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Chapter 2

Myeloablative T cell-depleted alloSCT with early sequential prophylactic donor lymphocyte infusion is an efficient and safe post-remission treatment for adult ALL

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ABSTRACT

The prognosis of adult patients with ALL remains unsatisfactory. AlloSCT is associated with a beneficial GVL response mediated by donor T cells. However, GVHD results in substantial mortality and long-term morbidity. T-cell depletion (TCD) of the graft reduces the severity of GVHD, but is associated with an increased relapse rate after alloSCT. Therefore, early sequential donor lymphocyte infusion (DLI) is likely to be necessary for a successful GVL reaction. Twenty-five adult ALL patients (10 Ph^+ ALL) were eligible for early DLI after initial disease control with myeloablative TCD-alloSCT in first CR (CR1), if active GVHD was absent at 3–6 months after alloSCT. Patients with a sibling donor or an unrelated donor were scheduled for 3.0×10^6 $CD3^+$ cells/kg or 1.5×10^6 $CD3^+$ cells/kg, respectively, at 6 months after alloSCT. Three patients died before evaluation (one early relapse). Five patients had active GVHD. Fourteen of the remaining seventeen patients received DLI (median time-to-DLI: 185 days). Overall, only 17% required long-term systemic immunosuppression for GVHD. With a median follow-up after TCD-alloSCT of 50 months, 2-year survival probability was 68% (95% confidence interval (CI) 49–87%). In conclusion, myeloablative TCD-alloSCT with early sequential DLI is an efficient and safe post-remission treatment for adult ALL patients in CR1.

Keywords: alloSCT, T-cell depletion, ALL, donor lymphocyte infusion, DLI

INTRODUCTION

The prognosis of adult patients with ALL remains unsatisfactory. Despite high CR rates after induction chemotherapy, 5-year OS ranges between 40 and 60% with standard consolidation/ intensification and maintenance treatment including hematopoietic SCT.[1,2] AlloSCT is associated with a beneficial antileukemia effect as compared with autologous SCT or chemotherapy maintenance for adult patients with ALL.[3–7] This beneficial effect is due to donor T cells mediating a GVL response, thereby preventing a relapse. However, GVHD and infectious complications result in a substantial non-relapse mortality (NRM) and alloSCT-associated morbidity. Therefore, recommendation of alloSCT from non-sibling donors has remained controversial for patients without high-risk ALL in first CR (CR1).[8]

T-cell depletion (TCD) of the stem-cell graft reduces the severity of GVHD, but is associated with an increased relapse rate after alloSCT, especially if patients are transplanted in second CR or with refractory disease.[2,9,10] Therefore, the concept of prophylactic donor lymphocyte infusion (DLI) has been developed.[11] DLI not only decreases relapse rate in ALL patients who are at high risk for relapse, but can also induce molecular remissions in patients with detectable minimal residual disease.[11,12] TCD-alloSCT with postponed administration of DLI is associated with a decreased severity of GVHD.[11,13] We describe here the results of a treatment strategy with myeloablative conditioning before TCD-alloSCT in CR1 for efficient medium-term leukemia control, followed by early sequential prophylactic DLI to establish a GVL response for definitive prevention of relapse. We postulated that this strategy should limit the incidence of early relapses in conjunction with a low incidence of severe GVHD.

MATERIALS AND METHODS

Study population

All patients who underwent myeloablative TCD-alloSCT for ALL in CR1 at Leiden University Medical Center, between January 2003 and June 2011 were included in this study. All patients gave informed consent. High-risk ALL was defined by high leukocyte count at diagnosis (>30 $\times$ 10^9/L in B-ALL and >100 $\times$ 10^9/L in T-ALL), failure to achieve CR after prephase and first induction therapy, and/or unfavorable karyotype at diagnosis, that is, t(9;22), t(4;11) and other 11q23 abnormalities, hypodiploidy or complex abnormalities (≥5, excluding hyperdiploidy). Data were analyzed as of October 2012.

Transplantation procedure and follow-up

The conditioning regimen consisted of CY 60 mg/kg i.v. at days –6 and –5 and TBI in all patients. Patients with a matched sibling donor received 9 Gy TBI on day –1. Patients with a mismatched sibling or an unrelated donor received 9 Gy TBI on day –8 or –7, 30 mg alemtuzumab i.v. divided between days –6 and –5, and cyclosporine 3 mg/kg i.v. (and corresponding oral dose after engraftment) as GVHD prophylaxis from day –1 until day + 60. *In vitro* TCD was performed by adding 20 mg of alemtuzumab to the stem-cell product.[9] $CD34^+$ cell dose was determined by flow cytometry. Starting in 2008, patients with Ph^+ ALL received 400 mg imatinib per day after engraftment until at least 3 months after DLI.

The day of granulocyte engraftment was defined as the first of 3 consecutive days of absolute granulocyte counts $>0.5 \times 10^9$/L. GVHD was graded according to modified Glucksberg and Shulman criteria.[13,14] BM chimerism was determined every 3 months during the first 2 years after alloSCT, and additionally at 6 weeks after DLI. In sex-matched patient– donor pairs, chimerism was determined on total BM leukocytes, and mononuclear cell or granulocyte fractions after ficoll separation, using a short-tandem-repeat-PCR-based protocol.[15] In sex-mismatched patient–donor pairs, FISH analysis was performed on unseparated BM leukocytes until 2007. Thereafter, chimerism analysis was performed analogous to sex-matched pairs. Mixed chimerism was defined as ≥1% patient cells in any of these cell fractions.

Relapse was defined as reappearance of ≥5% blasts in BM by morphology (hematological relapse), and/or by reappearance of a molecular marker, that is BCR-ABL (molecular relapse). NRM was defined as death in continuous CR. OS was defined as time from alloSCT until death from any cause. Study end points were incidence of acute GVHD, NRM, relapse and OS. All time intervals were calculated from the date of alloSCT onwards.

Eligibility for DLI

Eligibility for prophylactic DLI was defined as continuous CR1 with the absence of active GVHD, defined as acute GVHD grade ≥2 or chronic GVHD requiring systemic immunosuppression, between 3 and 6 months after alloSCT. In patients with bacterial infections (not with viral or fungal infections) DLI was postponed. If a patient with active GVHD at evaluation developed mixed chimerism after tapering of immunosuppressive drugs, then DLI could be administered at that time point. Unmanipulated lymphocytes were collected from the original donors by leukapheresis without G-CSF priming. The number of $CD3^+$ cells was analyzed by flow cytometry. Donor cells were administered either on the day of collection, or they were temporarily frozen in the vapor phase of liquid nitrogen. Patients with a matched sibling donor were scheduled for 3.0×10^6 $CD3^+$ cells/kg and patients with a mismatched sibling or an unrelated donor for 1.5×10^6 $CD3^+$ cells/kg, respectively, at 6 months after alloSCT.

Statistical analysis

Probabilities of OS were calculated with 95% confidence intervals (95% CIs) by the Kaplan–Meier method. Survival curves for different groups were compared using a log-rank test. *P*-values of <0.05 were considered as significant. Relapse and NRM were considered as competing events and were analyzed by means of cumulative incidence statistics. Occurrence of any degree of GVHD after alloSCT was also analyzed in a competing risk framework, taking death before occurrence of GVHD as a competing event. Statistical softwares used were SPSS, PASW Statistics 20, release 20.0.0 (IBM, Amsterdam, the Netherlands, 2011) and R2.1.5.0 software, library 'cmprsk' (http://cran.r-project.org).

RESULTS AND DISCUSSION

The study population consisted of 25 patients (median age at alloSCT: 38 years, range 19–54), corresponding to 83% of all adult ALL patients referred to our center in the study period (Table 1). All 5 patients (17%) who underwent alternative treatment are described below. Ten patients (40%) had Ph^+ ALL and eighteen patients (72%) had high-risk ALL (cytogenetic abnormalities were unavailable in one Ph^- patient). Nine Ph^+ patients (90%) received 400 mg imatinib daily from induction to alloSCT. Median time from diagnosis to alloSCT was 202 days (range 99–354 days). Thirteen patients (52%) were transplanted from a sibling donor. Three patients received a BM graft (12%) and 22 patients (88%) received G-CSF mobilized peripheral blood stem cells with a median $CD34^+$ cell dose of 8.0×10^6 $CD34^+$ cells/kg (range $4.2–14.5 \times 10^6$ $CD34^+$ cells/kg). All 25 patients showed granulocyte engraftment after a median of 18.5 days (range 10–36 days) after alloSCT. No rejection of the graft occurred.

Despite TCD, only one patient (Ph^- ALL) suffered an early relapse (before planned DLI) at day + 92 and died at day + 165. Two patients suffered NRM within 3 months after alloSCT from miliary tuberculosis (day + 66) and gancyclovir- and foscarnet-refractory CMV pneumonitis (day + 91), respectively. Five patients were not eligible for early DLI due to active GVHD between 3 and 6 months after alloSCT as pre-defined by the treatment strategy. One of these patients died from NRM due to invasive pulmonary aspergillosis on day + 163. The remaining 17 patients were eligible for DLI. Three of these patients did not receive DLI for undocumented reasons. One of these three patients (Ph^- ALL) suffered a hematological relapse on day + 201 and died on day + 314.

Prophylactic DLI was administered to 14 patients at a median interval of 185 days (range 108–659 days) from alloSCT. One patient died 4 days after DLI from adenovirus infection (diagnosed 71 days before DLI) and could not be evaluated for the development of GVHD after DLI. After DLI, 3 of 13 patients (23%) developed acute GVHD (grades 1 and 2) of whom one died due to infectious complications. Two patients (one Ph^+ ALL and one

Table 1 Baseline characteristics and general outcomes

No.	Diagnosis (high risk)	Age (years)	Patient/ donor sex	Donor type (match)	Acute GVHD first 6 Mo	IS at 6 Mo	Time to DLI (days)	$CD3^+$ cells infused/kg bw	Acute GVHD after DLI	Relapse (days after alloSCT)	Follow-up (Mo)	Current status
1	Ph + ALL (yes)	36	M/F	RD (10/10)	Grade 3	Yes	NA	NA	NA	No	27	CR/alive
2	Ph + ALL (yes)	38	M/M	RD (10/10)	Grade 2	Yes	NA	NA	NA	No		CR/alive
3	Ph + ALL (yes)	48	F/M	RD (A-MM)	No	No	659	1.5 × 10E6	No	No	108	CR/alive
4	Ph + ALL (yes)	54	M/M	RD (10/10)	No	No	180	3.0 × 10E6	Grade 1	No	105	CR/alive
5	Ph + ALL (yes)	45	F/M	RD (10/10)	No	No	140	1.0 × 10E6	No	Yes (533, molecular)	50	CR/alive
6	Ph + ALL (yes)	20	M/M	UD (C-MM)	Grade 3	Yes	NA	NA	NA	No	87	CR/alive
7	Ph + ALL (yes)	50	M/M	UD (10/10)	Grade 2	NA	NA	NA	NA	No	5	NRM
8	Ph + ALL (yes)	28	F/F	UD (A-MM)	Grade 2	No	177	1.5 × 10E6	No	No	48	CR/alive
9	Ph + ALL (yes)	42	F/F	UD (10/10)	Grade 1	No	428	1.5 × 10E6	No	No	40	CR/alive
10	Ph + ALL (yes)	50	M/M	UD (DQ-MM)	No	No	219	0.05 × 10E6[a]	Grade 2	No	19	NRM
11	B-ALL (no)	46	F/M	RD (10/10)	Grade 1	NA	NA	NA	NA	Yes (92)	5	Relapse/dead
12	B-ALL (no)	26	M/M	RD (10/10)	No	No	NA	NA	NA	No	68	CR/alive
13	B-ALL (no)	21	F/F	RD (10/10)	Grade 1	No	108	1.0 × 10E6	No	Yes (188)	7	Relapse/dead
14	B-ALL (no)	38	F/M	RD (10/10)	Grade 2	No	211	1.0 × 10E6	No	No	7	NRM
15	B-ALL (no)	26	F/M	UD (10/10)	Grade 1	NA	NA	NA	NA	No	3	NRM
16	B-ALL (yes)	27	F/F	UD (10/10)	No	No	189	1.5 × 10E6	No	No	86	CR/alive
17	B-ALL (yes)	42	M/M	UD (10/10)	No	No	146	1.5 × 10E6	Grade 1	No	79	CR/alive
18	B-ALL (yes)	29	M/M	UD (DQ-MM)	Grade 1	No	167	1.5 × 10E6	No	No	15	CR/alive
19	T-ALL (yes)	42	F/M	RD (10/10)	Grade 1	No	NA	NA	NA	Yes (201)	10	Relapse/dead
20	T-ALL (no)	29	M/M	RD (10/10)	Grade 1	No	NA	NA	NA	No	33	CR/alive
21	T-ALL (yes)	19	M/M	RD (10/10)	Grade 1	No	NA	NA	NA	No	23	CR/alive
22	T-ALL (yes)	45	M/F	RD (10/10)	Grade 2	No	141	0.3 × 10E6	No	No	28	CR/alive
23	T-ALL (yes)	26	M/M	UD (10/10)	No	NA	NA	NA	NA	No	2	NRM
24	T-ALL (yes)	36	F/F	UD (DR-MM)	Grade 2	No	226	1.5 × 10E6	No	No	87	CR/alive
25	T-ALL (no)	28	F/F	UD (10/10)	Grade 1	No	204	1.5 × 10E6	No	No	78	CR/alive

Abbreviations: bw = body weight; DLI = donor lymphocyte infusion; F = female; IS = systemic immunosuppression; M = male; Mo = months after transplant; NA = non-applicable; No. = patient number; NRM = non-relapse mortality; Ph + ALL = Philadelphia chromosome positive B-cell ALL; RD = related donor; UD = unrelated donor; (X-) MM = (locus-)mismatch. [a] Patient received low-dose DLI due to persisting infectious complications (*Aspergillus* and *Pseudomonas* species), which persisted after DLI; after DLI, this patient developed an immune thrombocytopenia and a pericardial effusion.

Ph$^-$ ALL) showed increasing mixed chimerism after DLI and subsequently relapsed. The Ph$^+$ patient suffered a molecular relapse on day + 533 despite imatinib maintenance and DLI after alloSCT. After combination therapy with DLI, IFN-α and nilotinib,[16] this patient is in continuing second molecular CR and has full donor chimerism at 3 years after relapse. The Ph$^-$ patient had a hematological relapse within 12 weeks after DLI and died from progressive disease. At the end of follow-up, 11 of 14 patients receiving DLI (79%) were alive and in CR.

As expected, the overall incidence of severe GVHD in our study was low. One-year cumulative incidences of grade 2 and grade 3 acute GVHD were 28% (95% CI 10–46%) and 8% (95% CI 0–19%), respectively. Given the detrimental impact of chronic GVHD on quality of life, we determined the percentage of patients with a follow-up of >1 year who required systemic immunosuppression for GVHD at 1 year after alloSCT.[17] This was observed in 3 of 18 patients (17%) only.

This is the first study with long follow-up presenting the outcome of myeloablative TCD-alloSCT with pre-planned sequential DLI in adult ALL patients in CR1. Overall, 14 of 25 study patients (56%) received prophylactic DLI. Median follow-up of surviving patients was 50 months (range 15–108 months). Two-year OS was 68% (95% CI 49–87%). Two-year cumulative incidences of NRM and relapse were 20% (95% CI 4–36%) and 16% (95% CI 1–31%), respectively. There was no significant difference in survival between patients with a sibling donor or an unrelated donor ($P = 0.78$, Figure 1a).

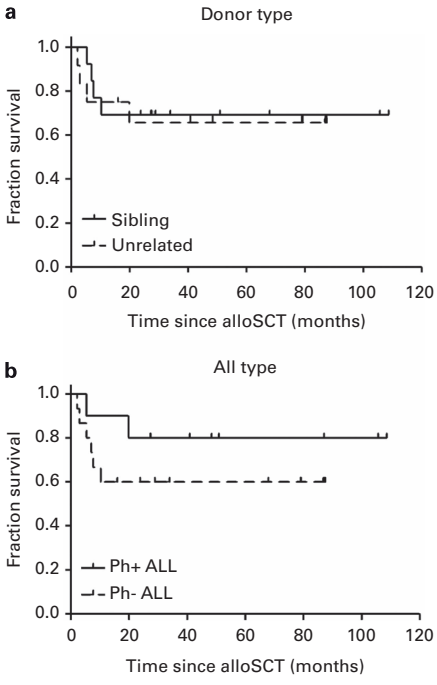

Figure 1 Kaplan–Meier plots of probabilities of OS after alloSCT. (**a**) Outcome of 13 patients with a sibling donor (solid line) and 12 patients with an unrelated donor (dashed line). (**b**) Outcome of 10 Ph + ALL patients (solid line) and 15 Ph ALL patients (dashed line).

To explore whether the favorable outcome could be due to possible systematic selection of favorable patients for transplantation, we studied the reasons for alternative treatment for all five adult ALL patients (aged 18–55 years) who were treated without receiving a myeloablative transplant in CR1 during the same time period at our institution. Reasons for alternative treatment were severe cardiomyopathy (n = 1, this patient underwent non-myeloablative TCD-alloSCT), or non-high-risk disease (n = 4, two of these patients relapsed and underwent alloSCT in CR2). Since the majority of patients included in our study had high-risk ALL, the favorable outcome observed is unlikely due to selection of good-risk patients for TCD-alloSCT.

In our cohort, 2-year OS of Ph^+ patients was at least as good as for Ph^- patients: 80% (95% CI 55–100%) and 60% (95% CI 35–85%), respectively (P = 0.27, Figure 1b). In the pre-imatinib era, a 2-year OS of 44% was reported for myeloablative TCD-alloSCT in children and adolescents with Ph^+ ALL in CR1.[10] While incidence and severity of GVHD was low, the main reason for failure was a high relapse rate of 40%. Concomitant long-term therapy with tyrosine kinase inhibitors may have an important role in prevention of relapse before DLI and during the development of the definitive GVL response.[18–20]

The necessity and optimal duration of imatinib maintenance after alloSCT for Ph^+ ALL cannot be defined by our study. Tyrosine kinase inhibitors are known to exert substantial side effects and may even inhibit donor-derived GVL activity due to immunosuppressive effects.[21,22] In our study, imatinib maintenance was restarted in five Ph^+ patients after alloSCT with a median duration of 450 days (range 12–542 days) after alloSCT. Imatinib was stopped prematurely in two Ph^+ patients because of intolerable nausea (after 12 days) and NRM (fungal death), respectively. In the first patient, imatinib was restarted 2 months later, and stopped at 3 months after DLI.

Finally, sensitive detection of molecular relapse by means of quantitative PCR of the BCR-ABL fusion transcript in Ph^+ ALL allows efficient salvage by switching to a second-generation tyrosine kinase inhibitor in combination with DLI and IFN-α.[16,23,24] This combination aims to induce a rapid GVL reactivity to prevent a virtually incurable hematological relapse and achieve long-term freedom from relapse as indicated by the only informative patient in our cohort.

In conclusion, this single-center experience in a predominantly high-risk adult ALL population indicates effective disease control with low risk of NRM by myeloablative TCD-alloSCT in CR1 with early sequential DLI for preventing relapse. The low overall impact of GVHD and the favorable outcome of Ph^+ patients support a combined strategy of targeted therapies with TCD-alloSCT followed by prophylactic DLI, which should be evaluated in a prospective study. Ultimately, the combination of targeted therapy and post transplant immunological interventions may lead to less intensive transplantation strategies, like reduced-intensity conditioning, to offer alloSCT for elderly and frail patients.[25]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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