Pathol. Oncol. Res. (2014) 20:61–66
DOI 10.1007/s12253-013-9658-5

RESEARCH

Clinical Outcome of Hematopoietic Stem Cell Transplantation for Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph + ALL): Experience From a Single Institution

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Received: 10 March 2013 / Accepted: 3 June 2013 / Published online: 3 July 2013

Abstract To identify factors affecting transplant outcome, data from 65 Philadelphia Chromosome-positive acute lymphoblastic leukemia (Ph + ALL) patients who had undergone allogeneic hematopoietic transplantation (allo-HSCT) in our institution were analyzed. The probability of OS (overall survival) and DFS (disease free-survival) at 3 years after allo-HSCT was 40.1 % and 38 %, respectively. Multivariate analysis showed that gender and disease status (p=0.0059, p=0.0039, respectively) were significant factors for OS. Among 51 patients with CR (complete remission), multivariate analysis showed that the factors associated with OS included gender (p=0.014), number of white blood cell at diagnosis (p=0.025), and the source of stem cells (bone marrow <BM > versus. cord blood; BM stem cell source was associated with favorable OS, p=0.042). Twenty-one patients relapsed after allo-HSCT with a median of 207 days (range, 19–1,324 days). The estimated cumulative incidence of relapse at 3 years was 39.4 %. Patients with CR showed a lower relapse rate at 3 years (34.2 %) when compared with patients with non-CR (62.7 %). Among 21 patients, eight patients received imatinib-based chemotherapy and 13 received chemotherapy without imatinib before HSCT. In terms of treatment after relapse, seven patients received chemotherapy with imatinib and 13 received chemotherapy without imatinib. Five patients underwent a second HSCT. One patient survived, and 20 patients died. In this study, disease status at time of allo-HSCT had a significant impact on OS, DFS, and relapse. Imatinib administration given before allo-HSCT was not associated with favorable outcome. Second-generation tyrosine kinase inhibitors may be more suitable candidates for Ph + ALL before and after allo-HSCT.

Keywords Philadelphia Chromosome-positive acute lymphoblastic leukemia (Ph + ALL) · Allogeneic hematopoietic stem cell transplantation (allo-HSCT) · Tyrosine kinase inhibitor (TKI) · Complete remission (CR)

Introduction

Adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) following conventional chemotherapy alone have poor long-term survival (<20 %) [1]. Although the use of tyrosine kinase inhibitors (TKIs) alone or in combination with chemotherapy has resulted in complete response rates as high as 75–95 % in these patients [2, 3], the results are transitory [2]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first complete remission (CR) is considered a curative treatment. Allo-HSCT from a human leukocyte antigen (HLA)-matched donor in first CR improved the leukemia-free survival rate to 40–60 % [4]. This study retrospectively analyzed the clinical features and treatment outcomes of patients with Ph + ALL patients who underwent transplant in our institution.

Patients and Methods

Patients

Between September 1989 and September 2010, 82 patients with Ph + ALL were transplanted in our institution. Ph+ALL

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was diagnosed by the presence of Philadelphia through chromosome and/or fluorescence in situ hybridization (FISH) analysis, and positivity for BCR-ABL fusion transcripts was characterized by real-time quantitative polymerase chain reaction (RQ-PCR) analysis. Seventeen patients undergoing auto-, second transplantation, or reduced-intensity allogeneic stem cell transplantation were not included in this analysis. The clinical features of 65 patients were reviewed in detail.

Statistical Analysis

Data were analyzed using SPSS (IBM Corp., Tokyo, Japan). The probabilities of overall survival (OS) and disease free-survival (DFS) were estimated using the Kaplan-Meier product limit method. Univariate analysis was performed using Cox regression models or the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression model or the competing risk regression model, as appropriate. A p value of 0.05 was considered to represent statistical significance.

Covariates considered in univariate and multivariate analyses were: gender, age at HSCT (<40 years vs. ≥40 years), disease status (CR vs. non-CR), the duration from diagnosis to transplant (<7 months vs. ≥7 months), white blood cell (WBC) counts at diagnosis (<20,000/μl vs. ≥20,000/μl), donor status, stem cell source (bone marrow <BM>, peripheral blood <PB>, or cord blood <CB>), acute graft versus host disease (aGVHD) (present vs. absent), chronic GVHD (cGVHD) (present vs. absent), BCR-ABL subtype (major vs. minor), treatment (with TKI vs. without TKI) before HSCT.

Results

Patient Characteristics

Table 1 shows the characteristics of the 65 patients analyzed in the present study.

Subjects comprised 41 males and 24 females (median age, 40 years; range, 17–60 years).

The disease status before allo-HSCT was CR in 51 patients and non-CR in 14 patients. Regarding the BCR-ABL transcript types, 47 patients were positive for minor BCR-ABL, 10 were positive for major BCR-ABL, and eight were unknown. Before HSCT, 39 patients received imatinib-based chemotherapy, and 26 patients received chemotherapy without imatinib. The majority of the donors were HLA-matched unrelated (n=34) and related (n=20), followed by mismatched unrelated CB (n=11). All patients received fractionated total body irradiation (TBI) followed by cyclophosphamide and/or cytarabine. No patient received TKIs after HSCT. For prophylaxis against GVHD, cyclosporine (CsA) and short-term methotrexate (sMTX) was used for 45 patients, and tacrolimus (FK506) and sMTX combinations were used for 18 patients. The median duration from diagnosis to HSCT was 7 months (range, 2–28 months). The median follow-up period for survivors was 559 days (range, 15–5,300 days).

Table 1 Patient characteristics (n=65)

- Age: 17–60 (median:40)
  - –39: 23
  - 40–54: 24
  - 55–-: 4
- Gender :
  - Male: 41
  - Female: 24
- HSCT donor
  - Related: 20
  - Unrelated: 45
- Hematopoietic stem cell source
  - Bone marrow:47
  - Peripheral blood: 7
  - Cord blood: 11
- Conditioning regimen
  - CA+CY+TBI: 64
  - CY+TBI: 1
- GVHD prophylaxis:
  - CsA+sMTX: 45
  - FK506+sMTX: 18
  - CsA: 1
  - CsA+MMF: 1
- Disease status
  - CR: 51
  - Non CR: 14
- Pretreatment
  - Imatinib based chemotherapy : 39
  - Conventional chemotherapy: 26
- Transcript types
  - Major BCR-ABL: 10
  - Minor BCR-ABL: 47
  - Unknown: 8
- WBC at diagnosis
  - 21,500/μl (500~301,900/μl)
- Days from the diagnosis to HSCT
  - 7 month (2–28 months)
- The follow-up period
  - 559 days (15–5300 days)

CA cytarabine, *CY* cyclophosphamide, *TBI* total body irradiation, *GVHD* graft-versus-host-disease, *CsA* cyclosporine, *sMTX* short-term methotrexate, *FK506* tacrolimus, *CR* complete remission, *WBC* white blood cell, *HSCT* hematopoietic stem cell transplantation

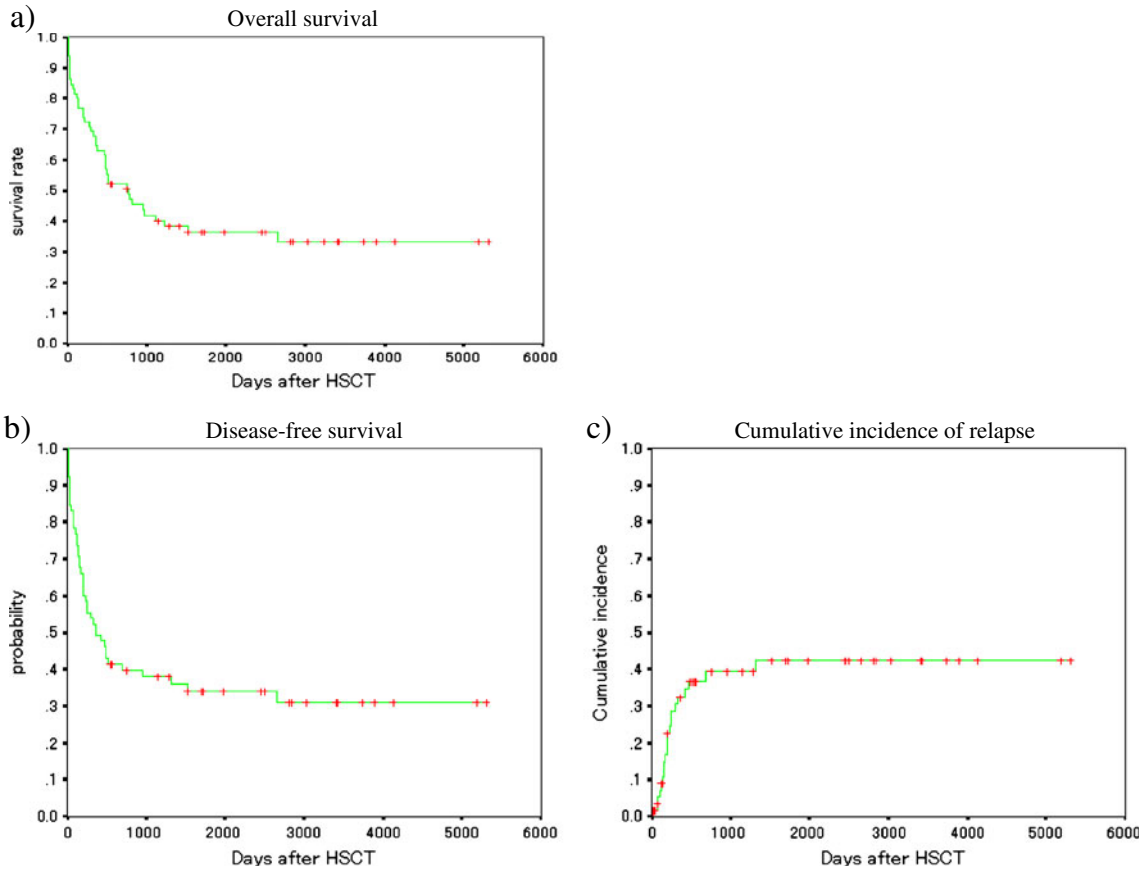

Fig. 1 Transplantation outcomes of 65 patients with Philadelphia Chromosome-positive acute lymphoblastic leukemia (Ph+ALL). **a** Overall survival, **b** disease-free survival and **c** cumulative incidence of relapse

Outcomes

OS and DFS

The probability of OS and DFS at 3 years after HSCT was 40.1 % and 38 %, respectively (Fig. 1a and b).

Table 2 shows the result of risk factor analysis for OS among all 65 patients. In univariate analysis, disease status (CR vs. non-CR), the duration from diagnosis to transplant, and the number of WBC at diagnosis were significantly associated with OS (p=0.002, p=0.018, p=0.01, respectively). In multivariate analysis, factors influencing OS were gender

Table 2 Results of univariate and multivariate analysis of overall survival among 65 patients with Ph+ALL

Factor		Univariate analysis		Multivariate analysis	
		RR (95 % CI)	p	RR (95 % CI)	p
Gender	Male vs female	1.60 (0.83–3.23)	0.16	4.14 (1.48–13.22)	0.006
Age	<40 years vs ≧40 years	0.94 (0.50–1.74)	0.85	0.98 (0.34–2.83)	0.98
Disease status	Non-CR vs CR	3.24 (1.60–6.25)	0.002	7.11 (1.86–30.73)	0.004
Diagnosis to HSCT	<7 month vs ≧7 month	0.47 (0.24–0.87)	0.018	1.19 (0.33–4.18)	0.78
WBC at diagnosis	<20,000/μl vs ≧20,000/μl	0.43 (0.21–0.82)	0.01	0.90 (0.29–2.93)	0.87
Donor status	Related vs unrelated	0.66 (0.32–1.27)	0.22	1.30 (0.35–4.73)	0.68
Stem cell source	BM vs PB	0.92 (0.38–2.73)	0.87	0.57 (0.12–2.73)	0.47
	BM vs CB	0.89 (0.42–2.11)	0.79	0.81(0.16–4.67)	0.81
aGVHD	Present vs absent	0.73 (0.39–1.40)	0.34	1.04 (0.38–2.96)	0.94
cGVHD	Present vs absent	0.84 (0.37–1.79)	0.66	0.54 (0.16–1.67)	0.29
BCR/ABL	Major vs minor	0.99 (0.36–2.25)	0.99	0.61 (0.13–2.25)	0.48
TKI use	Without vs with	1.10 (0.59–2.05)	0.74	1.48 (0.51–4.29)	0.46

Ph + ALL Philadelphia Chromosome-positive acute lymphhoblastic leukemia, *HSCT* hematopoietic stem cell transplantation, *WBC* white blood cell, *aGVHD* acute graft-versus-host-disease, *cGVHD* chronic graft-versus-host-disease, *TKI* tyrosine kinase inhibitor, *vs* versus, *CR* complete remission, *BM* bone marrow, *PB* peripheral blood, *CB* cord blood, *RR* relative risk, *CI* confidence interval

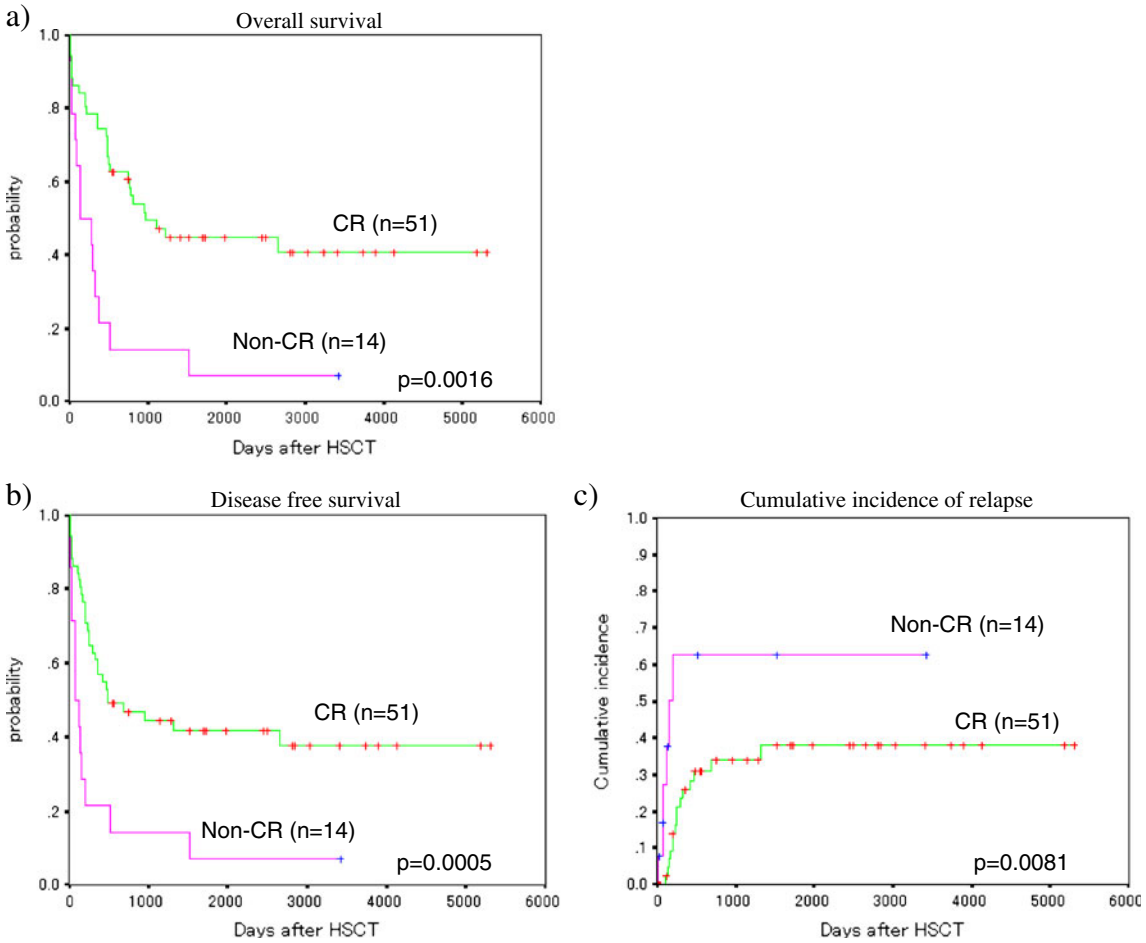

Fig. 2 Transplantation outcomes of 51 patients with complete remission (CR) and 14 patients with non-CR. **a** Overall survival, **b** disease-free survival and **c** cumulative incidence of relapse

(p=0.006) and disease status (p=0.004). According to univariate and multivariate analysis, the disease status was only factor associated with unfavorable OS. The 3-year OS was 49.3 % for patients with CR and 14.2 % for patients with non-CR (Fig. 2a). According to univariate and multivariate analysis, disease status was only factor associated with unfavorable DFS. The 3-year DFS was 44.4 % for patients with CR and 14.2 % for patients with non- CR (Fig. 2b).

Risk factors for OS and DFS among 51 patients with CR were analyzed, regarding the same factors as gender, age at HSCT (<40 years vs. ≥40 years), disease status (CR vs. non-CR), the duration from diagnosis to transplant (<7 months vs. ≥7 months), WBC counts at diagnosis (<20,000/μl vs. ≥20,000/μl), donor status, stem cell source (BM, PB or CB), aGVHD (present vs. absent), cGVHD (present vs. absent), BCR-ABL subtype (major vs. minor), and treatment (with TKI vs. without TKI) before HSCT (data not shown). In univariate analysis, the number of WBC at diagnosis was significantly associated with OS (p=0.008). In multivariate analysis, factors influencing OS included gender (p=0.014), number of WBC at diagnosis (p=0.025) and the source of stem cells (BM vs. CB, BM stem cell source associated with favorable OS, p=0.042). According to univariate and multivariate analysis, the number of WBC at diagnosis was the only factor associated with unfavorable OS. The 3-year OS was

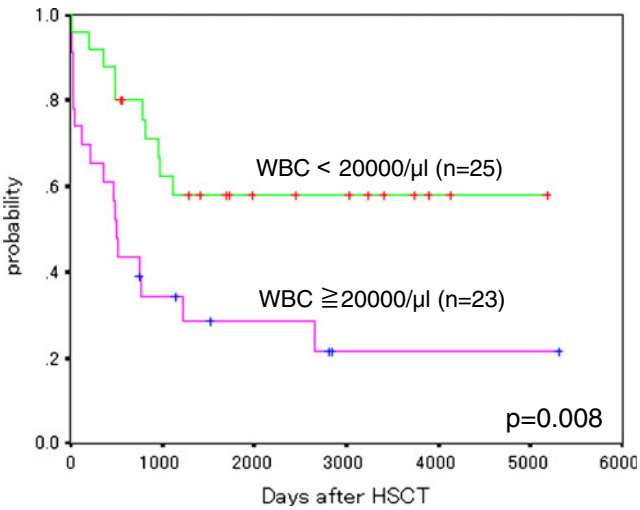

Fig. 3 Transplantation outcomes of 25 patients whose white blood cell (WBC) at diagnosis was less than 20,000/μl and of 23 patients whose WBC at diagnosis was more than 20,000/μl

62.2 % for patients with WBC <20,000/μl at diagnosis and 34.2 % for patients with WBC ≥20,000/μl at diagnosis (Fig. 3).

Relapse

Twenty-one patients relapsed after HSCT at a median of 207-days (range, 19–1,324 days). The estimated cumulative incidence of relapse at 3 years was 39.4 % (Fig. 1c). Among 21 patients, 15 patients had CR and six had non-CR at HSCT. Patients with CR showed a lower relapse rate (34.2 %) when compared with patients with non-CR (62.7 %) at 3 years (p=0.01, Fig. 2c). Before HSCT, eight patients received imatinib-based chemotherapy and 13 received chemotherapy without imatinib. In terms of treatment after relapse, seven patients received chemotherapy with imatinib and 13 received chemotherapy without imatinib. Five patients underwent a second HSCT. One patient survived and 20 patients died. The one patient who survived relapsed at 241 days after HSCT and survived for 8 years after a second HSCT. The main cause of the death was recurrence in 15 of the 19 patients who died.

Patients with Non-CR at HSCT

Fourteen patients underwent HSCT for non-CR. Before HSCT, five patients received imatinib-based chemotherapy, and nine received chemotherapy without imatinib. One patient survived and 13 died. Among the 13 patients who died, the causes of the death were recurrence (six patients), infection (four patients), GVHD (two patients), and graft failure (one patient).

Discussion

Allo-HSCT for patients with Ph + ALL in first CR is considered a curative approach. Allo-HSCT in first CR improves the leukemia-free survival rate to 40–60 % [4]. Similar to earlier reports, the present study showed that the probability of DFS at 3 years after HSCT was 49.3 % for patients in CR.

Prognostic factors for Ph + ALL patients undergoing allo-HSCT include age [5, 6], transplant decade [6], the number of WBC at diagnosis [7], disease status [5, 6], related allo-HSCT [5], TBI [5], aGVHD [6], cGVHD [5], imatinib-based chemotherapy before allo-HSCT [3, 8], BCR-ABL transcript types [1, 8, 9], and minimal residual disease (MRD) [10]. In this study, disease status at time of allo-HSCT had a significant impact on OS, DFS, and relapse, according to multivariate analysis. Among patients with CR, only the number of WBC at diagnosis, and not imatinib-based chemotherapy or BCR-ABL transcript types, predicted worse outcomes.

Fourteen patients underwent HSCT for non-CR. One patient survived and 13 died. Similar to previous reports [5], the 3-year survival rate in the present study was 7.1 % for patients with non-CR. Therefore, remission status at the time of allo-HSCT is an important determinant of outcomes.

Twenty-one patients relapsed after HSCT. In terms of treatment after the relapse, seven patients received chemotherapy with imatinib, but this treatment regimen failed to control the disease. Imatinib has very limited efficacy in treating relapsed Ph+ALL. The effect of the first-generation TKI, imatinib, before and after allo-HSCT has been investigated in several studies [3, 11, 12], but results have been contradictory. In this study, imatinib administration given before allo-HSCT was not associated with OS, DFS, or relapse. Dasatinib is a second-generation TKI with 300-fold greater activity than imatinib in vitro; it is effective against several BCR-ABL mutations that confer resistance to imatinib [13]. Recently, dasatinib has been used as first-line treatment for patients with Ph+ALL [14, 15]. There are only a few reports [16, 17] of maintenance therapy with dasatinib after allo-HSCT in Ph+ALL. For example, Caocci et al. [16] showed that during the maintenance treatment, MRD was negative in all eight surviving patients, including in two patients who tested MRD-positive after HSCT. Therefore, second-generation TKIs may be more suitable candidates for Ph + ALL before and after allo-HSCT.

Conflict of Interest The authors declare no conflict of interest.

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