ARTICLE

Imatinib dose reduction in major molecular response of chronic myeloid leukemia: results from the German Chronic Myeloid Leukemia-Study IV

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ABSTRACT

Standard first-line therapy of chronic myeloid leukemia is treatment with imatinib. In the randomized German Chronic Myeloid Leukemia-Study IV, more potent BCR-ABL inhibition with 800 mg ('high-dose') imatinib accelerated achievement of a deep molecular remission. However, whether and when a de-escalation of the dose intensity under high-dose imatinib can be safely performed without increasing the risk of losing deep molecular response is unknown. To gain insights into this clinically relevant question, we analyzed the outcome of imatinib dose reductions from 800 mg to 400 mg daily in the Chronic Myeloid Leukemia-Study IV. Of the 422 patients that were randomized to the 800 mg arm, 68 reduced imatinib to 400 mg after they had achieved at least a stable major molecular response. Of these 68 patients, 61 (90%) maintained major molecular remission on imatinib at 400 mg. Five of the seven patients who lost major molecular remission on the imatinib standard dose regained major molecular remission while still on 400 mg imatinib. Only two of 68 patients had to switch to more potent kinase inhibition to regain major molecular remission. Importantly, the lengths of the intervals between imatinib high-dose treatment before and after achieving major molecular remission were associated with the probabilities of maintaining major molecular remission with the standard dose of imatinib. Taken together, the data support the view that a deep molecular remission achieved with high-dose imatinib can be safely maintained with standard dose in most patients. Study protocol registered at *clinicaltrials.gov 00055874*.

Introduction

Approved first-line therapies of chronic myeloid leukemia (CML) are the tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, nilotinib and bosutinib.[1-5] Imatinib led to distinctively improved progression-free and overall survival of chronic phase CML patients as compared with previous conventional treatment standards in CML.[6,7] Second-generation TKIs, such as nilotinib and dasatinib, but also a higher dose of imatinib (800 mg/day), induce deep molecular response (MR) faster[8,9] and in a larger proportion of patients.[10,11] As a consequence, deep molecular remission (an essential eligibility criterion for TKI discontinuation) can be achieved earlier and in more patients when compared to imatinib standard dose.[12,13] However, the benefit of pursuing highly-potent BCR-ABL-kinase inhibition once deep MR has been achieved is less clear. Moreover, for those patients in deep MR, which (for whatever reason) require long-term treatment, the tolerability and prevention of organ damage through clinically relevant and potentially irreversible side effects, such as pulmonary hypertension, diabetes, hypercholesterinemia, and cardiovascular morbidity become the most important priority.[14-17] Thus, if high-potency BCR-ABL inhibition is not needed to sustain remission or improve survival, then the risk of potentially harmful side effects from second- or third-generation TKI must be weighed against the long-term safety of using imatinib,[18-20] especially when also considering that generic imatinib is more cost effective. By analyzing the outcome of 800 mg to 400 mg imatinib dose reductions performed in at least stable major molecular remission (MMR) within the randomized German CML-Study IV,[8,21] we aimed to address the clinically important questions of in which patients and at what time after initiation of strong BCR-ABL inhibition with 800 mg imatinib less potent BCR-ABL inhibition with standard dose imatinib is sufficient to maintain stable MMR.

Methods

Patients and Chronic Myeloid Leukemia-Study IV protocol

All patients investigated in this study were treated within the randomized German CML-Study IV.[8,21] Imatinib monotherapy at 800 mg/day was one of the five arms in this trial. The study protocol was registered at *clinicaltrials.gov 00055874*. Randomization took place from July 2002 through March 2012. During a pilot-phase of 3 years, only high-risk patients according to the Euro score[22] were randomized to imatinib 800 mg/day. In 2005, imatinib 800 mg/day was started as a full study arm.

To avoid selection bias towards high-risk patients, in this retrospective analysis, only patients randomized from 2005 were evaluated.

Definition of high-dose imatinib treatment

Imatinib at a dose of 800 mg/day for at least 6 months was classified as high-dose therapy. Six months was chosen because the presence of MMR after 6 months significantly increased the probabilities of patients going on to achieve deep MR later.[8] A high-dose treatment interval began with the first dose of 800 mg/day and ended at the time of imatinib dose reduction to 400 mg/day. An intermittent 600 mg/day interval which directly preceded or followed a high-dose treatment interval with 800 mg/day was still considered high-dose treatment because the effective median dose of imatinib in the 800 mg arm was seen to be only 600 mg in the CML-Study IV.[8]

The molecular analyses are described in the *Online Supplementary Appendix*.

Statistical analysis

Survival without loss of MMR was defined as the time between the start of reduced imatinib therapy with 400 mg/day either until loss of MMR or until the date of the last evaluation of MR status with the date linkable to the reduction period, as defined in the *Online Supplementary Methods*. Probabilities of molecular relapse-free survival (RFS) were estimated by the Kaplan-Meier method. The association between a variable and molecular RFS was assessed by Cox regression.[23] For identification of cutoffs, the minimal *P*-value approach was used while assuming that the smallest group should contain at least 10% of patients.[24] Bootstrap resampling and kernel density estimation were carried out to assess the stability of a cutoff.[25,26]

Point estimates are given together with their 95% confidence intervals (95%CI). In the case of the hazard ratios (HR), for estimation of the 95%CI, the profile likelihood was used and *P*-values were calculated from the likelihood ratio test. All analyses are descriptive and exploratory. Apart from the minimal *P*-value

approach, the significance level of the two-sided *P*-value was 0.05 for all statistical tests. Analyses were carried out with SAS v.9.4 or R v.3.4.3.

Ethical approval

The CML-Study IV was performed in accordance with the Declaration of Helsinki, and was approved by the central ethics committee of the Medizinische Fakultaet Mannheim and the local ethics committees of all participating centers. Written informed consent was obtained from all patients prior to entering the CML-Study IV.

Results

Imatinib dose reduction in the 800 mg cohort of the Chronic Myeloid Leukemia-Study IV

Of 1551 patients with newly diagnosed chronic phase CML, 422 were randomly assigned to 800 mg imatinib per day. Of these, two patients violated CML-Study IV inclusion criteria, ten were part of the pilot study, and a further ten were excluded from this analysis due to missing treatment data (see the CONSORT flow diagram in Figure 1).

Of the remaining 400 patients randomized to 800 mg imatinib, 92 patients had never received imatinib 800 mg/day and 163 patients never achieved MMR within the imatinib 800 mg/day interval. Of the remaining 145 patients, 39 had never reduced the 800 mg/day dose or had no observation time after dose reduction. A further 21 had an 800 mg/day interval of less than 6 months (i.e. not high-dose imatinib by our definition). Two patients were excluded because they had more than 6 weeks without any therapy between ending 800 mg/day imatinib and recommencing 400 mg/day. Eight patients were not considered because treatment with 400 mg/day lasted for less than 6 months. After exclusion of a further seven patients who had not been monitored by the central molecular diagnostic laboratory of the CML-Study IV, 68 patients were evaluable for our analyses.

Data entry was closed on July 21, 2015.

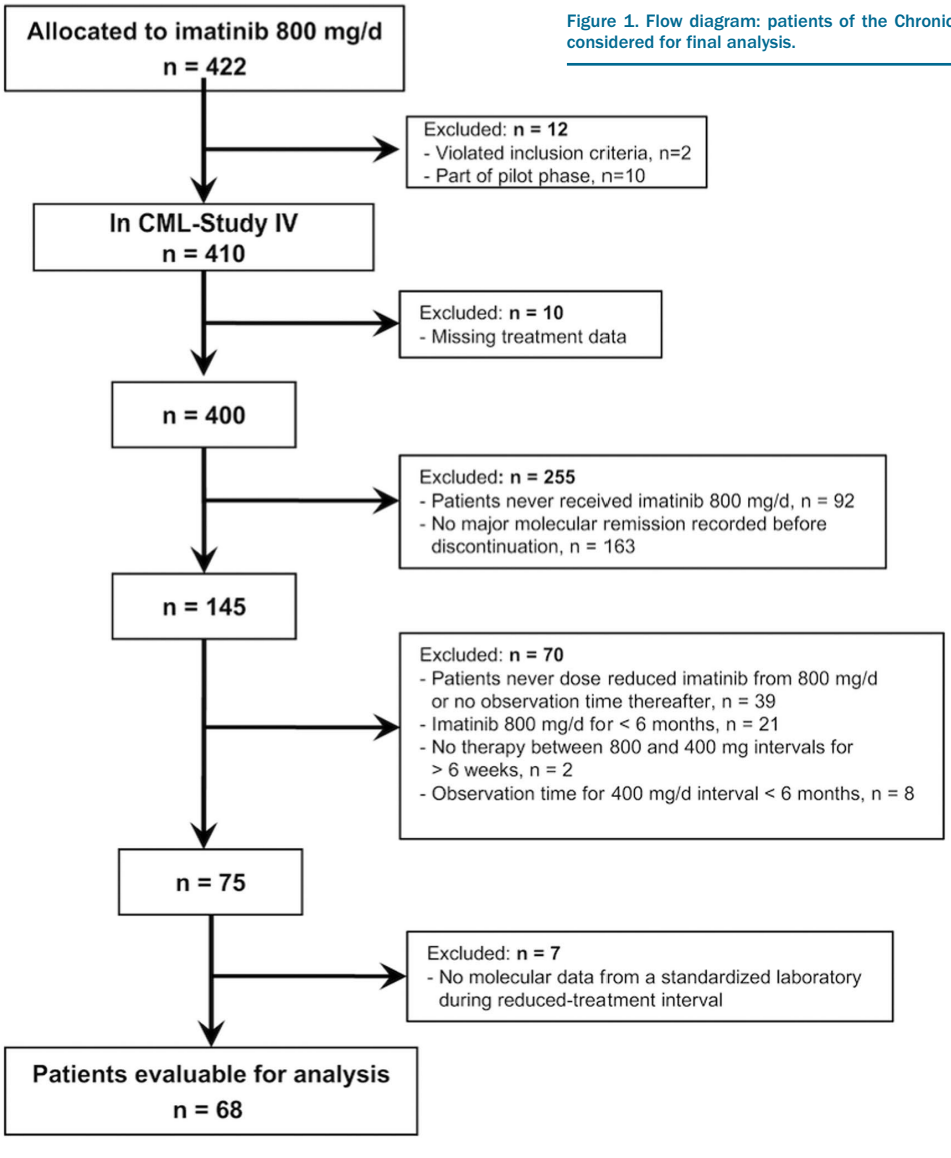


Figure 1. Flow diagram: patients of the Chronic Myeloid Leukemia-Study IV considered for final analysis.

Table 1. Univariate Cox regression estimating the influence on relapse-free survival after reduction to imatinib at 400 mg.

Variable	n / Loss of MMR	Estimation of coefficient β	Standard deviation of estimated β	Hazard ratio	Lower 95%CI limit for hazard ratio	Upper 95%CI ratio limit for hazard ratio	P
Variables recorded at diagnosis							
Age (years)	68 / 7	-0.001	0.03	1.00	0.94	1.06	0.97
Gender	68 / 7						0.28
Male	48 / 6	baseline	–	–	–	–	–
Female	20 / 1	-1.04	1.08	0.36	0.02	2.08	–
Spleen size below costal margin (cm)	68 / 7	0.16	0.06	1.17	1.03	1.31	0.02
White blood cell count ($x10^9$/L) / 100	68 / 7	1.01	0.25	2.76	1.69	4.73	0.0001
Blasts in peripheral blood (%)	68 / 7	0.24	0.11	1.27	0.99	1.55	0.06
Eosinophils in peripheral blood (%)	68 / 7	0.19	0.07	1.21	1.02	1.37	0.03
Basophils in peripheral blood (%)	68 / 7	0.09	0.07	1.10	0.93	1.25	0.24
Platelet count ($x10^9$/L) /1000	68 / 7	-2.44	2.35	1.00	0.00	3.40	0.24
Sokal score	68 / 7						0.57
Low risk	29 / 2	baseline	–	–	–	–	–
Intermediate risk	27 / 3	0.60	0.91	1.82	0.30	13.79	–
High risk	12 / 2	1.05	1.01	2.87	0.34	24.15	–
Euro score	68 / 7						0.04
Low risk	30 / 1	baseline	–	–	–	–	–
Intermediate risk	34 / 4	1.42	1.12	4.13	0.61	80.86	–
High risk	4 / 2	3.04	1.23	20.98	1.99	454.17	–
EUTOS score	68 / 7						0.01
Low risk	62 / 4	baseline	–	–	–	–	–
High risk	6 / 3	2.26	0.77	9.56	1.88	43.50	–
ELTS score	68 / 7						0.01
Low risk	44 / 1	baseline	–	–	–	–	–
Intermediate risk	19 / 4	2.30	1.12	9.98	1.48	195.25	–
High risk	5 / 2	3.17	1.23	23.71	2.25	513.27	–
Variables recorded under treatment and their influence after stopping treatment at 800mg/day							
Time with 800mg dosage, months	68 / 7	-0.05	0.03	0.95	0.891	0.998	0.04
Time from start of 800mg until MMR, months	68 / 7	0.13	0.05	1.14	1.02	1.27	0.02
Time from MMR until end of 800mg, months	68 / 7	-0.15	0.07	0.86	0.72	0.96	0.0006

CI: Confidence Interval; MMR: major molecular remission; EUTOS: European Treatment and Outcome Study; ELTS: EUTOS long-term survival.

Patients' characteristics are shown in *Online Supplementary Table S1*. Median age was 52 years and 71% of the 68 patients were male.

Treatment course of patients with imatinib dose reduction to 400 mg

Twenty-five of the 68 patients on high-dose imatinib (37%) started their primary treatment directly with 800 mg/day (first treatment interval). Forty patients (59%) increased to 800 mg/day after a first period of 400 mg imatinib. Three patients only started the 800 mg imatinib dose later.

Median time on high-dose imatinib therapy was 31 months (range: 6-98 months) for the 68 patients who later reduced imatinib treatment to 400 mg (*Online Supplementary Table S1*). In this cohort, the median duration of treatment with 400 mg/day after dose reduction was 34 months (range: 6-78 months). For 53 out of 68 patients (78%), this was the last reported treatment and dose. Five patients (7%) eventually stopped any TKI therapy following imatinib dose reduction to 400 mg. In one patient, no information regarding treatment after dose reduction to 400 mg was available. The remaining 9 out of 68 patients (13%) received a more potent ABL-kinase inhibition: 600 mg imatinib (n=1), 800 mg imatinib (n=5), nilotinib (n=2), or dasatinib (n=1).

Molecular relapse-free survival after imatinib dose reduction to 400 mg

Seven of 68 patients experienced a loss of MMR during the reduction interval (Figure 2). This resulted in a 1-year molecular relapse-free survival (RFS) of 90% (95%CI: 81-

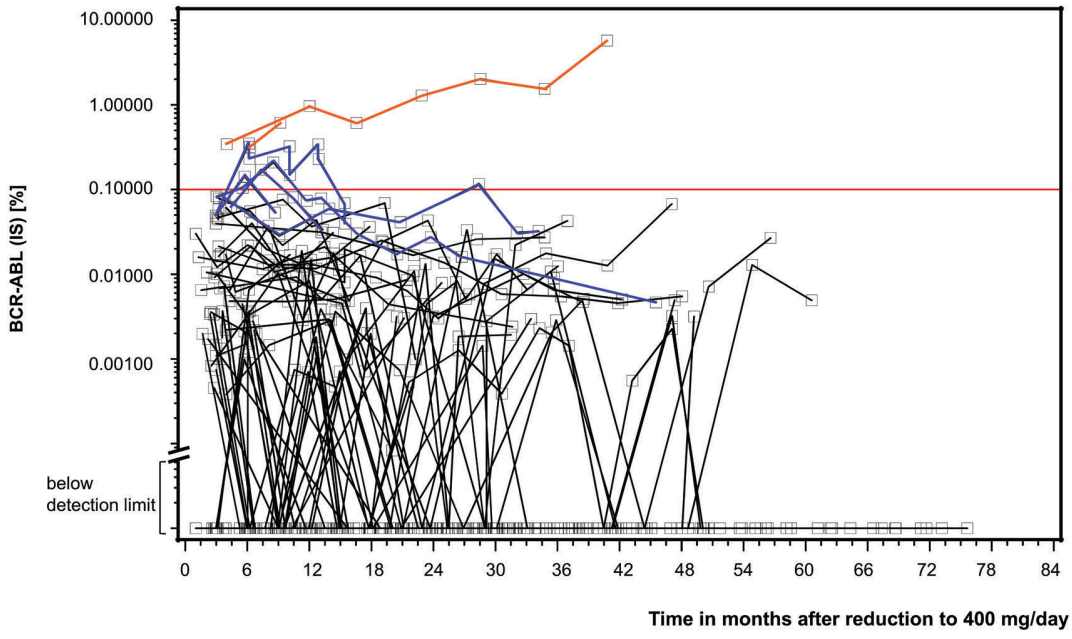


Figure 2. Courses of BCR-ABL (IS) in 68 patients with imatinib dose reduction. Results below the horizontal red line represent at least major molecular response (MMR). Sixty-one patients have never lost MMR (courses with black lines). Five patients with loss of MMR regained MMR while continuing with reduced imatinib dose at 400 mg/day (blue lines). Two patients with loss of MMR did not regain MMR while on the lower imatinib dose and were switched to nilotinib or imatinib at 600 mg/day, respectively (orange lines).

96%). With only one MMR loss occurring later than 12 months after dose reduction, the 3-year molecular RFS was 88% (95%CI: 77-94%) (Figure 3). However, MMR loss was only temporary in five of the seven patients; these patients regained MMR while still on the lower 400 mg imatinib dose. Only two patients with MMR loss were switched to more potent ABL-inhibition with nilotinib or 600 mg imatinib to regain MMR (Figure 2). It is worthy of note that, at the time of stopping high-dose treatment, 43 of 68 patients were at least in MR4, 33 of them even at least in MR4.5. Of the 43 patients, 10 lost MR4 at some point; none lost MMR.

Clinical variables and high-dose imatinib treatment durations prior to and after achieving major molecular response were associated with probabilities of relapse-free survival

Of the clinical variables evaluated at diagnosis, larger spleen size below costal margin (HR: 1.17, 95%CI: 1.03-1.31; *P*=0.02), higher white blood cell count (WBC) (HR: 2.76, 95%CI: 1.69-4.73; *P*=0.0001), and a higher percentage of eosinophils (HR: 1.21, 95%CI: 1.02-1.37; *P*=0.03) were significantly associated with probabilities of lower RFS (Table 1). Furthermore, the high-risk groups according to the Euro and the European Treatment and Outcome Study (EUTOS) scores, as well as the intermediate- and high-risk groups according to the EUTOS long-term survival (ELTS) score, suggested significantly worse molecular RFS than their corresponding low-risk groups.

The longer the total treatment time at 800 mg/day, the higher were the probabilities of RFS (HR: 0.95, 95%CI: 0.891-0.998; *P*=0.04). However, as in the EURO-SKI study, which analyzed TKI discontinuation, the main focus was to investigate treatment time after dividing this time interval into the time of high-dose treatment before and after achievement of MR.[27]

Four of the 68 patients had already achieved MMR with 400 mg imatinib/ day prior to the high-dose treatment interval. The median time to achieving MMR was 5 months (range: 0-23 months) (*Online Supplementary Table S1*). The longer the time with treatment at 800 mg/day until achieving MMR, the lower were the probabilities of RFS (HR: 1.14, 95%CI: 1.02-1.27; *P*=0.02). Using the minimum *P*-value approach, with the prerequisite that the smallest group contained at least 10% of the patients, a cutoff of 13 months was observed ($P_{adjusted}$=0.007). This cutoff was confirmed with bootstrap resampling: in 1000 bootstrap samples, the cutoff of 13 months was most frequently chosen. For the 56 patients who had an MMR within 13 months while on treatment at 800 mg/day, the probability of molecular RFS 12 months after stopping high-dose treatment was 94% (95%CI: 84-98%), whereas it was 74% [95%CI: 39-91%; HR: 7.39 (95%CI: 1.62-37.74)] for the 12 patients who had an MMR after more than 13 months of high-dose treatment (Figure 4A).

The median time from achievement of MMR until dose reduction to 400 mg was 23 months (range: 0-93 months) (*Online Supplementary Table S1*). The longer the time with MMR while on treatment at 800 mg/day, the higher were the probabilities of RFS (HR: 0.86, 95%CI: 0.72-0.96; *P*=0.0006). Using the minimum *P*-value approach, with the prerequisite that the smallest group contained at least 10% of the patients, a cutoff of 8.5 months was observed ($P_{adjusted}$=0.011). This cutoff was confirmed with bootstrap resampling: in 1000 bootstrap samples, the cutoff of 8.5 months was most frequently chosen. For the 53 patients who were more than 9 months on high-dose treatment after achievement of MMR, the probability of molecular

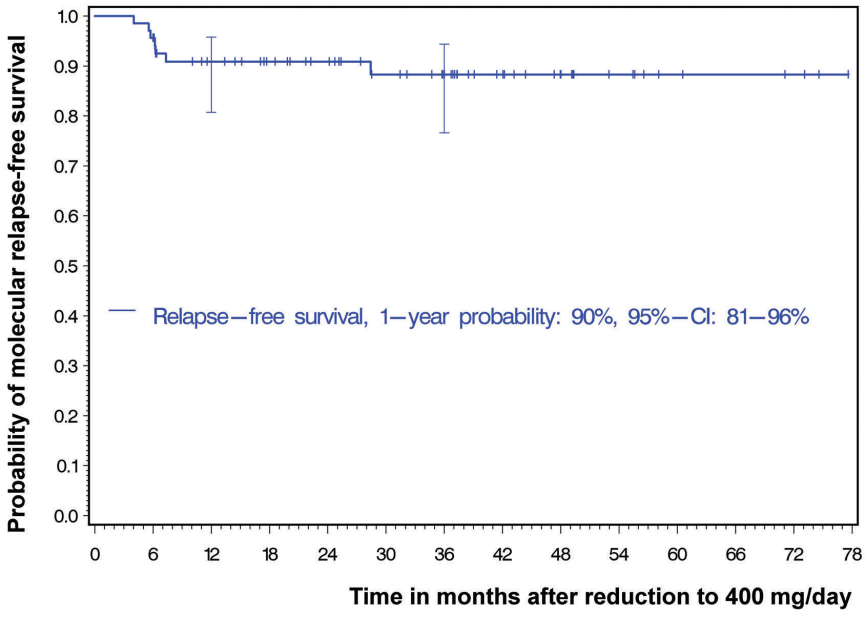


Figure 3. Probabilities of molecular relapse-free survival after dose reduction to imatinib at 400 mg/day. At 12 and 36 months, horizontal crossbars indicate the upper and lower limit of the 95% confidence interval (CI) for the estimated probability.

Number of patients still at risk (n) at different months of observation

Months	0	12	24	36	48	60	72
Patients at risk, n	68	52	41	29	14	5	3

RFS 12 months after stopping high-dose treatment was 98% (95%CI: 87-99%), whereas it was 65% [95%CI: 34-84%; HR: 0.096 (95%CI: 0.014-0.449)] for the 15 patients who were only on high-dose treatment for 9 months or less after achieving MMR (Figure 4B).

Discussion

The concept of starting CML therapy upfront with more potent BCR-ABL inhibition than is achievable with 400 mg imatinib has been introduced to prevent early disease progression and induce deep MR faster and more effectively.[2] However, it is not known in which patients and when after the initiation of a more potent BCR-ABL kinase inhibition (second/third-generation TKI or 800 mg imatinib) a deep MR can be maintained after de-escalation to 400 mg imatinib.

Trials investigating dose reductions are rare. In the DESTINY study, the dose of second-generation TKIs was reduced to half the respective standard dose.[28] However, in terms of BCR-ABL inhibitory potency, even reduced second-generation TKI doses such as those used in the DESTINY trial demonstrate significantly more BCR-ABL inhibition than 400 mg imatinib. To our knowledge, a controlled switch from highly potent BCR-ABL kinase inhibition with 800 mg imatinib or second/third-generation TKI to 400 mg/day imatinib has never been performed prospectively.

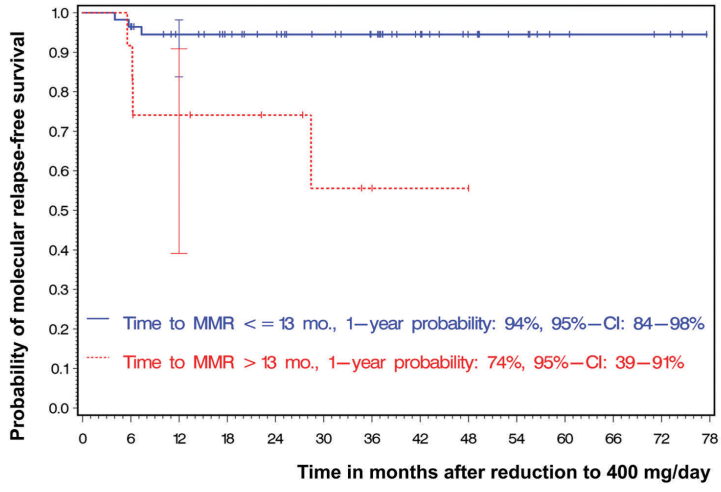
On the other hand, a reduction of imatinib treatment intensity to 400 mg is frequently required in patients who achieve a deep MR but experience toxicities or acquire/have worsening comorbidities of a type that prevents the further use of second-generation TKI. Furthermore, those patients with deep MR who relapse after TKI cessation or who do not wish to discontinue their TKI, and therefore require life-long TKI therapy, are all candidates for a dose de-escalation to imatinib 400 mg.

Here, we studied the stability of a deep MR in patients of the German CML-Study IV who had MMR or better response for at least 6 months when they reduced imatinib from 800 mg to 400 mg per day. We wished to gain insight into whether treatment duration with 800 mg imatinib has an impact on subsequent maintenance of deep MR with imatinib at the 400 mg standard dose. We also searched for clinical variables associated with maintenance of at least MMR after dose reduction of imatinib.

We found that, if BCR-ABL-monitoring once every three months is ensured, imatinib dose reduction from 800 mg to 400 mg/day in patients with stable MMR did not compromise efficacy or risk sustained MMR in most patients, as only two of seven patients who had lost MMR on 400 mg imatinib required a rescue treatment with more potent BCR-ABL-kinase inhibitors. This also suggests that if standard dose imatinib treatment and BCR-ABL monitoring are ensured, a single loss of MMR might not require immediate re-intensification of TKI treatment.[29] Secondly, despite only 7 events, statistical modeling suggested that achieving an MMR within 13 months under 800 mg imatinib, as well as staying on 800 mg imatinib for at least 9 months after achievement of MMR, are both good predictors of a successful continuous MMR maintenance under the standard imatinib dose of 400 mg.

Interestingly, with the exception of WBC count, all other prognostic markers identified for a successful imatinib dose reduction have previously also been reported as predictors for treatment-free remission (TFR).[7,22,27,30] Based on this, it is tempting to speculate that the biology of TFR

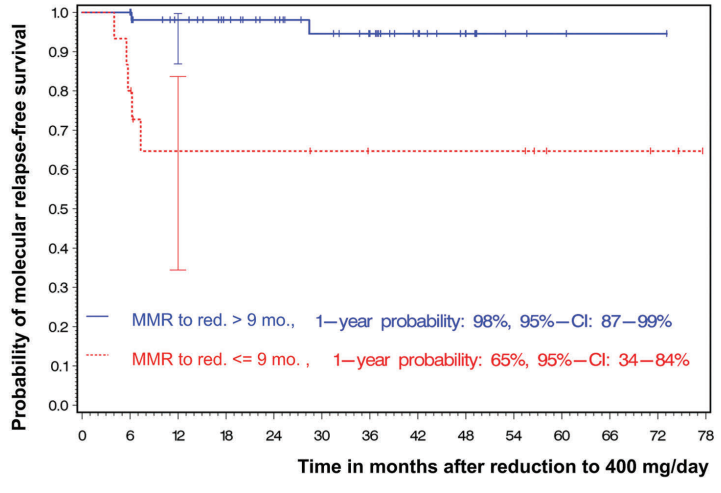
A



Number of patients still at risk (n) at different months of observation

Months	0	12	24	36	48	60	72
Time to MMR <= 13 mo., n	56	45	36	27	13	5	3
Time to MMR > 13 mo., n	12	7	5	2	1	0	0

B



Number of patients still at risk (n) at different months of observation

Months	0	12	24	36	48	60	72
MMR to reduction (red.) > 9 mo., n	53	44	33	23	8	2	1
MMR to reduction (red.) <= 9 mo., n	15	8	8	6	6	3	2

Figure 4. Factors influencing the probabilities of molecular relapse-free survival after imatinib dose reduction to 400 mg/day. (A) Impact of time to major molecular response (MMR) and molecular relapse-free survival. (B) Impact of interval between MMR and imatinib dose reduction and molecular relapse-free survival. At 12 months (mo), horizontal cross-bars indicate the upper and lower limit of the 95% confidence interval (CI) for the estimated probability.

and rapid MR are mechanistically linked. For example, immuno-biological features such as CD86^{+} plasmacytoid dendritic cell counts were recently shown to be associated with both TFR rate and rapid, deep MR under TKI therapy.[31,32]

With 68 patients and 7 events only, the cutoffs and our prognostic analyses remain exploratory and should be confirmed independently. In summary, here we show that if MMR was achieved within 13 months on 800 mg imatinib, a reduction of treatment intensity to 400 mg imatinib is feasible with a high probably that MMR will be maintained. From these results, we speculate that a switch from a second-generation TKI to 400 mg imatinib is unlikely to lead to a loss of MMR. This is no trivial speculation because there are no data to support it, and a prospective clinical trial investigating a switch from second-generation TKI to imatinib will probably never be performed.

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