JBUON 2016; 21(1): 227-234
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Factors affecting survival in acute leukemia with donor lymphocyte infusion in the first relapse after allogeneic stem cell transplantation

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Summary

Purpose: *Relapse of leukemia relapsing after allogeneic (allo) stem cell transplantation (SCT) remains an important problem. Cytoreductive chemotherapy followed by donor leukocyte infusion (DLI) is one of the treatment modalities in relapsed patients. The current study evaluated the factors affecting overall survival (OS) in allo-SCT patients who received DLI after the first relapse.*

Methods: *In this retrospective study 54 patients (26 with acute myeloid leukemia [AML] and 28 with acute lymphoblastic leukemia [ALL]) in their first relapse after allo-SCT who received fludarabine-based chemotherapy followed by DLI were evaluated.*

Results: *The relative risk for mortality was significantly higher in patients with acute leukemia (AL) within the high-risk group who went through transplantation (risk ratio: 4.866; 95% CI: 2.029-11.670;p<0.001) and in transplants performed in the remission phases following the first complete remission (risk ratio: 2.371; 95% CI: 1.154 – 4.872; p=0.019). Additionally, the relative mortality risk of transplantation in patients with acute leukemia (AL) with a number of DLIs applied (risk ratio: 0.456; 95% CI: 0.29 – 0.717; p=0.001) and non-myeloablative regimen (risk ratio: 0.229; 95% CI: 0.053–0.992; p=0.049) was significantly lower.*

Conclusion: *Efforts to enhance the number of DLIs, thus the number of infused cells, may result in better OS in cases with AL with relapse.*

Key words: *acute leukemia, allogeneic stem cell transplantation, donor lymphocyte infusion, relapse*

Introduction

As a result of the rapid improvements in the field of stem cell transplantation, the researchers noticed that depleting T-cells from the bone marrow or peripheral blood stem cell sources decreased considerably the rate of development of severe graft versus host disease (GVHD). However, in the following stage, depletion of stem cell sources from T-cells showed significant disadvantages, such as disease recurrence and predisposition to infectious complications [1].

Allo-SCT offers possibilities for cure in many hematological malignancies including ALs [2,3], but unfortunately relapse after transplantation remains an important problem [4,5]. Whether this is the best treatment option in patients with relapsed AL it is not certain; DLI is one of the treatment modalities for these patients [5,6]. As a result of the improvements in allogeneic transplants, DLI was indicated to cause graft versus leukemia (GVL) effects and be useful as an adjunctive method to fight the patient's underlying disease [7].

DLI has been used to treat patients that re-

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Received: 17/06/2015; Accepted: 14/07/2015

lapse after allo-SCT [1]. DLI was first used in 1990s in patients relapsed after allo-SCT, and it was effective in patients with chronic myeloid leukemia (CML) [8]. Although DLI was applied only to patients with relapsing CML at the beginning, data obtained in studies during the following time demonstrated that it can also be used in other hematological malignancies such as AL, multiple myeloma, and lymphomas [7].

Since DLI is minimally effective in advanced malignancies, which have a high tumor burden, cytoreductive chemotherapy prior to DLI is suggested to decrease the tumor burden and improve response rates [9].

The purpose of this study was to investigate the factors that may affect OS in patients with AL in their first relapse after allo-SCT, who received fludarabine-based chemotherapy followed by DLI.

Methods

Patient characteristics

AL patients who were in their first relapse after allo-SCT were retrospectively evaluated. Between March 2004 and March 2013, the data of 54 patients were collected from the patient files and were also confirmed with the data in the computed file system. The data included age, gender, pretransplant risk status for AL, the time from transplantation to DLI, blast percentage in bone marrow at DLI, HLA histocompatibility, stem cell source, GVHD status after transplantation, cell doses for DLI, administration schedule, and conditioning regimens for transplantation.

Pretransplant risk factors in patients with AML and ALL were defined separately. Cytogenetic risk was categorized according to the Southwest Oncology / Eastern Cooperative Oncology Group (SWOG /ECOG) criteria [10]. The recommendation to perform allo-SCT was made based on the presence of at least one of the following criteria: absence of a favorable karyotype, i.e., t(15;17), t(8;21), inv(16), or t(16;16) in the absence of other chromosomal aberrations; initial WBC >20 x109 /L; lactate dehydrogenase (LDH) >700 U /L; failure to achieve blast clearance after the first course of induction chemotherapy; presence of AML evolving from myelodysplastic syndrome (MDS) or therapy-related AML (tAML), or extramedullary disease [11]. Patients with ALL were classified as having poor-risk cytogenetics with either t(4:11), t(9;22), t(8;14), hypodiploidy or near triploidy, or more than 5 cytogenetic abnormalities [12]. Other ALL cytogenetic findings were classified as other abnormalities or normal. According to this score, the patients were divided and allocated in two groups with low or high risk.

Eligibility criteria

Patients who had once discontinued all immunosuppressive therapies without any flare ups of GVHD for at least two weeks were eligible for DLI. AL patients older than 18 years with their first relapse after allo-SCT were included in the study.

Definitions

All allo-SCTs were done from fullmatched sibling and missmatch sibling donors. Hematological relapse was defined as infiltration of bone marrow by ≥ 5% blasts. All patients received the same debulking chemotherapy regimen (FLAG) prior to the first DLI. The following drugs were administered: fludarabine 30 mg/m^2 once daily i.v. for 5 consecutive days (5 total doses); cytosine arabinoside 2 g/m^2 once daily i.v. for 5 consecutive days (5 total doses); and GCS-F 3μg/kg once daily s.c. from day -1 until the absolute neutrophil count (ANC) >1500/μl for 2 consecutive days. Donor lymphocytes were infused on the 6th day of chemotherapy in all patients. FLAG chemotherapy was administered only before the first DLI. An additional dose of DLI was administered in cases that did not develop GVHD and no remission.

DLI was defined as a transfusion of unstimulated CD3 (+) lymphoid cells collected from the original donor. The source of CD3 (+) lymphocytes was the peripheral blood in all patients. Schedule of escalating DLI cell doses was 1x10^7, 5x10^7, and 1x10^8 CD3 (+) cells/per kg, respectively, on day +6, day +34, and day +62.

Statistics

Data was analyzed with SPSS software version 20.0 for Windows (SPSS Inc., Chicago, Ill, USA). Distribution of the continuous variables was investigated with the Kolmogorov-Smirnov test and a homogeneity test was performed. Numerical variables with a normal distribution were statted as mean ± standard deviation, while numerical variables with a non-normal distribution were presented as median with range. The non-normal distribution of the numerical variables such as age, DLI cell doses, number of DLIs, and time from transplantation to DLI could not be normalized despite a logarithmic conversion. The properties of the two groups (AML and ALL) were compared using the chi square test for categorical variables and the Mann-Whitney U-test for continuous variables. For continuous variables, the median was used as the cut-off point. OS after DLI was the primary endpoint. Kaplan-Meier survival analysis with log rank test was used to estimate the probabilities of OS. The Cox regression test and multivariate regression analyses were used to determine the factors affecting mortality and relative risks. The statistical significance level was set at $p< 0.05$.

Results

Fifty-four patients were evaluated regarding the outcomes of chemotherapy followed by DLI

treatment. The cases included 28 males and 26 females (51.9% and 48.1% of the cases, respectively). The median patient age was 26 years (range 14-57). The median DLI cell dose administered to the patients was $7.2x10^7$/ CD3 (+) cells/per kg (range 2.7-16 x 10^7/kg). The mean time from transplantation to DLI was calculated as 4.5 months (range 1-39). The median number of DLI applied to the patients was 2 (range 1-3), while 59.3% (N=32) of the cases received more than one DLI. The high-risk group included 55.6% (N=30) of the cases. Cytogenetic characteristics (13;44.8%) and resistance to chemotherapy (12;41.4%) were the most important high risk factors in the high risk group.

Table 1. Patient characteristics and overall survival by group

Characteristics	*Number of cases N (%)*	*Overall survival at 1st year (%)*	*Estimated survival time (months mean±SD)*	*p value*
Age, years				
<40	47 (87)	64	27.49±3.67	0.189
>40	n=7 (13)	28.6	14.85±6.61	
Sex				
Male	28 (51.9)	54.4	26.52±4.93	0.893
Female	26 (48.1)	64.8	25.37±4.29	
Diagnosis				
AML	26 (48.1)	60.9	30.65±5.07	
ALL	28 (51.9)	62.7	18.32±72.58	0.151
GVHD				
Present	27 (50)	69.2	30.01±4.83	0.189
Absent	27 (50)	49.8	21.73±4.16	
Acute leukemia risk status				
Low risk	20 (37)	88.8	43.88±5.42	<0.001
High risk	30 (55.6)	42.8	14.81±2.28	
Number of DLI				
1	22 (40.7)	34.4	11.91±2.29	<0.001
>1	32 (59.3)	74.8	35.12±4.56	
Disease status CR1	39 (72.2)	70.7	30.21±4.07	0.014
> CR1	15 (27.8)	29.2	13.93±3.41	
Bone marrow blast ratio (%)				
< 5	20 (37)	75	33.53±5.48	0.064
> 5	30 (63)	49.4	21.95±3.93	
Tissue match				
Full match	49 (90.7)	57.5	25.03±3.4	0.355
Incompatible/unrelated	5 (9.3)	73.3	33.66±10.73	
Amount of stem cells administered				
<median	18 (33.3)	55	30.21±6.62	0.488
> median	36 (66.7)	61.9	23.01±3.37	
Regimen				
Myeloablative	49	57.6	23.03±3.33	0.032
Non-myeloablative	(90.7)			

AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, SD: standard deviation, CR: complete remission, GVHD: graft vs host disease, DLI: donor leukocyte infusion

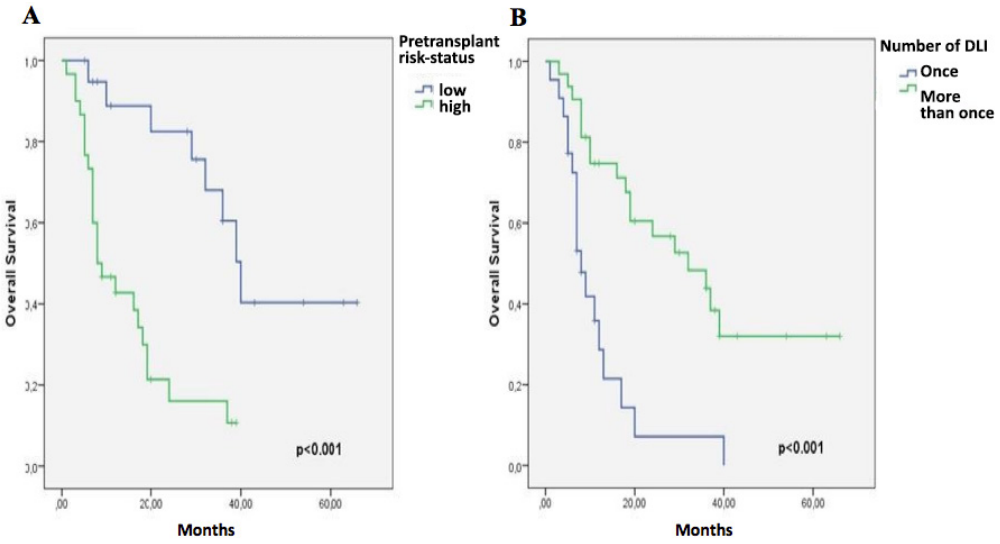

Figure 1. Kaplan-Meier curves for overall survival according to pre-transplant risk status (**A**) and number of DLI after transplant (**B**).

A total of 10 (18.5%) patients developed acute GVHD after DLI. GVHD was seen more frequently in patients who received more than one DLI compared to the patients who received only one DLI (p=0.7). No significant increase probability for increase of OS was noticed in patients who developed acute GVHD after DLI.

Parameters such as age, gender, diagnosis of AL, time from diagnosis to transplantation, tissue match, development of GVHD, number of stem cells administered and number of pretransplant bone marrow blast cells were not significant in terms of relative mortality risk (Table 1).

The survival rate of patients in the low risk group was higher than that in the high risk group (p<0.001); undergoing allo-transplant during the first complete remission led to higher OS compared to patients undergoing allo-transplant without first complete remission (p=0.014); using a non-myeloablative regimen resulted in higher OS than using a myeloablative regimen (p=0.032); and receiving more than one DLI post-transplant resulted in higher OS than in patients receiving only one DLI (p<0.001;Table 1). The Kaplan-Meier curves of pre-transplant risk status and the number of DLIs after the transplant are presented in Figure 1.

Cox regression analysis was performed to determine the relative risk of mortality from any reason. The results are presented in Table 2 and, according to the analysis, the relative risk of mortality was significantly higher in patients with AL who received a transplant in the high risk group (risk ratio 4.866; 95% CI 2.029–11.670; p<0.001), and received a transplant during the remission phases following the first complete remission (risk ratio 2.371; 95% CI 1.154–4.872; p=0.019). In addition, the number of DLIs applied (risk ratio 0.456; 95% CI: 0.29–0.717; p=0.001) and AL cases who received a transplant with a non-myeloablative regimen (risk ratio 0.229; 95% CI 0.053–0.992; p=0.049) significantly decreased the relative mortality rate.

The most effective factor on mortality was the number of DLIs administered when the factors significantly affecting mortality were analyzed using multivariate Cox regression analysis (Table 3). Other factors significantly affecting mortality were high risk status in patients with AL and the chemotherapy regimen administered.

Discussion

AL relapsing after allo-SCT has poor prognosis. Some therapeutic modalities have been applied in the management of relapsed cases including chemotherapy, second transplantation from another donor, DLI, and supportive care [4]. In the current study, we found that the increased number of DLIs in patients with low risk for AL, performing the allogeneic transplant during the first complete remission, and without myeloablative regimens were predictive for a better OS in relapsed AL patients after allo-SCT.

The elimination of leukemic cells after allo-SCT results in part from a mechanism of adoptive immunotherapy called GVL effect [13]. The adoptive transfer of donor immunity has an important role in the induction and maintenance of remission [14]. One of the limitations of immu-

Table 2. Relative risk of death due to any cause

Risk factors	*RR*	*(95 % CI)*	*p value*[§]
Age	1.025	(0.996 - 1.055)	0.093
Gender			
Male*	1		
Female	0.895	(0.542 - 2.018)	0.895
Diagnosis			
AML*	1		
ALL	1.642	(0.822 - 3.279)	0.160
Disease phase			
CR_1*	1		
Post-CR_1	2.371	(1.154 - 4.872)	0.019
Risk status in acute leukemia			
Low risk*	1		
High risk	4.866	(2.029 - 11.670)	<0.001
GVHD			
None*	1		
Present	0.634	(0.327 - 1.113)	0.177
BM blast ratio (%)			
<5*	1		
>5	1.893	(0.932 3.844)	0.078
Period from time of diagnosis to transplantation (months)			
< 12	1		
>12	0.771	(0.416 - 1.430)	0.409
Time passed between Tx and DLI	0.945	(0.880-1.014)	0.114
Preparatory regimen			
Myeloablative*	1		
Non- myeloablative	0.229	(0.053 – 0.992)	0.049
Tissue match			
Relative with full match*	1		
Incompatible	0.520	(0.125 – 2.171)	0.370
Amount of stem cells administered	0.910	(0.744 – 1.113)	0.359
Number of DLIs	0.456	(0.29 – 0.717)	0.001

[§]Cox regression analysis. Parameters with a * represent reference group. CI: confidence interval. CR: complete remission, GVHD: graft versus host disease, DLI: donor leukocyte infusion, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia

Table 3. Multivariate Cox regression analysis of mortality

Factors	*Relative risk (95 CI%)*		*Wald value*	*p value*
Number of DLIs	0.379	(0.216–0.665)	11.426	0.001
Risk status	4.203	(1.552–11.38)	7.981	0.005
CT regimen	0. 209	(0.037-0.838)	4.757	0.029
Disease phase	1.16	(0.510-2.638)	0.125	0.724

DLIs: donor lymphocyte infusions, CT: chemotherapy, CI: confidence interval

notherapy is its relatively slow onset of action. It is well documented that the clinically evident GVL effect of DLI requires a period from weeks to months to be apparent [15]. Patients may die from rapid disease progression before GVL effects have the chance to destroy leukemic cells. Immunotherapy may be less effective in patients with rapidly growing disease [16] so that in these patients the most rational approach may be debulking the tumor burden before DLI with chemo/radiotherapy [17].

Relapsed AML following allo-SCT is a challenging condition. General remission rates and 2-year OS are approximately 15-42% and 15-20%, respectively. The option of DLI is likely not an effective method to put the cases in remission. The ability of DLIs to provide remission is approximately 15-20%. In the absence of systemic chemotherapy, the effect of DLI alone is extremely weak. The most likely reason for DLI ineffectiveness in relapsed AML cases post-transplant may be the heavy tumor burden and high cell proliferation rate. Tumor burden in post-transplant relapsed AML cases should decrease with systemic chemotherapy.

Cytoreduction before DLI was first reported by Levine et al. who in a retrospective study, reported the results of cytosine arabinoside-based chemotherapy regimen prior to DLI; the 2-year OS was 19%, while no significant improvement in DFS and OS was noticed [5]. The most com-prehensive paper about DLI in the first relapse of AML patients after allo-SCT was published by the European Group for Blood and Marrow Transplantation in 2007. In that study, 399 patients with AML in their first relapse after hematopoietic stem cell transplantation (HSCT) who were treated with DLI were retrospectively evaluated. The estimated mean survival at 2 years was 21±3% for patients that received DLI and 9±2% for patients that did not receive DLI. Younger age, female gender, favorable cytogenetics, reduced conditioning for transplantation, a longer time interval from transplantation to relapse, lower tumor burden at relapse, and remission at the time of DLI were associated with superior survival [6]. In the present study, age, gender, conditioning regimens, interval from transplantation to DLI, and bone marrow blast ratio at the time of relapse were evaluated and showed that longer interval from transplantation to DLI and increased number of DLI were associated with longer OS. Bone marrow status at the time of DLI, gender, age, and conditioning regimens did not impact OS. The probability of OS at 2 years for both AML and ALL groups were 27 and 25%, respectively. The estimated survival at 2 years (27%) for the AML group was comparable with previously published studies. The response rates of DLI in patients with ALL and AML ranged between 0-19% and 15-29%, respectively [17,18].

ALL of B-cell or precursor B-cell responds poorly to DLI compared to myeloid leukemia (CML and AML). Although remission is achieved in some patients with chemotherapy and DLI, the duration of remission is generally short. It is well known that weeks and months are needed to achieve a marked GVL effect with DLI. ALL is a rapidly growing disease contrary to CML, and DLI alone falls short to control the disease without a significant decrease in leukemia burden. Whenever it is necessary to administer DLI in patients, rescue chemotherapy is required. Combinations of chemotherapy and DLI provide the best survival rates.

Although it is known that ALL responds poorly to DLI compared to AML, some patients may go into remission with chemotherapy followed by DLI [1]. The European Group for Blood and Marrow Transplantation reported that no patient with relapsed ALL achieved remission from DLI alone [14]. In the current study, the probability of one-year OS after FLAG followed by DLI was similar in both AML (56%) and ALL (62%) groups. In patients with ALL, host lymphoid cells may play an antagonistic role to the effect of DLI and GVL, given that the fludarabine-based chemotherapy may reduce the host lymphoid cells and provide a milieu for donor T cells so that the GVL effect occurs. Patients who received a lymphoid cell depleting regimen prior to DLI developed significantly greater GVHD [19]. This emphasizes the role of the chemotherapy regimen as stimulant of GVHD and could be explained either by providing greater space for donor lymphocytes to expand *in vivo* [16]. The depletion of host T cells helps the donor T cells to expand after being infused in the recipient [20]. The combination of chemotherapy to lower the tumor burden and create a space for host T cells and to optimize the effect of DLI may be an important approach. In the current study, better OS results were obtained with increasing number of DLIs after the fludarabine-based regimen. The best OS, and with statistical significance, was seen in patients who had received more than 2 DLIs. As the number of infused T cells increases with additional DLIs, this may play a role in providing a better anti-leukemic effect.

The life expectancy of patients with AL var-

ies according to the patient subgroup, prognostic features, and phases of disease. The risk status at the time of diagnosis in patients with AL is the most helpful factor to predict prognosis and the success of allogeneic transplantation. Factors such as main cytogenetic features, white blood cell count at the time of diagnosis, age, and response to chemotherapy are considered in the risk stratification. The risk stratification at the time of diagnosis was demonstrated to have a significant effect on the relative mortality risk in the present study, and OS in cases with AL who received a transplant with a low risk status were higher.

One of the factors affecting life expectancy after allogeneic transplantation is the phase of disease at the time of transplantation. Allogeneic hematopoietic stem cell transplantation (AHKHN), performed during the first remission, especially in high-risk patients, was reported to be more effective compared to standard chemotherapy protocols and AHSCT performed after the first remission period followed by consolidation regimens [21]. The stage of disease at the time of transplantation was demonstrated to have a significant effect on mortality risk in the present study, and OS rates in cases with AL who received a transplantation during the first complete remission was higher.

In conclusion, administering chemotherapy regimens, especially those including lymphocyte depleting agents, such as fludarabine, before DLI may have an effect on the treatment of patients with relapsed AL after allo-SCT. Efforts to enhance the number DLIs, thus the number of infused cells, may result in better OS. Although a recently published paper by Bar et al. [22] reported that the initial cell dose did not have an effect on OS, the current study demonstrated that an increased number of DLI and cumulative $CD3^+$ cell dose improves OS. New and extended prospective studies are required to expose the effects of DLI $CD3^+$ cell dose on the outcomes in relapsed AL patients after allo-SCT.

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