Chronic Myeloid Leukemia

Efficacy of imatinib mesylate as maintenance therapy in adults with acute lymphoblastic leukemia in first complete remission

Seven Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) patients in first complete remission received maintenance therapy with imatinib alone. Two-year progression-free survival was 75%. Quantitative polymerase-chain-reaction (qPCR) monitoring of BCR-ABL showed that: (i) *persisting* molecular complete response (CR) was associated with long-lasting CR; (ii) molecular relapse did not invariably mean hematologic relapse; (iii) only the wide and rapid increment of BCR-ABL values was predictive of leukemia relapse.

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Imatinib mesylate has been shown to induce remissions in more than two-thirds of patients with relapsed/refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ALL), although for short time. Serial quantitative reverse-transcriptase polymerase-chain-reaction (qRT-PCR) monitoring of BCR-ABL has shown utility in predicting leukemia relapse and bridging the time to bone marrow transplantation (BMT).[1-5] We evaluated the efficacy of imatinib alone for long-term maintenance therapy in seven consecutive Ph+ALL patients in first hematologic complete remission (hCR), and the usefulness of a strict minimal residual disease (MRD) follow-up to identify patients who may benefit from prolonged imatinib maintenance.

Table 1A summarizes the clinical characteristics of the seven patients. At diagnosis, karyotypic analysis showed the t(9;22) translocation in all patients, and revealed additional chromosomal alterations in three (43%) out of the seven patients, namely +14, del(10q) and del(20). In five patients induction treatment was a multiagent chemotherapy regimen, detailed in Table 1A. The other two patients, older than 65 years, received prednisone 40 mg/m^2 daily and imatinib 800 mg/day for 30 days as induction treatment. At the end of induction, all patients were in complete remission (CR) and received maintenance treatment with imatinib 800 mg/day until toxicity or leukemia relapse (Table 1A). MRD monitoring was performed on bone marrow aspirates collected at admission, at the end of induction treatment and then, monthly, during the maintenance therapy. Molecular CR (mCR) was defined as described by Gabert *et al*.[6] The definition of hCR and the algorithms for MRD evaluation were drawn from Scheuring *et al*.[3] and were modified as follows: *minimum BCR-ABL* level: the lowest measured relative BCR-ABL level prior to an increase or identical value; *increased BCR-ABL* level: the highest value after the minimum (it was considered if the sample was obtained at least 15 days prior to hematologic relapse [hRel]; *magnitude* of increase: the log ratio between the *increased* BCR-ABL and the minimum, as defined above; *persisting* mCR: mCR sustained for at least three months and *short* mCR: mCR detected in a single observation or sustained for less than three months. Kaplan-Meier curves and the hazard rate were calculated using STATA (release 8) software. Overall survival (OS) and progression-free survival (PFS) are shown in Figures 1A and B. The hazard rate was 0.00021617. Six out of seven patients (86%) were still in hCR at a median follow-

Table 1 A. Characteristics of patients at baseline and their treatment outcome.

Characteristics	*Patients*
Median age, y (range)	59 (34-79)
Sex, no (%)	
Male	3 (43)
Female	4 (57)
Subtype of ALL, no. (%)	
c-ALL	5 (72)
Pre-B-ALL	1(14)
Pro-B-ALL	1(14)
$p190^{Bcr-Abl}$ vs $p210^{Bcr-Abl}$, no. (%)	
m-Bcr-Abl	4 (57)
M- Bcr-Abl	3 (43)
Karyotype, no. (%)	
Additional cytogenetics abnormalities	3 (43)
t(9;22)	7 (100)
CNS leukemia, no. (%)	0 (0%)
Induction chemotherapy regimen, no. (%)	
DNM+VCR+ PDN for 30 days	5 (71)
PDN 40 mg+Imatinib 800 mg/day for 30 days	2*(29)
Outcome of Induction	
hCR	7 (100)
Consolidation/maintenance regimen, no. (%)	
Imatinib 800 mg/day	7 (100%)
CNS Prophylaxis during induction and maintenance	
MTX i.t. 15 mg/monthly for 16 months	7 (100%)

*DNM: daunorubicin; PDN: prednisone; VCR: vincristine; MTX: methotrexate; hCR: hematologic complete remission. *Two patients over 65 years old.*

Table 1B. BCR-ABL/β2microglobulin after best MRD value and its relation to relapse.

BCR-ABL level	*Number of patients*	*Number of relapses (%)*
> 10^{-4}	2	1 (50)
< 10^{-4}	2	0

Table 1C. Adverse events during imatinib treatment.

Toxicity	*Grade I or II, no. (%)*	*Grade III or IV, no. (%)*
Nausea/vomiting	6 (86)	1 (14)
Periorbital edema	7 (100)	–
Cutaneous rash	1 (14)	–
Weakness	5 (71)	–
Anemia	2 (28)	–
Neutropenia	4 (57)	3 (43)
Thrombocytopenia	4 (57)	3 (43)

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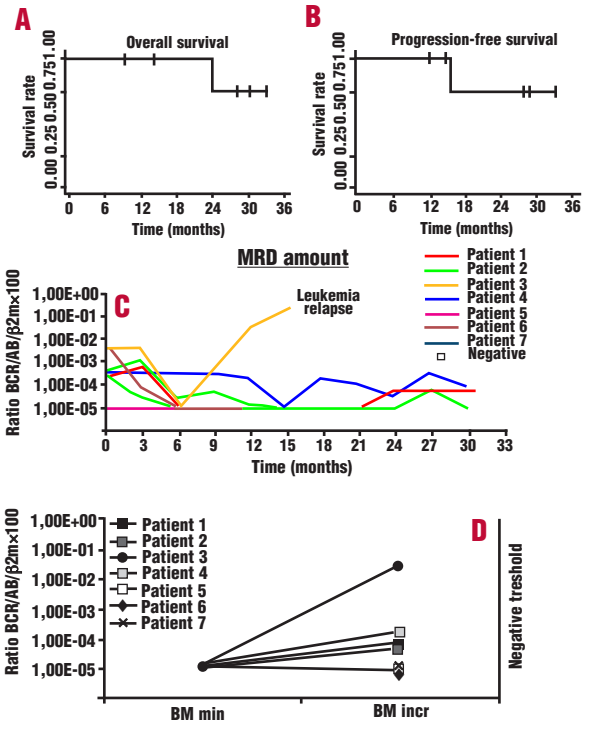

Figure 1. A-B. Response to imatinib maintenance by Kaplan-Meier analysis. Overall survival and progression-free survival calculated from the start of maintenance with imatinib for all seven patients. **C.** MRD follow-up. MRD monitoring of all seven patients monitored from 4 weeks after the start of imatinib. The median follow-up is 729.4 days; (range 364.8-1003.2 days). 1×10^{-5} represents the negative threshold of the RT-PCR technique used. **D.** Magnitude of BCR-ABL/β2 microglobulin increase. At the time of evaluating of BCR-ABL/β2 microglobulin increase, all the patients had a negative BCR-ABL value as *minimum BCR-ABL* level. Patient 3 relapsed, showing an increase of 3.3 log. The median increase in the other three patients was 0.63 log (0.63 log, 0.58 log and 1.18 log). The remaining three patients did not have a *BCR-ABL* increase and are still in mCR.

up of 729 days (range 364.8 to 1003.2 days). Only one (14%) patient, who had been treated with the chemotherapy induction regimen, relapsed 456 days and died 729 days after the start of imatinib. The median BCR-ABL value after four weeks of imatinib was 4.1×10^{-4} (range 1×10^{-5}- 4.5×10^{-3}). All the patients achieved mCR at least once. Four out of the seven patients (57%) are still in mCR. The mCR persisted for a median of 182.4 days (range 91.2-638.4 days). All of the five patients with persisting mCR are still in CR as is one of the two patients with short mCR. At a median of 319.2 days (range 91.2 to 364.8 days) from molecular relapse (mRel), three (75%) out of four patients maintained the hCR (Figure 1C). An increase of MRD were observed in four (67%) of the seven patients. The magnitude of increase is shown in Figure 1D. The BCR-ABL/β2microglobulin ratio after the best MRD value and its relation to relapse are shown in Table 1B. Adverse events are shown in Table 1C. In accordance with previous reports of low hepatic toxicity of imatinib treatment,[4,7] none of our patients developed liver function abnormalities during imatinib maintenance. Of note, only one patient had presented severe hepatic toxicity (WHO grade IV), on day +20 of the induction chemotherapy, which was withdrawn.

This is the first reported homogenous series in which imatinib alone was used successfully as maintenance treatment. Our data show 2-year OS and PFS higher than those reported in the literature for Ph+ALL patients treated with either chemotherapy, or allogeneic BMT, or imatinib as salvage treatment (75% versus 15%, 64% and 22%, respectively).[1-5,7-9] In agreement with the literature data,[3,4,8] we observed: (i) a longer period of mCR in long-term responders, with BCR-ABL levels either lower than the 10^{-2} threshold after four weeks of imatinib, or lower than 10^{-4} after the best MRD value; (ii) a rapid increase of BCR-ABL level of more than 2 log in the only patient who relapsed. Because of the limited sample size and low relapse rate, we could not identify a threshold predictive of good response or of imminent relapse.

Similarly, we could not correlate the additional cytogenetic abnormalities with the clinical outcome of the patients. In contrast with previously reported data,[3,10] mRel was not invariably associated with hRel in our patients, probably, due either to the different disease status of the patients (first CR versus relapsed/refractory), or to the mechanism of action of imatinib, more specific than the graft-versus-leukemia effect, at least in some cases, or to the higher dose of imatinib administered (800 mg vs 600 mg/daily). Recently, a dose increase of imatinib has been demonstrated to induce higher rates of major cytogenetic remission and mCR in chronic myeloied leukemia,[11] and to restore the mCR state in Ph+ALL patients who have had a molecular relapse either after allogeneic BMT or during imatinib as salvage treatment.[12,13]

Issues that need to be addressed include the optimal duration of treatment, whether imatinib may replace or support chemotherapy and whether such strict MRD monitoring may help to identify which patients could delay or avoid BMT, especially in the case of unavailability of a sibling donor.

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