The effect of prior exposure to imatinib on transplant-related mortality

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Background and Objectives. Imatinib is an effective treatment for chronic myeloid leukemia (CML) and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). However, relapse is common in patients with advanced or high risk disease. Such patients may be eligible for allogeneic stem cell transplantation (SCT), raising the question whether imatinib therapy may compromise the outcome of subsequent SCT.

Design and Methods. We retrospectively analyzed 70 patients with CML and 21 with Ph+ ALL who had received imatinib prior to SCT. Data were retrieved by directly contacting centers. Multivariate analysis was used to define factors associated with major outcomes (engraftment, graft-versus-host disease, relapse, non-relapse mortality) in addition to descriptive statistics. For the CML patients major outcomes were compared with those of historical controls drawn from the EBMT registry.

Results. At SCT, 44% of CML patients were in accelerated phase or blast crisis and 40% of ALL patients had active disease compared to 84% and 95% prior to imatinib. At 24 months, estimated transplant-related mortality was 44% and estimated relapse mortality 24%. Factors associated with shorter overall and progression-free survival were advanced disease at SCT and a female donor/male recipient pairing. No unusual organ toxicities were observed. Compared to historical controls, prior imatinib treatment did not influence overall survival, progression-free survival or non-relapse mortality, while there was a trend towards higher relapse mortality and significantly less chronic graft-versus-host disease.

Interpretations and Conclusions. Within the limits of a heterogeneous and relatively small cohort of patients, we found no evidence that imatinib negatively affects major outcomes after SCT, suggesting that imatinib prior to SCT is safe.

Key words: immunophenotype, biclonality, intraclonal evolution, B-cell chronic lymphoproliferative disorders, FISH.

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Imatinib has become the standard drug treatment for patients with chronic myeloid leukemia (CML) in all phases of the disease.[1] While the majority of patients in chronic phase achieve a complete cytogenetic response[2] disease persistence at the molecular level is the rule.[3,4] In accord with this, rapid disease recurrence has been observed in the majority of patients in whom imatinib was discontinued, including patients who had attained a complete molecular response,[5,6] raising concerns that even patients with an excellent response may remain at risk of relapse. Even more important, relapse after an initial response is common in patients with advanced disease.[7,8] Although novel therapeutic approaches, particularly alternative Abl kinase inhibitors, are emerging as an effective salvage therapy for patients with relapsed disease,[9,10] it is questionable whether any drug treatment will be able to eradicate advanced disease and result in durable remissions. In contrast to drug therapy, allogeneic stem cell transplantation (SCT) is capable of eradicating CML in the majority of patients, although at the price of considerable morbidity and mortality.[11] Not surprisingly, the number of CML patients undergoing allogeneic SCT has declined very considerably after the introduction of imatinib.[12] Thus, allogeneic SCT is frequently used as salvage therapy in the case of primary or acquired resistance to imatinib, or in patients at high risk of relapse, such as those in second chronic phase after blast crisis. Given that an increasing number of patients undergo SCT as salvage after imatinib failure or as definitive therapy for high-risk disease, the question arises whether imatinib therapy may adversely affect the outcome of a subsequent SCT. In order to address this issue we conducted a retrospective analysis within the European Group for Blood and Marrow Transplantation (EBMT) and at Oregon Health & Science University (OHSU). This analysis included patients who underwent SCT for CML or Philadelphia+ acute lymphoblastic leukemia (ALL) subsequent to imatinib therapy. Additionally, for the CML patients, major outcomes were compared with those of a historical control group selected from the EBMT registry.

Design and Methods

All EBMT centers were contacted by e-mail or fax and asked to report patients who underwent SCT for CML and Ph+ ALL after a period of treatment with imatinib. In case of a positive response, a specific questionnaire was sent that focused on transplantation-related parameters. Eighty-six patients from 23 European transplant centers and five from OHSU were identified. The majority of the

patients had been enrolled in successive clinical trials designed to test the efficacy of imatinib in patients with CML in accelerated phase, CML in chronic phase after failure of interferon-α (IFN) and Ph+ ALL. Approval for this retrospective data collection was obtained from the local institutional review boards of the participating centers.

Definition of disease state

In all patients, Ph positivity had been demonstrated by cytogenetic analysis. Blast crisis of CML was diagnosed when ≥30% blasts were present in the bone marrow (BM) or peripheral blood (PB). Criteria for accelerated phase were any of the following: BM and/or PB blasts between 15 and 30%; BM and/or PB blasts plus promyelocytes >30%; platelets <100×10^9/L (not related to therapy); PB basophils>20%. ALL was defined as ≥30% lymphoblasts in the BM or PB.

Definition of response to imatinib

Complete hematologic response was defined as BM blasts <5%, no immature myeloid cells in the PB, platelets >100×10^9/L, neutrophils >1.5×10^9/L, and no symptoms of leukemia. In the case of CML in blast crisis or accelerated phase, the response could also be a return to chronic phase. All other hematologic responses were classified as partial responses. Only responses lasting at least 4 weeks were considered. Major cytogenetic response was defined as 1-34% Ph+ metaphases in the BM, and a complete cytogenetic response as 0% Ph+ metaphases, based on the analysis of at least 20 metaphases. Complete remission of ALL was defined as <5% blasts in the blood and marrow, with complete recovery of PB counts. Partial remission (PR) was defined as reduction of BM or PB blasts to between 5 and 30% and/or incomplete PB recovery.

Molecular response

The diagnosis of molecular response was based on reverse-transcription polymerase chain reaction (RT-PCR) negativity according to the protocols in use at the various centers. The sensitivity of the assays used is likely to vary considerably between centers.

Definition of engraftment and graft-versus-host disease

Patients who died early (<day 29) were excluded from the analysis of engraftment. Neutrophil engraftment was defined as having occurred on the first of three consecutive days with counts >0.5×10^9/L. Platelet engraftment was defined as having occurred on the first of seven consecutive days with platelets >20×10^9/L and without platelet transfusions. Acute graft-versus-host disease (GvHD) and chronic GvHD were defined according to the Seattle criteria.[13]

Statistics

Differences among groups were evaluated by the chi-squared test on the appropriate cross-tabulations for the discrete variables, and by a Mann-Whitney test for the continuous variables. Survival probabilities for overall survival and progression-free survival were estimated according to the Kaplan-Meier product limit method and differences among groups were tested by the log-rank test. Outcomes with competing risks (relapse rate, non-relapse mortality, and time to engraftment) were described by estimating the cumulative incidence curves by the proper non-parametric estimator, and testing the differences using Gray's test. Multivariate regression models were used to compare the outcomes of imatinib cases with respect to historical controls adjusting for the main prognostic factors; for binary outcomes (as such the occurrence of GVHD) a logistic regression model was used while for differences in times to events a Cox proportional hazards model was employed. The statistical analyses were performed using SPSS version 10.0.7 (2000), except for the estimation of the cumulative incidence and Gray's test which were performed using R 1.6.2 (2003) and the software *cmprsk* by T. Gray, version 2 1-2 (2000).

Results

Patients' demographics and imatinib therapy

Ninety-one patients who had received imatinib prior to SCT were reported: 70 with CML (77%) and 21 (23%) with Ph+ ALL (Table 1). Two of these patients subsequently received a second allograft because of graft rejection, and both patients died. These deaths were considered as related to the first transplant, and only the data from the first allograft were included in the analysis. The median age at transplantation was 43 (range, 3-63) years for the CML patients and 37 (range, 17-58) years for the ALL patients. The median disease duration from diagnosis to transplant was 23 (range, 3-284) months for the CML patients, and 6 (range, 3-14) months for those with ALL. CML patients had received imatinib for a median of 97 (range, 18-751) days and ALL patients for 45 (range, 12-205) days. Imatinib therapy was discontinued at a median of 10 (range, 2-329) days prior to SCT in CML patients, and at a median of 9 (range, 5-114) days in ALL patients. Prior to imatinib therapy, the majority of CML patients were in accelerated phase (31%) or blast crisis (53%) and all but one ALL patient had active disease. Of the CML and ALL patients, 56 (80%) and 13 (62%) responded to imatinib. Sixteen CML patients (23%) and two ALL patients (9%) received conventional salvage therapy before proceeding to SCT. At the time of transplantation, 56% of CML patients were in chronic phase and 60% of ALL patients were in complete remission.

Allogeneic transplants

Indications for SCT

For the CML patients, the indications for SCT as given by the centers were risk of relapse in 30 (42.8%), insufficient response in 18 (25.7%), disease progression in 16 (22.9%), and imatinib-related toxicity in six patients (8.6%). Toxicities were elevated liver function tests in two, pancytopenia in two, and were not specified in the remaining two patients. For the ALL patients, the indications were risk of relapse in 12 (57.1%), insufficient response in six (28.6%) and disease progression in three (14.3%). Thirteen of 47 (27.7%) patients transplanted before May 1, 2001, were in relapse, compared to six of 44 (13.6%) patients transplanted after this date (p=0.125).

Table 1. Demographics and response to imatinib.

	CML		ALL	
Number of patients (%)	70 (77)		21 (23)	
Sex, male, number of patients (%)	44 (62.9)		13 (61.9)	
Age (years), median (range)	43.1 (3.4–63.1)		37.5 (17.2–58.5)	
Disease phase, number of patients *(%)*	*Pre-IM*	*Pre-Tx*	*Pre-IM*	*Pre-Tx*
Chronic phase or better*	11 (15.7)	39 (55.7)	NA	NA
Accelerated phase	22 (31.4)	9 (12.6)	NA	NA
Blast crisis	37 (52.9)	22 (31.4)	NA	NA
Complete remission	NA	NA	1 (4.7)	12 (60.0)
Active disease	NA	NA	20 (95.3)	8 (40.0)
Imatinib therapy (days), median (range)	97 (18–751)		45 (12–205)	
Response**to imatinib, number of patients (%)				
Yes	56 (80)		13 (61.9)	
No	9 (13.9)		7 (33.3)	
Unknown	5 (7.1)		1 (4.8)	
Salvage therapy after imatinib, number of patients (%)				
Yes	16 (22.9)		2 (9.5)	
No	53 (75.7)		19 (90.5)	
Unknown	1 (1.4)			
Response to salvage, number of patients (%)				
Yes	11 (68.8)		1 (50.0)	
No	4 (25.0)		1 (50.0)	
Unknown	1 (6.2)			
Interval cessation of imatinb to transplantation (days), median (range)	10 (2-329)		9.5 (5-114)	
Interval diagnosis to transplantation (months), median (range) (2.6–14.0)	22.6 (2.6–284.7)		6.0	

**Includes any cytogenetic remission and any hematologic remission, as long as the criteria of accelerated phase or blast crisis are not fulfilled; ** Includes any response, including return to chronic phase. NA: not applicable; Tx: allogeneic transplant.*

Table 2. Transplants.

Variable	*Number of patients (%)*
Donor type	
HLA-identical sibling	26 (28.6)
Matched unrelated donor	41 (45.1)
HLA mismatch	14 (15.4)
HLA-type unknown	9 (9.9)
Gender mismatch	
Female donor, male recipient	19 (20.9)
Other	69 (75.8)
Unknown	4 (4.4)
Conditioning intensity	
Conventional	61 (67.0)
Reduced intensity	30 (33.0)
Antithymocyte globulin	
Yes	41 (45.1)
No	45 (49.5)
Unknown	5 (5.5)
Busulfan	
Yes	15 (16.5)
No	76 (83.5)
Total body irradiation	
Yes	49 (53.9)
No	12 (13.2)
Reduced intensity conditioning	30 (32.9)
Stem cell source	
Peripheral blood stem cells	61 (67.0)
Bone marrow	22 (24.2)
Other	7 (7.7)
Unknown	1 (1.1)
Cell dose, median (range)	
Nucleated cells ($x10^8$/kg)	6.0 (0.14–30.25)
$CD34^+$ cells ($x10^6$/kg)	5.4 (0.06–17)
GvHD prophylaxis	
Cyclosporine A	88 (97.8)
Methotrexate	55 (61.1)
Mycophenolate mofetil	21 (23.1)
Prednisone	9 (9.9)
T-cell depletion	12 (13.2)
Unknown	1 (1.1)
Gender mismatch	
Female donor, male recipient	19 (20.9)
Other	69 (75.8)
Unknown	4 (4.4)

Donors, conditioning, grafts

Donors were HLA-matched siblings in 26 cases (28.6%), matched unrelated donors in 41 (45.1%), and other donors in 23 (25.3%). In 19 cases a male recipient received a graft from a female donor (20.9%). Sixty-one patients (67.0%) received conventional conditioning. Regimens based on at least 12 Gy total body irradiation (TBI) or an alkylating agent (16 mg/kg busulfan or 750 mg/m^2 thiotepa) plus cyclophosphamide (120 mg/kg) were considered conventional. In 30 patients (32.9%) reduced intensity conditioning regimens were used. Nine of these received a regimen consisting of 2 Gy TBI/fludarabine[14,15] and five patients were treated with FLAMSA (4 Gy TBI, 120 mg/m^2 fludarabine, 120 mg/m^2 cytarabine 8 g/m^2 and amsacrine 400 mg/m^2)[16] (Table 2). Various other regimens were used in the remaining patients. Overall 25/30 patients received fludarabine as part of their reduced conditioning regimen. Peripheral blood stem cells were used in 61 patients (67.0%), BM in 22 (24.2%), and cord blood in 5 (5.5%). Two patients (2.2%) received both BM and peripheral blood stem cells. In one patient, the source of transplant is not known. T-cell depletion was done in 12 patients (13.2%). A median of 5.4 (range, 0.06–17)×10^6 $CD34^+$/kg and 6.0 (range, 0.14–18.6)×10^8 nucleated cells/kg were transplanted. GvHD prophylaxis included cyclosporine A in 88 patients (97.8%), methotrexate in 55 (61.1%) and mycophenolate mofetil in 21 patients (23.1%).

Major outcomes

Engraftment

Eighty-two patients (90.1%) engrafted, three failed to engraft and one experienced late graft failure. Five patients (5.5%) died before day 29 and were thus not evaluable for engraftment. Of the three patients who failed to engraft, two had received conventional and one minimal conditioning. The patient with late graft failure had received reduced intensity conditioning. All four patients with graft failure had CML and were transplant-

Table 3. Engraftment and acute GvHD.

Engraftment overall, number of patients (%)	
Yes	82 (90.1)
No	3 (3.3)
Death < day 29	5 (5.5)
Late graft failure	1 (1.1)
Neutrophil count > 0.5×10⁹/L	
Day 30	85%
Day 60	90%
Day 90	90%
Platelet count > 2010⁹/L (%)	
Day 30	74%
Day 60	82%
Day 90	82%

Acute GvHD	*grade*	*Number of patients (%)*
Overall	0-1	48 (52.7)
	2-4	38 (41.8)
Skin	0-1	51 (56.0)
	2-4	35 (38.5)
Liver	0-1	68 (74.7)
	2-4	18 (19.8)
Gut	0-1	70 (76.9)
	2-4	16 (17.6)

ed from unrelated donors, and an HLA mismatch was present in two cases (DRB1 in one case, and precise type of mismatch unknown in the second). Engraftment of neutrophils (>0.5×10⁹/L) and platelets (>20×10⁹/L) was analyzed using a competing risk model. The percentage of patients with neutrophil engraftment was 85% on day 30 and 90% on day 60 and 120. Platelet engraftment had occurred in 74% of patients by day 30 and in 82% on day 60 and 120.

Graft-versus host-disease and severe organ toxicities

Grade 2-4 acute GvHD was observed in 38 patients (41.8%), affecting the skin in 35 patients (38.5%), liver in 18 (19.8%) and gut in 16 patients (17.6%). Five patients were not assessable for acute GvHD (Table 3). Sixty-five patients survived at least 100 days and information on chronic GvHD is available for 60 of them. Limited and extensive chronic GvHD each occurred in 11 patients (16.9%), while 38 patients (58.5%) did not develop GvHD.

Information on organ-specific toxicities was available for approximately 85% of patients. Grade 3/4 mucositis was observed in 36 patients (46.8%) and grade 3/4 infections in 29 (40.8%). Less common grade 3/4 organ toxicities were pulmonary (16 patients, 20.3%), renal (13 patients, 16.5%), cardiac (9 patients, 11.4%) and neurological (7 patients, 9.5%).

Overall survival and progression-free survival

The estimated median follow-up of the cohort is 21.64 months. At this time, 57 patients had died, 39 (68.4%) from causes other than progression of disease and 18 (31.6%) from progression of disease. Non-relapse mortality was due to infection (41.0%), GvHD (25.6%), veno-occlusive disease (5.1%) and other causes (28.2%). Fatal infections (n=16) were of viral etiology in six patients, fungal in four and bacterial in three. Simultaneous bacterial and fungal infections were diagnosed in two patients and the etiology could not be determined in one patient. The estimated median overall survival was 8.85 (95% CI, 3.02–14.68) months from transplantation, and the estimated median progression-free survival was 6.48 (95% CI, 3.77–9.19) months. In order to determine factors associated with overall and progression-free survival, we analyzed baseline characteristics (as described in the methods) for their association with these outcomes in a proportional hazards model (Table 4). CML patients in accelerated phase or blast crisis and ALL patients with active disease at the time of the transplant were at significantly higher risk of death [HR 2.97 (95% CI, 1.70–5.19)] and disease progression [HR 3.30 (95% CI, 1.95–5.56)]. Similarly, male patients transplanted from a female donor were also at increased risk of death [HR 1.94 (95% CI, 1.06–3.57)] and progression [HR 2.28 (95%, 1.28–4.07)]. Patients transplanted after conventional conditioning had superior overall survial [HR 0.55 (95% CI, 0.32–0.95)] but not progression-free survival. Further analysis revealed that advanced disease phase [HR 4.83 (95% CI, 2.22–10.54)] but not the type of conditioning regimen or the recipient/donor gender constellation influenced relapse risk. In contrast, both advanced disease phase [HR 2.35 (95% CI, 1.16–4.75)] and the male recipient/female donor pairing [HR 2.52 (95% CI, 1.20–5.28] were associated with higher non-relapse mortality (Table 4).

Regardless of subsequent outcome, 33 patients (36.3%) were negative for *BCR-ABL* by RT-PCR, 22 (24.2%) were in hematologic or cytogenetic remission and 21 (23.1%) had active disease at the last follow-up visit. In 15 patients (16.5%), the remission status at the last follow-up visit is unknown. Eleven patients (12.1%) received donor lymphocyte infusions, and five of these patients responded. Thirteen patients (14.3%) were re-started on imatinib after the transplant. Four of these patients responded, four did not and the response is unknown in the other five.

Comparison with a historical control group of CML patients

To establish whether imatinib therapy prior to transplantation may have an impact on major outcomes we selected a historical control group from the EBMT registry. This analysis was limited to CML patients. We selected patients who had been transplanted in 1998 or 1999, the 2 years immediately preceding the widespread use of imatinib in clinical trials in Europe, in the same centers as the imatinib cases. From among these patients we selected a sub-population in whom the distribution of time interval between diagnosis and transplant was similar to that in the imatinib patients. The only other selection criterion was the availability of data on basic characteristics such as disease status at the time of transplantation. Follow-up for the analysis of this population (1378 patients in total) was truncated at 24 months for comparability. Not unexpectedly, the two groups showed significant differences with respect to a number of variables, including age, phase of disease at transplant, disease dura-

Table 4A. Overall and progression-free survival: median and Cox proportional hazards model.

Outcome	Median (95% CI) months	Factor	HR (95% CI)	p
Overall survival	8.85 (3.02–14.68)	Disease phase (all others vs. CP or better* or ALL in CR)	2.97 (1.70–5.19)	< 0.0001
		Conditioning intensity (conventional vs. reduced)	0.552 (0.32–0.95)	0.033
		Gender mismatch (f→m vs. all others)	1.94 (1.06–3.57)	0.033
Progression-free survival	6.48 (3.77–9.19)	Disease phase (all others vs. CP or better* or ALL in CR)	3.30 (1.95–5.56)	< 0.0001
		Conditioning intensity (conventional vs. reduced)	0.68 (0.41–1.14)	0.143
		Gender mismatch (f→m vs. all others)	2.28 (1.28–4.07)	0.005

**Includes any cytogenetic remission and any hematologic remission, as long as the criteria of accelerated phase or blast crisis were not fulfilled. ALL: acute lymphoblastic leukemia; CI: confidence interval; CP: chronic phase; CR: complete remission; HR: hazard ratio.*

Table 4B. Relapse and non-relapse mortality: Cox proportional hazards model.

Outcome	Factor	HR (95% CI)	p
Relapse	Disease phase (all others vs. CP or better* or ALL in CR)	4.83 (2.22– 10.54)	< 0.0001
	Conditioning intensity (conventional vs. reduced)	0.61 (0.28–1.31)	0.206
	Gender mismatch (f→m vs. all others)	2.04 (0.79–5.27)	0.143
Non-relapse mortality	Disease phase (all others vs. CP or better* or ALL in CR)	2.35 (1.16–4.75)	0.018
	Conditioning intensity (conventional vs. reduced)	0.75 (0.37–1.50)	0.414
	Gender mismatch (f→m vs. all others)	2.52 (1.20–5.28)	0.014

**Includes any cytogenetic remission and any hematologic remission, as long as the criteria of accelerated phase or blast crisis were not fulfilled. ALL: acute lymphoblastic leukemia; CI: confidence interval; CP: chronic phase; CR: complete. remission; HR: hazard ratio.*

Table 5. Comparison of demographics, disease and transplant features between the imatinib and the control group.

Variable (n=70)	IM group (n=1308)	Control group	p
Disease phase			
First chronic phase	8.6%	77.6%	<0.001
Accelerated phase	12.9%	12.8%	
Blast crisis	31.4%	3.3%	
Other*	47.1%	6.3%	
Gender: Male	62.9%	59.1%	0.53
Age: median	43.1	39	0.012
Time diagnosis to transplant: median	22.6	22.6	<0.001
Donor type			<0.001
HLA-identical sibling	29.9%	60.3%	
Other	70.1%	39.7%	
Gender mismatch f→m	24.6%	24.2%	0.94
Reduced intensity conditioning	38.6%	8.7%	<0.001
Source of stem cells: BM	24.6%	65.5%	<0.001
T-cell depletion	11.4%	18.6%	0.13
Total body irradiation	70%	50.5%	<0.001
Busulfan	18.6%	20.9%	0.64
Antithymocyte globulin	47.1%	2.8%	<0.001

*BM: bone marrow; *includes all patients in remission from previous accelerated phase or blast crisis who do not fulfill the criteria of accelerated phase and blast crisis.*

Table 6. Comparison of major outcomes.

Outcome	Imatinib	Control	Univariate p	Multivariate p
Graft failure (%)	6.0	5.0	0.575	0.697
Acute GvHD grade 2-4 (%)	44.8	41.4	0.589	0.633
Chronic GvHD (%)	36.7	58.8	0.002	0.027
Overall survival at 24 months (%)	33.7	63.4	<0.001	0.993
Progression free survival at 24 months (%)	28.8	50.7	<0.001	0.835
Relapse at 24 months (%)	42.7	20.2	<0.001	0.091
Non-relapse mortality at 24 months (%)	31.0	29.1	0.177	0.233

tion, donor type, stem cell source and conditioning regimen (Table 5). The two groups were then compared for graft failure, GvHD, relapse and non-relapse mortality and survival (Table 6).

Univariate analysis showed significantly shorter overall survival and progression-free survival and a higher relapse rate in the imatinib group. In contrast, no significant difference was observed for graft failure and non-relapse mortality (Figure 1). Interestingly, the incidence of chronic GvHD was significantly lower in the imatinib group. We then applied multivariate regression models to analyze the association between imatinib therapy and outcomes adjusting for the main prognostic factors. Imatinib therapy had no influence on overall survival, progression-free survival or non-relapse mortality. There was a trend towards a higher risk of relapse in the imatinib group that did not reach statistical significance (p=0.091). Known associations between variables such as disease phase at transplant or T-cell depletion with relapse were confirmed. The association of imatinib therapy with a lower incidence of chronic GvHD was confirmed in the multivariate model (OR=0.44, p=0.027).

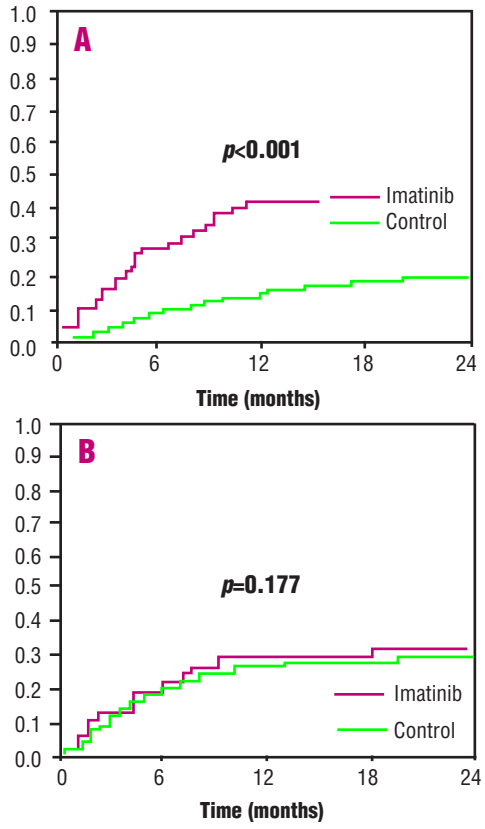

Figure 1. (A) Relapse and (B) non-relapse mortality in CML patients allografted with or without prior imatinib therapy.

Discussion

Imatinib, although generally very well tolerated, has some side effects that may raise concerns regarding the safety of a subsequent SCT. For example, approximately 20% of patients on imatinib develop dermatitis[8] which might predispose such patients to GvHD of the skin. Liver toxicity, another well-known side effect, could predispose patients to veno-occlusive disease. Of note, two other agents used for the treatment of CML have an adverse impact on transplant-related mortality. Busulfan is associated with increased pulmonary toxicity and interferon-α may increase the rate of graft failure if administered less than 3 months before SCT.[17] Although the latter association has not been universally confirmed,[18,19] these data do underline the need for careful evaluation of new therapeutic modalities with respect to their potential impact on transplant-related mortality. In our series of patients, 42.8% died from causes other than disease relapse. Although high, this figure is not unexpected given the unfavorable composition of the group under study. Even after treatment with imatinib, 39/91 patients (42.6%) had CML in accelerated phase or blast crisis or had active ALL. In addition the median age of the cohort (43 years) was relatively high, and two-thirds of the patients were transplanted from unrelated donors. Grade 3/4 organ toxicities were frequent, but no unusual toxicities were seen. Infections were the leading cause of death, followed by GvHD. In multivariate analysis advanced disease at the time of transplant and a female donor/male recipient pairing were associated with a higher rate of relapse and non-relapse mortality and consequently shorter progression-free and overall survival. By contrast, overall survival was superior in patients who received conventional conditioning. However, this may well reflect a selection bias as patients with a better performance status are likely to receive more aggressive conditioning regimens. None of the other factors, including the duration of imatinib therapy, the interval between stopping imatinib and transplantation or the use of conventional salvage therapy between discontinuation of imatinib and transplantation showed a significant association with overall or relapse-free survival. Interestingly, we also found no association between the stage of disease prior to imatinib therapy and progression-free or overall survival. This suggests that imatinib may indeed improve the outcome for patients who respond and are in remission at the time of transplantation, an observation that is in agreement with data from patients transplanted in second chronic phase after conventional chemotherapy for myeloid blast crisis.[20]

Although our data do suggest that pretreatment with imatinib does not result in excessive transplant-related mortality, it is obvious that conclusions are tentative at best, given the lack of a control group and the heterogeneity of the patients under study. To address this limitation, we compared major outcomes for the CML patients with a control group selected from the EBMT registry. To avoid a bias due to changes in transplantation practice, we decided to limit this comparison to patients who had been allografted in 1998 and 1999, the years immediately before imatinib became widely accessible in Europe within phase II and III trials. The only other criterion for selection was the availability of information on disease phase at the time of transplantation and a similar distribution of intervals between diagnosis and SCT. With this approach it became possible to analyze the influence of imatinib on major post-transplant outcomes. In univariate analysis the imatinib cohort had significantly shorter overall and progression-free survival and a higher rate of relapse. However, multivariate analysis, while confirming the adverse impact of known risk factors such as advanced disease phase at the time of SCT, higher age, and the use of unrelated donors on relapse and non-relapse mortality, this array did not show any significant associations with imatinib pretreatment, although there was a trend towards a higher risk of relapse that reached borderline significance (p=0.091). If confirmed, this would suggest that imatinib exposure modulates the disease, resulting in a higher relapse risk that is independent of the established factors, primarily disease phase. We do however, stress that the findings should be interpreted cautiously in view of the disparities between the two cohorts. Overall, however, at least in CML patients, imatinib therapy does not seem to adversely affect major outcomes of a subsequent allograft. Our results are in agreement with those of two other retrospective studies that suggested that SCT after prior imatinib therapy is safe.[21,22] In contrast, a recent case-control study reported a significantly higher incidence of grade II-IV acute GvHD and hyperbilirubinemia in

patients who had received imatinib prior to an allograft.[23] The transplant-related mortality rate in the latter patients was 72% compared to 35% in the control group (p=0.05). Details of this study have not yet been published but one apparent difference from our cohort is that 90% of patients received busulfan conditioning compared to 16.5% of our patients. While busulfan conditioning was not an adverse factor in our study and both patients who died from veno-occlusive disease had been conditioned with cyclophosphamide/TBI, the number of patients at risk is small and the issue certainly requires further investigation, ideally in a prospective fashion. Since imatinib has become the standard of care for CML in all phases of the disease, patients are usually started on imatinib as soon as the diagnosis has been established and SCT is limited to those patients who fail to respond adequately. Conducting a randomized trial will therefore pose considerable difficulties.

Interestingly, the incidence of chronic GVHD, both limited and extensive, was significantly lower in CML patients who had received imatinib before their transplants. This finding may be related to the frequent use of antithymocyte globulin in the imatinib group. Another possibility is differences in GvHD prophylaxis. Since the information in the EBMT database is limited to T-cell depletion, methotrexate and cyclophosphamide but many patients in the imatinib group received additional or other agents such as mycophenolate mofetil a direct comparison between the two groups is not possible. Imatinib itself has been shown to inhibit T-cell responses, probably by inhibiting Lck.[24,25] While imatinib given prior to transplant is obviously not expected to affect post-transplantation T-cell function directly, it is possible that the effects of imatinib given after the transplant may be falsely ascribed to pretransplant therapy. However, there is no evidence for this in our cohort, as the incidence of GvHD was not different between patients who did and did not receive imatinib post-transplant (27 vs. 40%, p=0.338).

While our data suggest that imatinib does not increase the risk of transplantation *per se*, it is obvious that patients who progress to accelerated phase or blast crisis will have a high risk of relapse and transplant-related mortality. This implies that standard risk patients on imatinib who are candidates for SCT should be closely monitored for signs of refractoriness or resistance. Given the high risk of relapse, it is probably appropriate to offer an allograft to eligible patients with advanced disease at diagnosis, with imatinib being used to reduce the leukemia burden prior to transplant. As time-dependent variables, such as the achievement of a major cytogenetic response at 3 months in patients with accelerated phase CML,[8] are powerful predictors of progression-free survival on imatinib these decisions are challenging and must be individualized.

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