haematological resistance or relapse as from 20 dose escalated patients 65% regained a hematologic response. With this study the authors demonstrated that some effect could be achieved by dose escalation after primary imatinib failure. However, the depth of response achieved with this procedure might be insufficient as only a minority of patients reached CCyR. This, however, is the goal of treatment as CCyR or MMR (however, this study does not report on molecular response) is known to be of high relevance for the long-term outcome in CML patients (Kantarjian et al., 2003).

Zonder et al. performed a dose escalation study in 12 CP CML and four CML patients in AP with signs of disease progression (Zonder et al., 2003) Again, some responses could be achieved but the majority of patients did not benefit from this treatment. Such a transient response has also been shown by Marin and colleagues (Marin et al., 2003). An Italian study (Breccia et al., 2010), however, was capable to demonstrate a prolonged response in patients with cytogenetic relapse, especially in patients with acquired cytogenetic resistance. According to the current ELN guidelines, patients with progressive disease or with cytogenetic resistance are currently considered as treatment failures and qualify for second generation TKIs or an allogeneic stem cell transplantation and not for dose escalation (Baccarani et al., 2009b).

In patients with suboptimal molecular response the benefit also seems to be limited, whereas dose escalation in patients with suboptimal cytogenetic response is more promising (Rea et al., 2009). However, data obtained from these studies have to be interpreted with caution as the patient numbers are rather low. A larger study was again presented by the MD Anderson Cancer Center. Out of 626 patients, 84 patients were dose escalated due to treatment failure on standard dose imatinib (Jabbour et al., 2009b). In 72 out of these patients the dose was increased from 400 mg to 800 mg per day and in 12 patients from 300 mg to 600 mg per day. 40% achieved a CCyR with a minority of patients reaching deep and prognostic meaningful responses. Patients that already had a previous CCyR seemed to especially benefit from dose escalation. Other patients showed disappointing low and insufficient response rates with a significantly worse EFS. A point of criticism with this study is that only 25 out of the 84 patients were tested for BCR-ABL mutations and mutations that are associated with high imatinib resistance have not been detected. In contrast to the patient cohort of the MD Anderson Cancer Center, the patient population of the IRIS trial was not previously treated with IFN-alpha. Within the latter, a

dose escalation was performed in a two-step manner. The first step was an escalation to 600 mg per day. If no sufficient response was noted two weeks later a further escalation to 800 mg per day was allowed. 39 patients were treated by dose escalation, but only a small proportion of patients reached a CCyR (Kantarjian et al., 2009). PFS for these patients was 84% and OS 89% three years after dose escalation. The criteria for resistance, however, were slightly different to the current ELN-guidelines (Baccarani et al. 2009b). Retrospectively, 48 patients would have fulfilled the criteria of imatinib resistance. Significantly different results, however, cannot be expected due to this fact. The Korean CML study group evaluated the efficacy of dose escalation in patients with suboptimal response or treatment failure according to the ELN-guidelines. In total they included 64 CML patients in CP, AP or BC and reported a CCyR rate of 23,9% at 12 months and a clear correlation between early molecular response and time to treatment failure (Koh et al., 2010).

4.3 Dose escalation versus second-generation Tyrosine Kinase Inhibitor (TKI) or IFN-alpha

The START trial compared the efficacy of imatinib dose escalation with the use of the second generation TKI dasatinib. Patients harbouring mutations associated with a high degree of imatinib resistance were excluded (Kantarjian et al., 2009). Patients previously treated with 400 to 600 mg imatinib per day were randomized to receive either 800 mg imatinib per day or dasatinib 70 mg twice a day. Treatment with dasatinib resulted in higher rates of CHR (93 vs 82%), MCyR (53 vs 33%), CCyR (44 vs 18%), MMR (29 vs 12%) and in a significantly prolonged PFS. A significant proportion of 70% of patients in this study, however, already were dose escalated to 500 or 600 mg of imatinib before the inclusion into the study, making the interpretation of these results difficult. If only patients are compared that were either dose escalated from 400 mg to 800 mg imatinib per day or received dasatinib, the results are less impressive in favour of dasatinib with almost identical rates in MCyR and CCyR.

The Spanish PETHEMA and the Australasian CML study group also compared high dose imatinib to alternative treatments in patients not achieving an optimal response (Cervantes et al., 2010). If patients did not achieve a CHR at 3 months they were randomized to continuation of standard dose imatinib or to high dose imatinib (800 mg/day). Patients not achieving a CCyR at 6 months were randomized to high dose imatinib or standard dose imatinib in combination with IFN-alpha and patients not achieving a MMR^{IS} at 18 months were dose escalated as well. 210 patients were included. At month 6, 17 patients had the dose of imatinib increased, 16 out of them reached a CCyR at month 18. 9 patients were dose escalated at month 18 and 8 achieved an MMR a few months later (Cervantes et al., 2010).

4.4 Early dose escalation

A very interesting approach has been investigated by the Australasian CML study group with the TIDEL II study (Yeung et al., 2010). This is a single arm study that allowed dose escalation at a very early time point based on the levels of the imatinib plasma levels that had to be above 1000 ng/ml. BCR-ABL levels of >10% at 3 months, >1% at 6 months or less than a MMR (i.e. >0.1%) at 12 months were indications for a switch to nilotinib. The MMR achieved by this approach was 66% at 12 months which is far better than published for

nilotinib in the ENESTnd and dasatinib in the Daisision trial (43 and 46%, respectively). The early escalation of imatinib upon suboptimal response, therefore, seems an interesting approach for future studies.

5. Accelerated phase and blast crisis

High dose imatinib in accelerated phase (AP) and blast crisis (BC) has been studied in phase II studies only (table 2). Talpaz et al. firstly reported the results on 181 patients with CML-AP. Initially, patients were enrolled in the STI 571 0109 study and were treated with 400 mg imatinib. In 119 patients the starting dose was increased to 600 mg per day after the final results of the phase I study confirmed the safety and efficacy of high dose imatinib. Analysis at 48 months revealed that 18% of patients remained on imatinib while 82% discontinued imatinib. The primary reasons for that included progression or lack of efficacy. Best observed responses were CHR in 40%, PCyR in 7% and CCyR in 20% of patients. The median OS was 43 months for CML-AP patients treated with 600 mg imatinib per day. The major prognostic factor was response: 72% of the patients with a MCyR at month three were alive at 48 months compared to 42% of patients without MCyR at month three (Talpaz et al., 2002). In a long term follow up report the same authors stated that 23% of the patients remained on study follow up with 9% still taking the study drug (Silver et al., 2009). The circumstance that initially a part of the patients was treated with 400 mg imatinib enabled a retrospective analysis comparing these patients with the other part of the patients treated with 600 mg upfront. These analyses revealed that CML patients in AP that started with 600 mg imatinib had a favourable OS and PFS compared to patients starting with 400 mg imatinib once daily. These facts led to the recommendation to use 600 mg imatinib per day as starting dose for the treatment of advanced CML. These results were confirmed by a similar phase II study, which was performed by Palandri et al. They treated 111 patients in CML-AP with 600 mg imatinib per day. After a median long term follow up of 82 months they have reported that 96% of the patients converted to CML-CP and 71% of patients achieved a CHR. 30% of patients reached a MCyR and 21% a CCyR. These responses were maintained for at least 4 weeks. After the prolonged follow-up 14% of the patients received a second-generation tyrosine kinase inhibitor and 19% of the patients were still alive on imatinib therapy. The median OS was 37 months, and was significantly associated with CHR or CCyR (Palandri et al., 2009).

Author	n	CML-phase	Dose imatinib [mg/d]	median OS
Talpaz et al., 2002	119	AP	600	43 months
Palandri et al., 2009	111	AP	600	37 months
Sawyers et al., 2002	229	BC	600	7 months
Palandri et al., 2008	92	BC	600	7 months

Table 2. Phase II studies investigating high dose imatinib in CML-AP and -BC

Efficacy of high dose imatinib in BC was investigated in the STI571 0102 study. 229 patients were enrolled in this phase II trial and treated with 400 mg or 600 mg imatinib per day (Sawyers et al., 2002). At 48 months, only 3% of patients still were on imatinib therapy while the remaining patients were off treatment due to progression or lack of efficacy. CHR was achieved in 9%, MCyR in 16%, and CCyR in 7% of patients. The estimated OS was 7 months for patients treated with 600 mg imatinib per day. Similar results were obtained in an Italian phase II study. Palandri et al. treated 92 patients in BC with 600 mg imatinib per day. The results are very similar to the STI571 0102 study by showing a median OS of 7 months and only a minority of patients reaching sufficient cytogenetic responses. These were maintained for at least 4 weeks and after a median follow-up of 66 months, 8% of the patients were alive (Palandri et al., 2008).

6. Conclusion

For the moment, sufficient data are not available to recommend an initial high dose imatinib therapy in CP CML patients in spite of well documented superior cytogenetic and molecular remissions that are obtained earlier by using higher imatinib doses. In contrast, a dose of 600 mg per day is recommended for the treatment of advanced phases (i.e. AP and BC). A dose increase as a consequence of suboptimal response or failure according to ELN or NCCN criteria is a valid option if no imatinib resistant point mutation on the one hand and no significant side effects with the 400 mg imatinib dose on the other hand are present at that time. Alternative options at that time are also already commercially available second generation TKIs like dasatinib or nilotinib. These latter two TKIs are meanwhile also registered for the first line treatment of CP CML and may diminish the need of further investigations on the use of high imatinib doses in the future.

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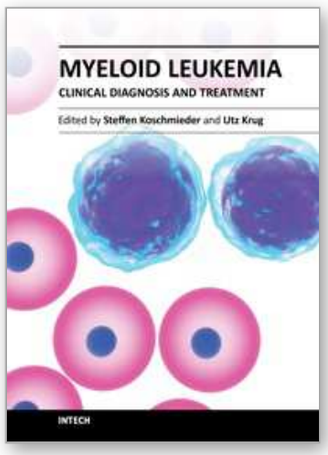
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This book comprises a series of chapters from experts in the field of diagnosis and treatment of myeloid leukemias from all over the world, including America, Europe, Africa and Asia. It contains both reviews on clinical aspects of acute (AML) and chronic myeloid leukemias (CML) and original publications covering specific clinical aspects of these important diseases. Covering the specifics of myeloid leukemia epidemiology, diagnosis, risk stratification and management by authors from different parts of the world, this book will be of interest to experienced hematologists as well as physicians in training and students from all around the globe.

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