

Therapy with imatinib mesylate (Glivec) preceding allogeneic stem cell transplantation (SCT) in relapsed or refractory Philadelphia-positive acute lymphoblastic leukemia (Ph+ALL)

B Wassmann¹, H Pfeifer¹, U Scheuring¹, SA Klein¹, N Gökbuget¹, A Binckebanck¹, H Martin¹, H Gschaidmeier², D Hoelzer¹ and OG Ottmann¹

¹Medizinische Klinik III, Abteilung für Hämatologie und Onkologie of the Johann Wolfgang Goethe-Universität, Frankfurt, Germany; and ²Novartis Pharma AG, Nürnberg, Germany

Imatinib has pronounced antileukemic activity in Ph+ALL, although responses are usually short. To determine whether imatinib may facilitate allogeneic SCT in relapsed or refractory Ph+ALL, we evaluated 46 consecutive, not previously transplanted patients who were enrolled in phase II studies of imatinib. Of 30 patients eligible for SCT, 22 (73%) were actually transplanted. Ten patients were in complete hematologic remission (CHR) ($n = 5$) or had a complete marrow response (CMR) ($n = 5$) at the time of SCT, 12 patients had again relapsed or were refractory. After SCT, 18 patients were in complete remission, one patient was refractory, three patients died prior to response assessment. Seven patients (32%) are in ongoing complete remission with a median follow-up of 9.4 (range 1.7–23.8) months. Seven patients (32%) relapsed a median of 5.2 months after SCT. Transplant-related mortality (TRM) was 36%. Probability of disease-free survival (DFS) is $25.5 \pm 9.8\%$ overall and $51.4 \pm 17.7\%$ when SCT was performed in CHR or CMR, compared with $8.3 \pm 8\%$ for SCT during overt leukemia ($P = 0.06$). In conclusion, imatinib is a well-tolerated salvage therapy prior to allogeneic SCT in patients with Ph+ALL, but requires that SCT be performed within a few weeks of starting treatment to avoid resistance. Disease status at time of transplantation is an important determinant of DFS and TRM.

Leukemia (2002) 16, 2358–2365. doi:10.1038/sj.leu.2402770

Keywords: Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL); BCR-ABL; tyrosine kinase; imatinib mesylate (Glivec); allogeneic stem cell transplantation

Introduction

The Philadelphia chromosome (BCR-ABL rearrangement) is the most adverse prognostic marker in acute lymphoblastic leukemia (ALL) and is detected in approximately 20–30% of adult ALL patients, predominantly in older patients.¹ Although complete remission rates of 60% to 80% are achieved with conventional intensive chemotherapy regimens, nearly all patients relapse, with a median remission duration of 9 months and poor survival rates (0–16%).^{2,3} Allogeneic stem cell transplantation is the only curative form of treatment to date, with long-term survival of 35–65% if performed in first complete remission (CR1).^{4–7} Beyond first remission, allogeneic transplantation is also the treatment of choice, despite poor long-term survival of 17% in 2nd or 3rd remission and of only 5% at 2 years from transplant in primary induction failure or relapse.^{4,8} Few long-term results of autologous BMT in Ph+ALL are available; in the largest series so far reported, the use of purged bone marrow or peripheral blood stem cells resulted in leukemia-free survival of 22% after a median of 52

months.⁹ However, none of the patients transplanted beyond CR1 survived long term.

Achievement of CR is a prerequisite for a favorable long-term outcome after allogeneic SCT.⁸ Salvage chemotherapy for Ph+ALL failing first-line therapy induces complete remissions in 30–60% of cases in most reported series, but they are of short duration.¹⁰ Also, severe treatment-related toxicity and mortality are frequent. This clearly indicates the need for more effective and tolerable forms of treatment to precede SCT. Imatinib mesylate (formerly STI571, Glivec) is an ABL-specific tyrosine kinase inhibitor shown in an early phase I trial to exert significant anti-leukemic activity against relapsed or refractory Ph+ acute leukemias.¹¹ The efficacy and reasonable toxicity of imatinib in patients with relapsed or refractory Ph+ALL was subsequently confirmed in multicenter phase II studies in which imatinib was given as a single agent in doses of 400 mg or 600 mg.¹² The results of these trials suggested that imatinib might be effectively used for remission induction prior to allogeneic SCT. We here describe the results of salvage therapy with imatinib and subsequent allogeneic SCT in consecutive patients with relapsed or refractory Ph+ALL whom we enrolled in the above mentioned phase II studies. We monitored the efficacy and tolerability of imatinib prior to transplantation and examined engraftment, transplant-related complications and overall outcome in the 22 patients who actually underwent allogeneic transplantation.

Patients and methods

Patients and prior chemotherapy

Between October 1999 and October 2001, 46 patients with relapsed or refractory Ph+ALL who had not previously received a transplant were referred to our institution for treatment with imatinib. All patients were evaluated for eligibility to undergo allogeneic SCT. The characteristics of the 22 patients eventually transplanted are detailed in Table 1. The median age was 43.5 (range 17–57) years. At study entry, four patients (18%) were in 1st relapse, two patients (9%) in 2nd relapse and 16 patients (73%) were referred with primary refractory disease ($n = 15$) or refractory 1st relapse ($n = 1$). Twenty-one patients had received first-line therapy according to the German multicenter ALL (GMALL) protocols 05/93 or 06/99,¹ one patient had previously been treated according to the BFM95 protocol of ALL in childhood and had received an autologous BMT following 1st relapse. Seventeen patients (77%) had received ≤ 3 cycles of prior chemotherapy, consistent with the large proportion of patients with primary refractory leukemia, whereas five of 22 patients (23%) had received ≥ 4 cycles of prior chemotherapy. Ten of 22 patients (45%) had received prophylactic CNS irradiation with 24 Gy accord-

Correspondence: OG Ottmann, Medizinische Klinik III, Abteilung für Hämatologie und Onkologie, Johann Wolfgang Goethe-Universität, Theodor-Stern-Kai 7, D-60590 Frankfurt, Germany
Received 24 May 2002; accepted 21 August 2002

Table 1 Patients' characteristics at start of imatinib therapy

Pat. No.	Age	Sex	Breakpoint	Karyotype	Disease status	Prior therapy	Prior complications (grade III/IV)
1	57	F	e1a2	t(9;22),-7	1st rel.	ind. 1, 2, consol.1	septicemia
2	57	M	e1a2	t(9;22),-7	prim. refr.	ind. 1, 2, consol. 1, CNS irradiation	—
3	57	F	e1a2	t(9;22),-7	prim. refr.	Ind. 1, 2	pulmonary and CNS aspergillosis with CNS aspergilloma resection
4	40	M	b2a2	t(9;22)	prim. refr.	ind. 1, 2, CNS irradiation, relapse protocol	—
5	34	F	e1a2	t(2;16), t(9;22),del(9)	prim. refr.	ind. 1, 2, CNS irradiation	—
6	27	F	e1a2	t(9;22), t(4;21), dic(15;16),+der(2)	1st rel.	ind. 1, 2 consol. 1, CNS irradiation	septicemia
7	29	F	b3a2	t(9;22)	refr. 1st rel.	ind. 1, 2, HAM, idarubicin, ind. 2, S-HAM	candida pneumonia and septicemia
8	54	F	e1a2	normal	2nd rel.	ind. 1, HAM, idarubicin/AraC, idarubicin/AraC	candida infection of liver and spleen
9	48	M	b3a2	t(9;22)+der(22)t(9;22)	1st rel.	ind. 1, 2, consol. 1, CNS irradiation, relapse protocol	septicemia
10	17	F	e1a2	Inv(4),+8, t(9;22),der(16),del(16)(p12),del(16)(q12),+18,der(22)	2nd rel.	BFM95(high risk), ALL-relapse BFM96, ABMT with TBI,VP16	fungal meningitis
11	43	F	e1a2	47XX,+8,t(9;22), del(9)	1st rel.	ind. 1, 2, CNS irradiation	—
12	50	M	e1a2	normal	prim. refr.	ind. 1, 2	—
13	47	F	e1a2	t(9;22), der(16), t(1;16)	prim. refr.	ind. 1	candida pneumonia
14	29	F	e1a2	t(9;22), der(16), t(1;16)	prim. refr.	ind. 1, 2, FLAG-Ida, Vcr, Pred, Cy; HDMTX, HDARA, VP16, Vind., AraC/VP16	subileus
15	34	F	e1a2	t(9;22)	prim. refr.	ind. 1, 2, consol. 1, CNS irradiation	—
16	48	M	b3a2	t(9;22),del(9)	prim. refr.	ind. 1, 2, consol. 1	—
17	57	M	M-bcr-abl	normal	prim. refr.	ind. 1, 2, CNS irradiation	—
18	41	M	b2a2	t(9;22),-7	prim. refr.	ind. 1, 2	—
19	36	M	b2a2	na	prim. refr.	ind. 1, 2	acute pancreatitis, septicemia
20	40	M	b2a2	na	prim. refr.	ind. 1, 2, CNS irradiation	—
21	47	F	b3a2	na	prim. refr.	ind. 1, 2	—
22	23	M	b2a2	normal	prim. refr.	ind. 1, 2, CNS irradiation	pneumonia, septicemia, artificial ventilation

na, not available; rel., relapse; prim. refr., primary refractory; refr. 1st rel., refractory first relapse; chemotherapy according to the German multicenter ALL (GMALL) protocols 05/93 or 06/99; ind. 1, induction phase 1; ind. 2, induction phase 2; consol. 1, consolidation 1; HAM, high-dose cytarabine (AraC); mitoxantrone; FLAG-Ida, fludarabine, cytarabine, G-CSF, idarubicin; Vcr, vincristine; Pred, prednisone; Cy, cyclophosphamide; HDMTX, high-dose methotrexate; Vind., vindesine.

ing to the German GMALL protocol 06/99. Details of prior chemotherapy are listed in Table 1.

First-line therapy had been associated with severe grade III/IV complications in 10 of 22 patients (45%), consisting of bacterial infections with septicemia ($n = 5$) and fungal infections (disseminated aspergillosis with CNS aspergilloma ($n = 1$), fungal meningitis ($n = 1$), candida septicemia with pulmonary candida infection ($n = 2$) and candida infection of liver and spleen ($n = 1$).

The BCR-ABL rearrangement was confirmed in all patients by RT-PCR and/or FISH analysis; cytogenetic analysis revealed a Ph chromosome in 15 of the 19 patients in whom a cytogenetic analysis was available. A duplicated Ph-chromosome was present in one patient. Ten of 15 patients (67%) with informative cytogenetic analysis had additional chromosomal aberrations (Table 1): monosomy 7 ($n = 4$), trisomy 8 ($n = 2$), t(1;16) ($n = 2$), t(2;16) ($n = 1$), t(4;21) ($n = 1$) and hyperdiploid karyotype with multiple aberrations ($n = 1$).

Imatinib therapy

Patients received imatinib as a single daily oral dose of 600 mg (Novartis CSTI571 109 trial and expanded access study CSTI571 114), mostly on an outpatient basis. Allopurinol was started 24 hours before initiation of imatinib. Treatment was continued until severe adverse effects or disease progression occurred. There was no dose reduction for hematologic toxicity within the first 28 treatment days. Details of study procedures are provided in a separate paper.¹² According to the study protocol bone marrow assessments including cytogenetic and FISH analysis were performed after 4, 8 and 12 weeks of therapy and thereafter every 3 months unless otherwise required for patient management.

Definition of response

A complete hematologic response (CHR) was defined according to conventional criteria as a reduction of marrow blasts to

<5% with no blasts in peripheral blood, hematopoietic recovery with absolute neutrophil counts (ANC) and platelet counts $\geq 1.5 \times 10^9/l$ and $\geq 100 \times 10^9/l$, respectively and no evidence of extramedullary disease. A complete marrow response (CMR) was defined as a reduction of marrow blasts to <5% with no blasts in peripheral blood, no evidence of extramedullary involvement but incomplete hematopoietic recovery. Partial response (PR) was defined as reduction of bone marrow blasts to 6–25%. Relapse was defined as disease recurrence with bone marrow blasts exceeding 5% or reappearance of PB blasts in a patient who had achieved a CHR or complete marrow response. Patients were considered refractory to imatinib if there was no elimination of PB blasts or of extramedullary disease, and/or a failure to reduce marrow blasts to below 25%. Time to progression was calculated as the time from start of imatinib therapy until relapse after initial response, or the interval when treatment was discontinued due to unsatisfactory therapeutic effect. These criteria were selected to conform to those in a previous publication of imatinib in Ph+ALL.¹² Routine safety assessments included clinical evaluation with documentation of adverse events and hematologic and biochemical laboratory tests. Toxicity was graded according to the Common Toxicity Criteria of the National Cancer Institute.

Allogeneic stem cell transplantation

Conditioning regimens: The 22 patients proceeding to allogeneic SCT were transplanted at 12 different BMT centers between April 2000 and December 2001. Details of transplant-associated data are given in Table 2. Twelve patients received a TBI-based conditioning regimen either in combination with cyclophosphamide (CY) ($n = 6$), CY/VP16 ($n = 4$), thiotepa/VP16 ($n = 1$) or VP16 ($n = 1$). Five patients received

an intensified conditioning regimen with radioimmunoconjugates (Re-188 labeled anti-CD66 monoclonal antibody) combined with either total body irradiation (TBI)/CY ($n = 2$), BU/CY ($n = 1$), fludarabine/melphalan ($n = 1$) or bisphosphonate targeted radionuclide therapy with ¹⁸⁶Re HEDP (hydroxyethylidenediphosphonate) combined with TBI/CY ($n = 1$). Fludarabine or busulfan-based regimens were used in five cases, two of which were dose reduced.

Transplant characteristics: Peripheral blood stem cell (PBSC) and bone marrow grafts were used in 15 and seven patients, respectively. The donor was a HLA-identical sibling or relative in nine cases, a mismatched HLA-identical sibling in one case, a matched unrelated donor in nine cases and a mismatched unrelated donor in three cases. *In vitro* T cell depletion with the CliniMACS (Miltenyi, Bergisch Gladbach, Germany) device was performed in three grafts (Pt. Nos. 12, 13, 21).

GVHD prophylaxis: GVHD prophylaxis is provided in detail in Table 2. Five patients received cyclosporine A (CsA) in combination with anti-thymocyte globuline (ATG) and methotrexate (MTX), two patients received CsA combined with ATG and mycophenolate mofetil (MMF), a combination of CsA with ATG was used in three patients. Six patients received CsA either combined with prednisone ($n = 2$), MMF ($n = 2$) or MTX ($n = 2$). Two patients received only CsA, one patient only ATG and one patient combined MTX and prednisone.

Table 2 Allogeneic SCT-associated data

Pat. No.	Status at SCT	Conditioning regimen	Type and treatment of transplant	Donor	GVHD prophylaxis
1	relapse	treosulfan, fludarabine	PBSC	MUD, female	CsA, ATG
2	CR	Flu/BuCY	BM	MUD, female	CsA, ATG, MTX
3	CR	TBI+CY	PBSC	sister, HLA-identical	na
4	relapse	radiobisphosphonates, TBI+CY	PBSC	sister, HLA-identical	CsA, prednisone
5	CR	BUCY	PBSC	sister, HLA-identical	CsA, prednisone
6	PD	RIT, BUCY	BM	MMUD, female, DQB1+DRB1	CsA, ATG, MTX
7	PD	TBI+CY+VP16	BM	MMUD, DRB1	MTX, prednisone
8	relapse	fludarabine, busulfan	PBSC	sister, HLA-identical	CsA, MMF
9	relapse	TBI+VP16	PBSC	brother, 1 Ag-mismatch	CsA, MTX
10	PR	RIT, fludarabine, melphalan	PBSC	MUD	CsA, ATG
11	CR	TBI+CY	BM	MUD, male	CsA, ATG, MTX
12	CR	TBI+CY+VP16	PBSC, TCD	sister, HLA-identical	CsA, ATG
13	PD	RIT, TBI+CY	PBSC, TCD	brother, HLA-identical	ATG
14	PD	TBI+CY	PBSC	nephew, HLA-identical	CsA, ATG, MTX
15	PD	TBI+CY	PBSC	MUD, HLA-identical	CsA, MTX
16	CR	TBI+CY	BM	MUD, HLA-identical	CsA
17	CR	TBI+TT+VP16	PBSC	sister, HLA-identical	CsA, MMF
18	relapse	TBI+CY	BM	MUD	CsA, ATG, MMF
19	CR	TBI+CY+VP16	PBSC	MUD	CsA, ATG, MTX
20	CR	BUCY	PBSC	daughter, HLA-identical	na
21	CR	RIT, TBI+CY	PBSC, TCD	MUD, male	CsA
22	relapse	TBI+CY+VP16	BM	MMUD, 2 Ag-mismatch	CsA, ATG, MMF

CR, complete remission (CHR or CMR); PD, progressive disease; PR, partial remission; TCD, T-cell depletion; TT, thiotepa; RIT, radioimmunotherapy; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; na, not available.

Statistical analysis

Follow-up was updated in April 2002. Descriptive statistics, Kaplan–Meier survival analysis and log-rank test and calculation of hazard ratios were performed using the GraphPad Prism software package.

Results

Eligibility for allogeneic SCT

Sixteen of 46 patients who had not previously undergone stem cell transplantation were considered ineligible for allogeneic SCT by our institution's criteria because of age (62–76 years) ($n = 11$), comorbidity ($n = 4$; age 44–57 years) or patient refusal to initiate an unrelated donor search ($n = 1$). Of the 30 patients allocated to receive an alloSCT, 18 received imatinib because of primary refractoriness to prior chemotherapy and 12 patients for relapsed ALL (1st relapse $n = 8$; 2nd relapse $n = 4$) Ph+ALL. Twenty-two patients (73%) actually proceeded to allogeneic SCT, which was performed 34 to 246 days (median 67 days) after starting imatinib. Imatinib was discontinued a median of 3 (1–14) days prior to conditioning therapy. Reasons for not performing a transplant in eight of the 30 patients were primary resistance to imatinib ($n = 5$), relapse before SCT ($n = 1$), patient refusal to a mismatched unrelated donor transplantation ($n = 1$) and lack of HLA-identical donor ($n = 1$).

Response to imatinib therapy

The 22 patients who proceeded to allogeneic SCT received imatinib for a median of 53 days (range 22–191 days). An early assessment of response by marrow cytology was performed in 17 patients and showed a reduction of bone marrow blasts to less than 5% and less than 10% in 13 (76%) and two (12%) patients, respectively. Two patients failed to show a significant reduction of BM blasts after 2 weeks. At this time, the bone marrow was profoundly hypocellular in 12 of the 15 responding patients.

Eighteen of the 30 patients (60%) allocated to receive an alloSCT achieved a complete hematologic remission (CHR) (27%, $n = 8$) or a complete marrow response (CMR) (33%, $n = 10$). Of the 22 patients actually transplanted, 16 (73%) had achieved either a CHR ($n = 7$) or CMR ($n = 9$) within 4 weeks of starting imatinib, two patients achieved a partial response and four patients were refractory. Responding patients progressed a median of 70 days (range 13–184 days) after initiation of treatment (Figure 1). Patients receiving an allogeneic SCT in complete remission (CR = CHR and CMR) were censored on the last day of imatinib therapy. Six of 16 (37.5%) CR patients relapsed between days 33 and 184 of imatinib therapy, four of whom had previously achieved a complete marrow response.

Toxicity

Imatinib was generally well-tolerated. Nausea grade I–II (41%), vomiting grade I–II (14%), periorbital edema and edema of the lower extremities grade I–II (18%) were the most frequent non-hematologic adverse effects. Grade I exanthema, myalgia and diarrhoea occurred in 5% each.

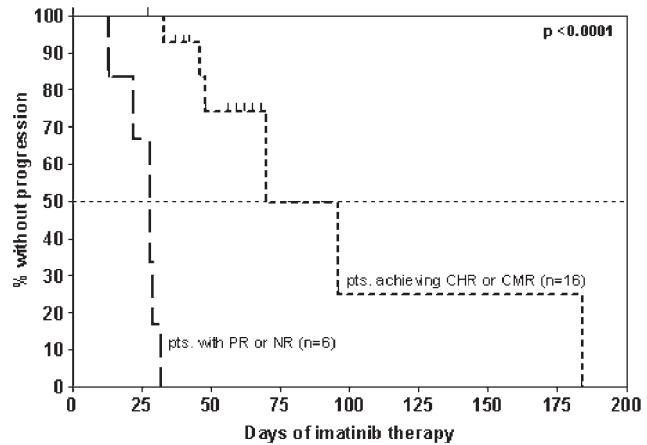


Figure 1 Time to progression calculated from the start of imatinib treatment. Analysis was performed separately for responding (CHR and CMR) and non-responding (NR) patients (including PR) by Kaplan–Meier analysis. Progression was defined as relapse based on the reappearance of greater than 5% lymphoid blasts in the bone marrow, any lymphoblasts in peripheral blood or evidence of extramedullary ALL in responding patients or the day of discontinuation of imatinib in non-responders.

Neutropenia and thrombocytopenia grade III/IV was present prior to imatinib therapy in 23% and 36% of patients, respectively. During imatinib therapy 41% of patients experienced grade III/IV neutropenia. Only one of eight patients with pre-existing grade III/IV thrombocytopenia reached stable platelet counts $>50 \times 10^9/l$. No severe adverse events due to neutropenia and thrombocytopenia developed during therapy. In particular, none of the five patients with previous aspergillus or candida septicemia had recurrence or exacerbation of fungal infections during imatinib therapy.

Elevations of liver enzyme levels of grade 3 or 4 occurred in one patient and necessitated interruption of therapy.

Allogeneic stem cell transplantation

The time interval between initiation of imatinib therapy and allogeneic SCT ranged from 34 to 246 days (median 67 days). Three patients (Pt. Nos. 8, 10 and 22) received additional salvage chemotherapy after imatinib had been discontinued because of refractory disease ($n = 1$) or relapse ($n = 2$). At the time of SCT 10 patients (nine with primary refractory disease, one with 1st relapse prior to imatinib) were in CHR ($n = 5$) or CMR ($n = 5$). Twelve patients were transplanted despite cytologic evidence of leukemia. This was due to relapse after initial CHR or CMR ($n = 6$), progression after PR ($n = 2$) and primary resistance to imatinib ($n = 4$). In one patient with primary resistance to imatinib, additional salvage therapy with thiotepea, melphalan and autografting back-up resulted in a PR at the time of SCT (Table 2).

Hematopoietic engraftment

All patients surviving beyond the first 28 days after transplantation ($n = 21$) showed myeloid engraftment (ANC $>0.5/nl$) within a median of 14 (8–23) days.

Unsupported platelet counts $>50 \times 10^9/l$ were reached in 10 of 14 evaluable patients after a median of 18 (14–34) days.

Clinical outcome after allogeneic stem cell transplantation

Outcome after allogeneic SCT is summarized Table 3. Eighteen patients fulfilled the criteria of a complete remission on at least one occasion after alloSCT, including 10 of the 12 patients with morphologic evidence of leukemia at the time of transplant. Three patients died prior to assessment of response. Overall TRM was 36% (eight of 22 patients), occurring 0.2 to 3.5 months after SCT. Details of transplant-related mortality (TRM) are listed in Table 3. Two of 10 patients transplanted in CHR/CMR and six of 12 patients with overt leukemia at time of SCT died of transplant-related causes. TRM was due to infectious complications ($n = 3$), grade IV GVHD ($n = 3$) and secondary graft failure after a mismatched, unrelated donor SCT ($n = 2$). In the latter two patients, the clinical course was marked by microangiopathic hemolytic anemia, acute kidney failure and alveolar hemorrhage (Pt. No. 6) and grade IV intestinal GvHD with septicemia (Pt. No. 7). Probability of TRM for all patients, for patients with ≥ 4 cycles ($n = 5$) and with ≤ 3 cycles ($n = 17$) of prior chemotherapy was $38.8 \pm 11\%$, $60 \pm 22\%$ and $31.7 \pm 12\%$, respectively ($P = 0.22$) (Figure 2). No parameters significantly associated with the probability of TRM were identified.

Six of the 10 patients transplanted in CHR or CMR (60%) are in ongoing complete remission after a median of 12.8 months (range 1.7–23.8 months). Two of these patients were

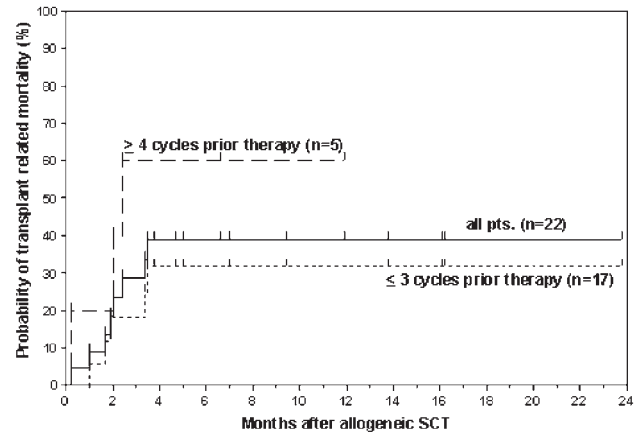


Figure 2 Kaplan–Meier estimate of overall treatment-related mortality and TRM in patients with ≥ 4 cycles and with ≤ 3 cycles of chemotherapy preceding imatinib therapy. For details of prior chemotherapy cycles see the Patients and methods section.

retreated with imatinib because of molecular evidence of disease and are in sustained molecular remission. In contrast, only one of 12 patients (8%) transplanted with overt leukemia remains in remission.

Relapse occurred in two of 10 patients transplanted in CHR

Table 3 Transplant-associated complications and outcome

Pat. No.	GvHD (grade)	Complications	DFS (mo.)	OS (mo.)	Status at last follow-up	Cause of death
1	bowel (4), skin (2)	disseminated aspergillosis, CMV reactivation	3.4	3.4	CR	disseminated aspergillosis, grade 4 GVHD
2	skin (3)	—	16.1	16.1	CR, imatinib for MRD+	—
3	—	acute renal failure, viral pneumonia	1.0	1.0	CR	respiratory failure, viral pneumonia
4	liver (1)	—	5.9	13.8	relapse	—
5	skin, bowel (2)	TTP, VOD	4.4	5.0	relapse	progressive disease
6	liver (1)	acute renal failure, microangiopathic hemolytic anemia, alveolar hemorrhage	1.7	1.7	CR	2nd graft failure, MOF
7	bowel (4), skin (2)	ileus, grand mal seizures, septicemia	2.0	2.0	CR	2nd graft failure, grade 4 GVHD, septicemia
8	bowel (4), skin (3)	—	6.1	6.6	relapse	progressive disease
9	bowel, skin, liver (4)	acute renal failure, VOD, pulmonary aspergillosis	5.2	11.9	isolated CNS relapse, MRD+	—
10	—	septicemia	0.2	0.2	—	septicemia, MOF
11	bowel (3)	—	16.2	16.2	CR	—
12	—	autoimmune hemolytic anemia	23.8	23.8	CR, imatinib for MRD+	—
13	bowel (2)	CMV reactivation	6.5	16.1	relapse treated with imatinib and α -IFN	—
14	—	pulmonary aspergillosis with resection, atypical pneumonia	2.4	2.4	CR, MRD+	respiratory failure, atypical pneumonia
15	skin (3), liver (2)	—	3.2	3.8	relapse	progressive disease
16	skin and bowel (2)	—	9.4	9.4	CR, MRD-	—
17	bowel (2)	—	3.7	4.7	relapse	—
18	liver (4)	progressive liver failure	1.9	1.9	CR	grade 4 liver GVHD, MOF
19	bowel and liver (4)	acute pancreatitis, liver toxicity, HUS, acute renal failure	3.5	3.5	CR, MRD+	grade 4 GVHD bowel and liver
20	—	—	1.7	1.7	CR	—
21	—	pulmonary aspergillosis, CMV reactivation	1.9	1.9	CR	—
22	skin and liver (2)	pulmonary infiltrates, impaired renal function	7	7	CR	—

TTP, thrombotic thrombocytopenic purpura; VOD, veno-occlusive disease; HUS, hemolytic uremic syndrome; CR, complete remission; MRD, minimal residual disease; MOF, multiorgan failure.

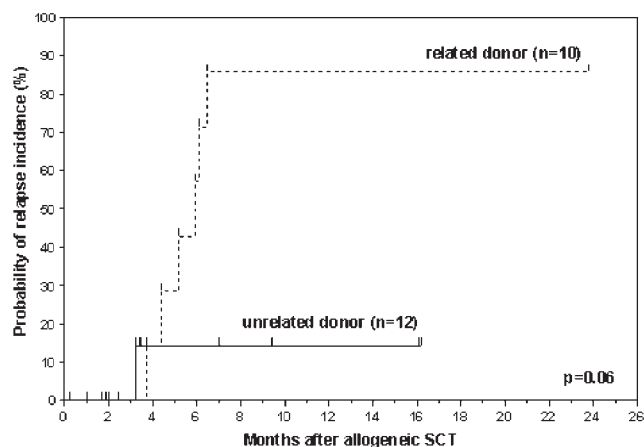


Figure 3 Probability of relapse by Kaplan–Meier analysis in patients receiving related vs unrelated SCT.

or CMR and in five of 12 patients transplanted with active disease. Relapses including one isolated CNS relapse occurred 3.2 to 6.5 months after SCT. The probability of relapse is $57.8 \pm 14.3\%$ at 23.8 months for all patients, $33.3 \pm 19\%$ for patients transplanted in CHR or CMR and $82.9 \pm 15.6\%$ for patients transplanted with relapsed/refractory disease ($P = 0.18$, NS). There was a trend towards a higher relapse incidence in univariate analysis for patients receiving a related donor SCT ($85.7 \pm 13.2\%$) compared to an unrelated donor SCT ($14.3 \pm 13.2\%$) ($P = 0.06$) (Figure 3).

The Kaplan–Meier estimates of disease-free (DFS) and overall survival (OS) for all patients are $25.5 \pm 9.8\%$ and $44.8 \pm 11\%$ at 12 months (Figure 4). Remission status at transplant appears to influence post-transplant disease-free survival, with a $51.4 \pm 17.7\%$ probability of DFS disease-free survival at 12 months for patients transplanted in remission (CHR or CMR) compared to $8.3 \pm 8\%$ DFS at 7 months in patients transplanted with relapsed or refractory disease, although this difference did not reach statistical significance ($P = 0.06$, Figure 5).

Acute graft-versus-host disease (GVHD)

Incidence of grade I–II and grade III–IV GVHD were 32% (seven of 22 patients) and 41% (nine of 22 patients). Grade

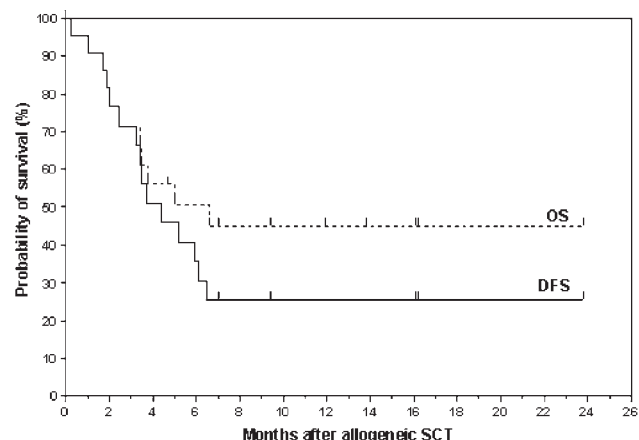


Figure 4 Disease-free survival (DFS) and overall survival (OS) calculated from the time of SCT by Kaplan–Meier analysis.

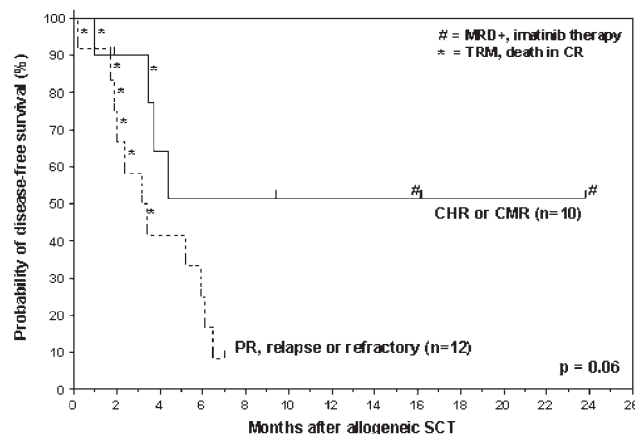


Figure 5 Kaplan–Meier analysis showing a trend towards superior disease-free survival in patients transplanted in remission (complete hematologic remission (CHR) or complete marrow response (CMR)) compared with those transplanted with active disease ($P = 0.06$ by log-rank test). The asterisks indicate the dates of deaths considered to be transplant-related. The other events were due to disease progression.

III–IV GVHD of the bowel and liver developed in six (27%) and three (13.6%) patients. Six of nine patients with grade III–IV GVHD died due to relapsing disease ($n = 2$) or GVHD-related complications ($n = 4$). Three of nine patients (33%) with grade III–IV GVHD experienced leukemic relapse. Details of grade and localization of GVHD are presented in Table 3.

Transplant-related complications

Two patients developed veno-occlusive disease (VOD) of the liver, two patients developed hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP) and were treated with plasmapheresis. Acute renal failure requiring intermittent hemodialysis was seen in four patients, autoimmune hemolytic anemia and microangiopathic hemolytic anemia in one patient each and one patient developed alveolar hemorrhage.

Severe infectious complications were observed in nine patients (aspergillosis $n = 4$, atypical or viral pneumonia $n = 3$, septicemia $n = 2$). None of the five patients with documented fungal infections during prior therapies experienced recurrence. Details of transplant-related complications are presented in Table 3.

Discussion

We demonstrate that imatinib facilitates allogeneic SCT in a relevant proportion of patients with primary refractory or relapsed Ph+ALL, and also show that severe time constraints are imposed on scheduling of the transplant by the short duration of response to imatinib. To realistically assess the potential of imatinib in this setting, we evaluated 46 consecutive patients who had not previously received an alloSCT and were enrolled at our center in two consecutive phase II trials of imatinib. Thirty of 46 patients (65%) were candidates for allogeneic SCT; 16 patients were considered ineligible primarily because of age and to a lesser extent comorbidity.

Although a stem cell donor was identified in 28 of the 30

eligible patients, only 22 (73%) of these patients were actually transplanted. This discrepancy is due largely to primary imatinib resistance in six of these patients, relapse before SCT and patient refusal to undergo mismatched alloSCT in two cases. No transplantation was cancelled because of mortality or treatment-associated complications. Our results are consistent with those of recent phase I and II trials, which reported overall response rates of 60–70% and a median response duration of 2.2 months.^{11,12} In our patients, median time to progression was 70 days (range 13–184 days). As we had not anticipated the brief nature of the responses when the phase II study was activated in 1999, several of our early patients relapsed considerably prior to scheduled alloSCT, and in the majority of these cases no transplantation was performed. Irrespective of our subsequent efforts to transfer patients to alloSCT more rapidly, relapse during imatinib therapy still occurred prior to transplantation, although more often immediately prior to scheduled myeloablative conditioning. In these cases, alloSCT was generally performed despite overt leukemia. Comparison of the median times to allogeneic SCT (67 days) and to progression on imatinib (70 days) highlights the difficulty of performing an allogeneic SCT at a sufficiently early time point. As a consequence, only 10 of the 22 patients who were actually transplanted, and of the 30 patients considered candidates for alloSCT, showed a complete response (CHR or marrow CR) at the time of transplant. Nine of these patients had been refractory to previous chemotherapy. DFS of patients transplanted during complete response is $51 \pm 18\%$ at 12 months, results that are encouraging in view of the dismal prognosis of patients with primary refractory ALL.¹⁰ In contrast, treatment outcome in the 12 patients who were transplanted with relapsing or refractory disease was dismal, with an $8 \pm 8\%$ probability of DFS at 7 months. This was due both to relapse as well as substantial transplant-related mortality (TRM), although the difference in TRM between patients transplanted with overt ALL vs complete response (50% vs 23%) was not statistically significant.

The cumulative incidence of (TRM) was $39 \pm 11\%$ and correlated with the intensity of prior therapy and remission status. These data are in line with published reports on TRM of up to 60% or more in patients transplanted beyond CR2 or with primary refractory disease or relapse.⁴ In view of the high risk of relapse prior to transplantation, we reasoned that imatinib should be given as long as possible until transplantation is performed, but were concerned about possible adverse drug interactions between imatinib and myeloablative or immunosuppressive therapy. Considering the half-life of imatinib of approximately 14 h, a wash-out period equivalent to four half-lives prior to the start of conditioning was recommended to minimize the theoretical risk of drug interactions. With a median time interval of 3 days (range 1–14 days) between the last dose of imatinib and start of myeloablative treatment in our series of 22 patients, there was no conclusive evidence that SCT-related toxicity was aggravated by prior use of imatinib. All patients surviving beyond 1 month after SCT engrafted and reached stable ANC counts and platelet counts within the expected time-frame. Secondary graft failures occurred in two patients (9%) transplanted with mismatch constellations and were attributed to HLA incompatibility. The incidence of severe (grades III–IV) acute GVHD was 41% and is similar to the previously reported incidence of grades III–IV acute GVHD of 35% and $31 \pm 8\%$ data.^{4,13} Despite being well within the range of published experience both TRM and rates of GVHD are considerable, however, suggesting that future studies

involving imatinib prior to SCT should monitor patients closely in terms of post-transplant toxicity.

Overall DFS of all patients in our small series was $25.5 \pm 10\%$ (median 6 months, range 0.2–23.8 months), which is comparable to published results of allogeneic transplantation for primary refractory or relapsed Ph+ALL,^{8,10} although the follow-up in our present study is still short. The profound impact of disease status at the time of transplant on treatment outcome in our study as well as in published series^{8,10} demonstrates the necessity of improving the CR rate and particularly the duration of response to imatinib-based therapy. In relapsing Ph+ALL, point mutations in the ATP binding site of BCR-ABL appear to be a frequent cause of clinical resistance to imatinib by interfering with its binding to the catalytic domain of this oncoprotein.^{14,15} In order to prevent the development and/or outgrowth of leukemic cell clones with such a mutation, future therapies are likely to be based on combinations of non-crossresistant treatment modalities.

In conclusion, imatinib is an effective and well-tolerated salvage therapy for patients with relapsed and refractory Ph+ALL and is able to induce cytologic remissions permitting alloSCT in a significant proportion of patients, particularly with primary refractory disease. As responses are usually short and outcome after alloSCT is promising only if performed during complete response, transplantation has to be performed rapidly. Future improvements will likely rely on therapeutic strategies combining imatinib, eg with chemotherapeutic agents, biologic response modifiers such as interferon-alpha or signal transduction inhibitors such as farnesyl transferase inhibitors.^{16–21} Strategies involving coadministration of agents should be clinically relevant both before and after allogeneic SCT.

Acknowledgements

We are indebted to Brigitte Gehrke, Anja Goodwin, Heike Nürnberger, Martine Pape, and Sandra Wagner for their excellent technical assistance, and to Angelika Spies for study management. We also thank the referring physicians for their excellent cooperation in caring for the patients throughout the study: G Mau, Braunschweig; FK Baur, W Heit, Essen-Werden; HG Höffkes, Fulda; F Ustaoglu, A Ho, Heidelberg; DW Beelen, M Pfreundschuh, Homburg/Saar; D Voliotis, P Staib, Köln; J Beyer, A Neubauer, Marburg; T Lipp, München-Schwabing; M Schleuning, HJ Kolb, München-Grohadern (LMU); M Stelljes, J Kienast, Münster; T Hegge, Osnabrück; J Casper, M Freund, Rostock; D Hähling, Schwerin; L Leimer, W Aulitzky, Stuttgart; C Denzlinger, L Kanz, Tübingen; D Bunjes, H Döhner, Ulm; M Prumbaum, R Schwerdtfeger, Wiesbaden (DKD). Supported by the BMBF, Competence Network Leukemias, grant No. 01GI9971 and by a grant from the Adolf Messer Foundation.

References

- 1 Gökbuget N, Hoelzer D, Arnold R. Treatment of adult ALL according to the protocols of the German multicenter study group for adult ALL (GMALL). *Hematol Oncol Clin North Am* 2000; **14**: 1307–1325.
- 2 Hoelzer D, Gökbuget N. New approaches in acute lymphoblastic leukemia in adults: where do we go? *Semin Oncol* 2000; **27**: 540–559.
- 3 Radich JP. Philadelphia chromosome-positive acute lymphocytic leukemia. *Hematol Oncol Clin North Am* 2001; **15**: 21–36.

- 4 Cornelissen JJ, Carston M, Kollman C, King R, Dekker AW, Lowenberg B, Anasetti C. Unrelated marrow transplantation for adult patients with poor-risk acute lymphoblastic leukemia: strong graft-versus-leukemia effect and risk factors determining outcome. *Blood* 2001; **97**: 1572–1577.
- 5 Snyder DS, Nademanee AP, O'Donnell MR, Parker PM, Stein AS, Margolin K, Somlo G, Molina A, Spielberger R, Kashyap A, Fung H, Slovak ML, Dagsis A, Negrin RS, Amylon MD, Blume KG, Forman SJ. Long-term follow-up of 23 patients with Philadelphia chromosome-positive acute lymphoblastic leukemia treated with allogeneic bone marrow transplant in first complete remission. *Leukemia* 1999; **13**: 2053–2058.
- 6 Dunlop LC, Powles R, Singhal S, Treleaven JG, Swansbury GJ, Meller S, Pinkerton CR, Horton C, Mehta J. Bone marrow transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. *Bone Marrow Transplant* 1996; **17**: 365–369.
- 7 Stockschrader M, Hegewisch-Becker S, Kruger W, Tom DA, Mross K, Hoffknecht M, Berger C, Kohlschutter B, Martin H, Peters S. Bone marrow transplantation for Philadelphia-chromosome-positive acute lymphoblastic leukemia. *Bone Marrow Transplant* 1995; **16**: 663–667.
- 8 Martin TG, Gajewski JL. Allogeneic stem cell transplantation for acute lymphocytic leukemia in adults. *Hematol Oncol Clin North Am* 2001; **15**: 97–120.
- 9 Martin H, Atta J, Klein SA, Fauth F, Bunjes D, Finckenstein F, Knauf W, Kolbe K, Kuse R, Langer W, Wassmann B, Weiss A, Hoelzer D: Autologous BMT/PBSCT in 40 patients with bcr-abl positive acute lymphoblastic leukemia: long-term follow-up of a GALL study. *The Hematology Journal* 2001; **1**: 187 (Abstr.).
- 10 Garcia-Manero G, Thomas DA. Salvage therapy for refractory or relapsed acute lymphocytic leukemia. *Hematol Oncol Clin North Am* 2001; **15**: 163–205.
- 11 Druker BJ, Sawyers CL, Kantarjian H, Resta DJ, Reese SF, Ford JM, Capdeville R, Talpaz M. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001; **344**: 1038–1042.
- 12 Ottmann OG, Druker BJ, Sawyers CL, Goldman JM, Reiffers J, Silver RT, Tura S, Fischer T, Deininger M, Schiffer C, Baccarani M, Gratwohl A, Hochhaus A, Hoelzer D, Fernandes-Reese S, Gathman I, Capdeville R, O'Brien S.G. A phase II study of Glivec (imatinib mesylate) in patients with relapsed or refractory Philadelphia chromosome-positive acute leukemias. *Blood* 2002; **100**: 1965–1971.
- 13 Sierra J, Radich J, Hansen JA, Martin PJ, Petersdorf EW, Bjerke J, Bryant E, Nash RA, Sanders JE, Storb R, Sullivan KM, Appelbaum FR, Anasetti C. Marrow transplants from unrelated donors for treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. *Blood* 1997; **90**: 1410–1414.
- 14 Von Bubnoff N, Schneller F, Peschel C, Duyster J. BCR-ABL gene mutations in relation to clinical resistance of Philadelphia-chromosome-positive leukemia to STI571. *Lancet* 2002; **359**: 487–491.
- 15 Hofmann WK, Jones LC, Lemp NA, de Vos S, Gschaidmeier H, Hoelzer D, Ottmann OG, Koefler HP. Ph+ acute lymphoblastic leukemia resistant to the tyrosine kinase inhibitor STI571 (Glivec) has a unique BCR-ABL gene mutation. *Blood* 2002; **99**: 1860–1862.
- 16 Hoover RR, Mahon FX, Melo JV, Daley GQ. Overcoming STI571 resistance with the farnesyltransferase inhibitor SCH66336. *Blood* 2001; **98**: 2585a (Abstr.).
- 17 Kano Y, Akutsu M, Tsunoda S, Mano H, Sato Y, Honma Y, Furukawa Y. *In vitro* cytotoxic effects of a tyrosine kinase inhibitor STI571 in combination with commonly used antileukemic agents. *Blood* 2001; **97**: 1999–2007.
- 18 Peters DG, Hoover RR, Gerlach MJ, Koh EY, Zhang H, Choe K, Kirschmeier P, Bishop WR, Daley GQ. Activity of the farnesyl protein transferase inhibitor SCH66336 against BCR/ABL-induced murine leukemia and primary cells from patients with chronic myeloid leukemia. *Blood* 2001; **97**: 1404–1412.
- 19 Thiesing JT, Ohno-Jones S, Kolibaba KS, Druker BJ. Efficacy of STI571, an abl tyrosine kinase inhibitor, in conjunction with other antileukemic agents against bcr-abl-positive cells. *Blood* 2000; **96**: 3195–3199.
- 20 Topaly J, Zeller WJ, Fruehauf S. Synergistic activity of the new ABL-specific tyrosine kinase inhibitor STI571 and chemotherapeutic drugs on BCR-ABL-positive chronic myelogenous leukemia cells. *Leukemia* 2001; **15**: 342–347.
- 21 Visani G, Isidori A, Malagola M, Alberti D, Piccaluga P, Martinelli G, Amabile M, Grafone T, Delfini C, Tura S, Baccarani M. Efficacy of Glivec (STI571) in conjunction with alpha-interferon in a case of relapsed p190 BCR-ABL positive acute lymphoblastic leukemia. *Blood* 2001; **98**: 587a–588a (Abstr.).