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A Comparison of Dexamethasone Plus Vincristine versus Standard Regimen in Induction Therapy of Adult Acute Lymphoblastic Leukemia Patients Undergoing Hematopoietic Stem Cell Transplantation

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ABSTRACT

Background: Current treatment options of acute lymphoblastic leukemia(ALL) include chemotherapy alone or hematopoietic stem cell transplantation (HSCT) following induction chemotherapy both along with CNS prophylaxis. The usual and standard induction regimens currently administered could have severe complications and mortality.

Materials and Methods: To lessen induction regimen complications in ALL patients who undergo HSCT, we used a cytoreduction induction regimen including dexamethasone (8 mg, IV, three times a day, for 28 days) and vincristine(1.4 mg/m^2, IV, on days 1,8,15 and 22) for 49 newly diagnosed adult ALL patients followed by an early sibling donor HSCT within two months. The results were matched with outcomes of HSCT in 172 ALL patients inducted by standard induction regimen.

Results: Median follow-up time was 5.41 years in the standard group and 5.27 years in the other. All patients of the case group (100%) achieved complete remission. Landmark analyses were performed to scrutinize the effect of treatments on different time intervals: first two years and 2nd to end years. Type of treatment had no significant effect on the hazard of death in the first landmark (HR=0.87, P=0.64). Cytoreduction regimen amplified the hazard of death 3.43 times more than the standard regimen in the second landmark (HR=3.43 P=0.035). Multivariate analysis showed that the cytoreduction regimen reduced the hazard of relapse about 22%, but not statistically significant (HR=0.78, P-value=0.24).

Conclusion: Overall, it seems despite achieving complete remission in induction therapy, depth of response is a critical predictor for long-term outcomes of HSCT in ALL patients, and the use of multiple agents may be necessary to decrease tumor cell burden and minimal residual disease(MRD).

Keywords: Acute lymphoblastic leukemia (ALL); Induction, Hematopoietic stem cell transplantation (HSCT); Cytoreduction

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy with an incidence of about 1.08 to 2.12 per 100,000 persons – years[1]. Treatment recommendations include three phases of remission induction, consolidation and maintenance along with CNS prophylaxis[2-5]. Patients treated only by chemotherapy show an approximately survival of about 30% and a high relapse rate , although survival rates of 70% and more have been recently reported in adult focused trials[3,4,6,7,8] . Hematopoietic stem cell transplantation (HSCT) from HLA identical donor following induction therapy has proven superior outcomes to chemotherapy, especially in those categorized as high-risk patients[9-12]. Individual uncontrolled trials report a disease-free survival between 40% and 60%[13,14]. The commonly used induction regimen consists of at least a glucocorticoid, vincristine, an anthracycline, cyclophosphamide and maybe L-asparaginase given over 4-6 weeks. Complications include infection, prolonged cytopenia, fungal infection, bleeding and hematologic toxicities, hepatic and central nervous system and thrombotic toxicities, which all could be severe and cause mortality[15,16], and also result in inability to proceed to next steps of treatment or deteriorate outcomes of stem cell transplantation. Therefore, these patients should be hospitalized in the oncology ward during induction chemotherapy and receive special care to manage the probable complications. Since we are a referral tertiary center with heavy load of patients waiting to be hospitalized in the oncology ward, ALL patients commonly have to spend some days in the emergency ward waiting for an oncology bed without receiving any standard treatment after they are diagnosed, therefore the need for a less toxic induction regimen was noted remarkable.

The goal of remission induction therapy is hematologic complete remission (CR) which is defined by a bone marrow containing less than 5% blast cells and return to normal hematopoiesis. Remission induction plays its prerequisite role in successful treatment through decreasing tumor cell burden. Therefore, a good consolidation could stabilize the treatment, eliminate any residual leukemic cells, and reduce chance of relapse. Conditioning regimen of HSCT induces immunosuppression in the host to accept donor cells and establish graft-versus-leukemia effect[17,18], which leads to further elimination of malignant cells. Moreover, it powerfully eradicates primary disease cells from marrow. Considering these effects of conditioning regimen on decreasing number of tumor cells, it was assumed that an induction regimen with less toxicity and relatively acceptable CR rate followed by an early HSCT as a powerful consolidation treatment could be as effective as almost heavy standard induction regimen combined with HSCT.

Literature shows that administration of only vincristine and prednisone as induction regimen in children suffering from ALL results in more than 90 % CR rate[19]. In 1976, Cancer Journal published an article reporting complete remission achievement by the use of vincristine and prednisone in most of studied adult patients[20]. A 61 % rate of complete remission in adults has also been shown by Takahashi study[21] and was confirmed by a rate of 66% reported by another study published in the same year[19]. According to these findings and presumptions, here, in Hematology-Oncology and Stem Cell Transplantation Research Center, Sharitai Hospital, eligible patients were offered to undergo HSCT with an induction regimen consisting of dexamethasone and vincristine and the outcomes were retrospectively compared with the outcomes of HSCT following standard induction therapy.

MATERIALS AND METHODS

Patients

Between January 2008 and December 2014, all newly diagnosed acute lymphoblastic leukemia patients that were physically, socially and psychologically eligible for allogenic fully matched identical sibling HSCT were offered to undergo HSCT following an induction therapy including dexamethasone and vincristine, which we called cyto-reductive regimen. Patients had been given fully and necessary explanations above probable risks and benefits of new treatment and were free to choose treatment approach. Our protocol conformed to the Declaration of Helsinki and the study was approved by institutional review board of

Hematology-Oncology and Stem Cell Transplantation Research Center of Tehran University of Medical Sciences and the Ethics Committee of Tehran University of Medical Sciences. Disease diagnosis was confirmed by morphologic study of bone marrow aspiration and biopsy as well as flow cytometry. Cytogenetic studies were performed for all patients. HLA typing were done immediately for those patients who signed the consent form and their siblings. Induction chemotherapy by cyto-reductive regimen was then immediately started. If HLA compatible sibling donor was found within 28 days, patients underwent HSCT regardless of disease status and were studied as cyto-reduction group (case group). If no suitable donor was found, the patient was excluded from the study and his induction therapy was changed to standard induction regimen. Standard (control) group was selected from other newly diagnosed ALL patients undergoing allogenic sibling HSCT who did not meet our study inclusion criteria or those treated with usual standard induction therapies in other centers and referred to ours for HSCT. Matching was done in terms of HSCT source (peripheral blood stem cell) and disease status at transplantation. All studied patients were followed up until death, relapse or the end of the expected follow-up time, which was Jan. 2019.

Patient's gender, age, disease status at HSCT, WBC (white blood cell) count at diagnosis, ALL phenotype (specific diagnosis), cytogenetic studies, CNS involvement, incidence of acute and chronic graft-versus-host disease (aGVHD and cGVHD), and treatment outcomes were collected by a check list and evaluated by a hematologist-oncologist to determine the primary risk of disease according to criteria adapted from results of Southwest Oncology Group 9400 study[14,22].

Induction chemotherapy and HSCT

HLA Class I and II were typed by PCR for all patients and HLA class I typing was performed by serology for their siblings .If there was compatibility of class I between donor and recipient, HLA class I and II were typed by PCR for donors.

Control group received a combination of cyclophosphamide, an anthracycline, a glucocorticoid and vincristine as remission induction therapy and underwent HSCT after achieving complete remission. Induction regimen of cyto-reduction group consisted of dexamethasone 8 mg intravenously (IV), three times a day, for 28 days and vincristine 1.4 mg/m^2 IV infusion on days 1,8,15 and 22. CNS prophylaxis was performed in both groups by intrathecal administration of cytosine arabinoside(50 mg), methotrexate (15 mg) and hydrocortisone(50 mg).Bone marrow aspiration and biopsy were done for all patients on days +14 and +28 post induction therapy. Hematopoietic stem cell transplantation was planned to be performed within one month after induction for all patients in cyto-reduction group, whether complete remission was obtained or not. In our center, HLA typing of donors and recipients are routinely performed twice to increase the reliability of matching and sometimes this process takes long, hence, some of patients from cyto-reduction group underwent transplantation within maximum two months after initial therapy.

Conditioning regimen of HSCT was similar in both groups and consisted of Busulfan(4 mg/kg, three times a day ,orally, from day -6 to -3) and Cyclophosphamide(60 mg/kg daily ,IV infusion on days -2 and -1). Cyclosporine A was administered in all patients. It was given intravenously at dose of 1.5 mg/kg/day from day -3 to +7 and then 3 mg/kg/day was intravenously infused from day +8 and it was changed to 6 mg/kg orally as soon as oral tolerance was achieved .Patients of both groups received methotrexate 10 mg/m^2 IV on day +1 and then 6 mg/m^2/IV on days +3,+6 and +11. All patients were hospitalized in reverse isolation room and received same usual care and also necessary prophylaxis and treatments after transplantation.

Outcomes and definitions

The outcomes of study were overall survival (OS), Disease free survival (DFS), relapse, non-relapse mortality (NRM), aGVHD and cGVHD, platelet and WBC engraftment time .OS was the time between HSCT to death from any cause. DFS was the time after transplantation, which no disease was found. Relapse was defined by presence of >5% bone marrow blasts and/or reappearance of underlying leukemia. Time to WBC engraftment was the first of

three consecutive days which WBC count gets over 1000× 10 ^{6}cells/L in at most one month after transplantation. Platelet engraftment time was first day of platelet count≥ 20000 × 10^{6} cells/L for seven consecutive days without any supportive platelet. NRM was determined as death due to causes unrelated to leukemia relapse. Acute and chronic GVHD were diagnosed according to published criteria[23].

Statistical analysis

Homogeneity between treatment pairs was evaluated using the chi-square test or Fisher exact test when appropriate for qualitative variables and Student's T-test or Wilcoxon rank sum test when appropriate for continuous variables. Kaplan–Meier curves were derived to determine OS and DFS[24], and were compared by means of the log-rank test at each landmark. Median follow-up time was established with the reverse Kaplan-Meier method.

Landmark analyses (or partly conditional modelling) which could assess outcomes of all patients at some fixed time after the onset of treatment were used to explain the effects of different prognostic factors on the OS in time: early and intermediate (within 2 years), or late (through 2 to end years). The landmarking paradigm offers a flexible and relatively simple way to depict the association between prognostic factor(s) and the time until an event. Cox proportional hazards model[25] was fitted using data of patients who were at risk at each landmark time point. Considering the definition of disease-free survival, landmark analysis was only done for overall survival, as those who have died without relapse did not have the chance of relapse after death.

After selection of baseline characteristics and clinical variables on the basis, univariable Cox proportional hazards models and multivariable Cox proportional hazards models have been fitted. Multivariable predictors of OS and DFS were determined based on the P-values at or below 0.2 in the univariable Cox proportional hazards models. Multivariable Cox proportional hazard analyses were used to determine the effects of plausible predictors in univariate analysis as an independent predictor of the OS and DFS adjusting for each other variables.

The afore-mentioned variable selection scenario was repeated three times; one for the whole period of study, one for the first landmark (within 2 years) and one for the second and last landmark (through 2 to end years). This means that all alive participants at the end of second year of follow up were included in the second analysis and were followed up until Jan. 2019. Uni/multivariate survival analyses were performed at each Landmark. This scenario was only applied for the OS.

The proportionality of hazards assumption was checked using the global proportionality of hazards test on the basis of Schoenfeld residuals in each of the three multivariable models. There were no departure from the proportionality of hazards assumption in all multivariable models (results not shown).

To account for the informative censoring in the presence of multiple endpoints, competing risks survival analysis was performed by means of nonparametric methods using the cumulative incidence competing risk method[26].Cumulative incidences of relapse and non-relapse mortality (NRM) were calculated by Gray's method. Death without relapse was considered as a competing event for relapse, and relapse was considered as a competing event for NRM.

Fine-Gray proportional hazard regression model was used to assess the effects of covariates on relapse incidence and NRM incidence. Like multivariate Cox PH regression, all the variables with a P-value at or below 0.2 in the univariate Fine-Gray proportional hazard regression were included in the corresponding multivariate analyses. A two-sided P-value of 0.05 or lower was considered to be statistically significant. Analyses were done with STATA version 11.2 and Packages "survival" and "cmprsk" in R software version 3.3.1.

RESULTS

Overall, a total of 221 ALL patients (median age, 25 years) allo-transplanted form a fully matched identical sibling were included in the analysis. Forty-nine patients chose to be inducted by vincristine and dexamethasone as the cyto-reduction group. Surprisingly, all patients of this group achieved complete remission (100%), so 172 patients with first

complete remission who had received standard induction regimen were selected as matched control group as well.

Median follow-up times were 5.41 years (S.E. = 0.34) and 5.27 years (S.E. = 0.50) in the standard and cyto-reduction treatment groups, respectively. Demographic characteristics of these patients according to the type of treatment approach are shown in Table-1. As we can see there were no significant differences between patients' age in two groups (P=0.67). Also, distribution of other demographic characteristics and patients' specific disease (B-lineage, T-lineage and unspecified) were the same in both groups (all P>0.175). One hundred and forty-three patients were determined as high risk patients. The distribution of high risk patients was the same in both groups (P=0.80). There was no significant difference between median WBC count at diagnosis (p=0.48).

Median times from date of diagnosis to date of HSCT were 246 (Range: 45-825) and 53 (Range: 8-161) days in the standard and cyto-reduction treatment group, respectively (P<0.0001). There was no significant difference between median times to platelet engraftment (P=0.55). On the other hand, time to WBC engraftment was statistically different between patients who received each treatment (P=0.003) and also distribution of patients with aGvHD was more frequent in cyto-reduction group (71.43% vs 49.42%, P=0.023). Seventy-three patients had cGvHD and its distribution was not different between two groups (P=0.68).

One hundred and eleven (n=111) patients died during the whole study time and distribution of death was different in two groups (45.93% in standard and 65.31% in cyto-reduction group, P=0.017). Of whom, eighty-eight died in the first landmark (38.37% and 44.90% in standard and cyto-reduction group, respectively (P=0.41)), while the remaining twenty-three patients died in the second landmark (13.00% and 37.04% in each group, respectively (P=0.004)). The most cause of death in the whole time analysis (both landmarks) was relapse (n=71, 63.29% and 65.62% in standard and cyto-reduction groups, respectively) and fifteen patients died from GvHD (13.92% and 12.50% in standard and cyto-reduction groups, respectively) as the second cause of death. From 71 patients who died from relapse in the whole time analysis,55 patients died in the first landmark (63.63% and 59.10% in standard and cyto-reduction group, respectively). The remaining 16 deaths from relapse happened in the second landmark with 61.54% and 80.00% in each group, respectively, again as the first cause of death.

We recorded an improvement of OS and DFS for patients in the standard group compared with those in the cyto-reduction. The OS improvement was statistically significant (P=0.033), while the DFS improvement was not (P=0.11). We also compared the relapse and NRM incidence between two groups. Analysis showed that the probabilities of relapse and also death due to causes other than relapse were both similar in two treatment groups. Five-year cumulative incidence of relapse in standard and cyto-reduction groups were 39.33 (31.84 - 46.73) and 44.89 (30.48 - 58.29), respectively (P=0.52) and the five-year cumulative incidence of non-relapse mortality were 16.93 (11.61 - 23.09) in standard group and 22.58 (11.95 - 35.26) in the other one (P=0.32). We should notice that these are unadjusted incidences of relapse and non-relapse mortality and these lack of difference should not be considered as they are really equal. More scrutinized assessment was done based on Fine-Gray regression modeling. The results are presented later in this part.

Univariate and multivariate analyses

The primary outcome of this study was to evaluate the effect of two treatments on the OS and DFS for the whole study time. Yet, landmark analyses were performed to scrutinize the effect of treatments on different time intervals (landmarks). All 221 cases of the study and those 127 patients who were alive after two years, were included in the respective landmark analysis.

The whole study time analysis: In the univariate analysis, type of treatment and three other factors including cGvHD, recipient sex and time between diagnosis and HSCT had significant effects on the hazard of death (OS model) at the 20% level of significance (HR=1.56, P=0.035; HR=0.63, P=0.03; HR=1.38, P=0.12; HR=0.99, P=0.02, respectively),

(Table-2). The multivariate analysis including these factors showed that cytoreduction regimen amplified the hazard of death about 19% which was not statistically significant while cGvHD significantly reduced the hazard of death about 35% (HR=1.19, P=0.50 and HR=0.65, P=0.04, respectively).

In univariate DFS modelling, sex, time between diagnosis and HSCT, type of treatment and cGVHD had significant effects on hazard of death or relapse (DFS model) at the 20% level of significance (Table 2).However, entering these candidate covariates together with the type of treatment in a multivariate cox regression modelling revealed that none of them had a statistically significant effect on the hazards of death or relapse (Table 2) .

Landmark analysis of OS: Based on OS univariate analyses, four factors were selected to be included in the multivariate OS cox modeling in the first landmark, Table-3. The multivariate cox modeling of OS showed that treatment had no significant effect on the hazard of death while cGvHD reduced the hazard of death about 50% (HR=0.87, P=0.64; HR=0.50, P=0.007, respectively) (Table 3).

In the second landmark, which we expected to see the long-term effect of the treatments on OS, we used the same variable selection approach for multivariate analysis. Multivariate analysis of OS with adjusting for the effect of time to platelet engraftment and also time between diagnosis and HSCT, showed that the cyto-reduction regimen amplified the hazard of death 3.43 times more than standard regimen in this period (HR=3.43, P=0.035), (Table 3). Figures- 1a and 1b show the adjusted OS of patients in the first and second landmarks.

We did not do the landmark analysis of DFS, because analysis showed that DFS of both treatment options got apart almost from somewhere before the first year of follow up. Instead, we did the relapse and NRM regression modeling for more clarification. The univariate and multivariate analyses of relapse incidence and NRM are presented in Table-4. We considered the same scenario of variable selection as we got in OS and DFS multivariate modeling. The multivariate analysis of relapse incidence showed that treatment approach did not have any effect on relapse (HR = 0.78, P-value =0.246) after adjusting for age, recipient sex, aGvHD, cGvHD, and time between diagnosis and HSCT. However, the multivariate analysis of NRM showed that patients who received cyto-reduction regimen had an augmented hazard of death from any cause other than relapse of about 37%, though this effect was not statistically significant (HR = 1.37, P-value = 0.24, Table-4).

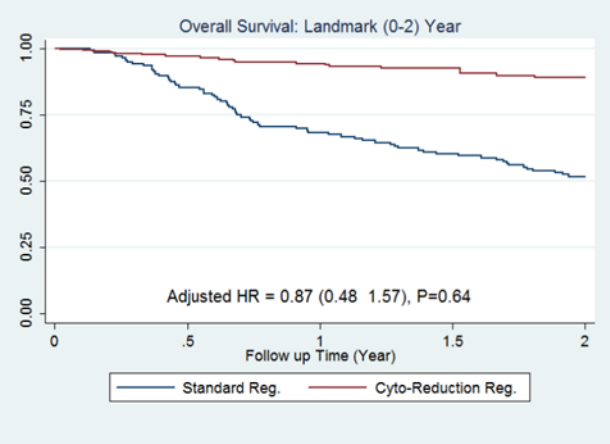

Figure 1a. Adjusted Overall Survival of all Patients by Treatment in the first landmark

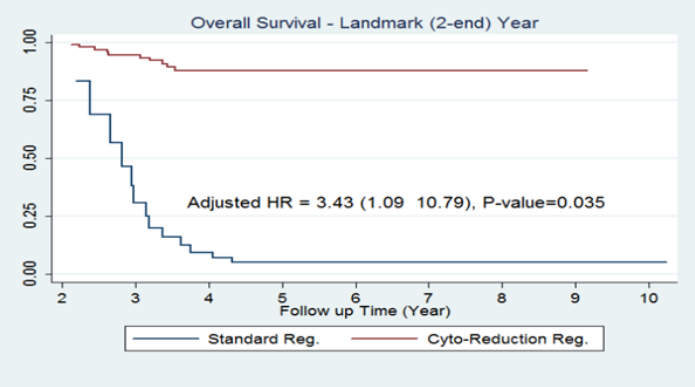

Figure 1b. Adjusted Overall Survival of all Patients by in second landmark

Table 1. Baseline demographic of patients and their comparative evaluation according to treatment groups

		Standard Induction	Cyto-reduction Induction	P
Treatment, n (%)		N=172	N=49	
Complete remission	CR1	172 (100%)	49 (100%)	----
Patient age, years, mean ± SD		28.42 ± 9.47	27.75 ± 9.61	0.667
Patient gender, n (%)	Male	112 (65.12%)	34 (69.39%)	0.577
	Female	60 (34.88%)	15 (30.61%)	
Donor gender, n (%)	Male	97 (56.40%)	28 (57.14%)	0.926
	Female	75 (43.60%)	21 (42.86%)	
Disease category, n (%)	ALL: B-lineage	126 (73.26%)	34 (69.39%)	0.175
	ALL: T-lineage	33 (19.19%)	14 (28.57%)	
	ALL: unspecified	13 (7.56%)	1 (2.04%)	
Risk	Standard	48 (27.91%)	14 (28.57%)	0.8
	High risk	113 (65.70%)	30 (61.22%)	
	Unknown	11 (6.40%)	5 (10.20%)	
Median WBC count at diagnosis, number per microliter (range)	All patients	15960 (600, 519000)	14000 (330, 198000)	0.48

SD: standard deviation; **N:** number, and **%** Percentage

Table 2. Univariate and multivariate cox regression model for OS and DFS

		OS				DFS			
		Univariate		Multivariate		Univariate		Multivariate	
		HR (CI %)	P	HR (CI %)	P	HR (CI %)	P	HR (CI %)	P
Age		1.00 (0.98 1.02)	0.93			1.01 (0.99 1.02)	0.35		
Sex	Female	Ref.	0.12		0.11	Ref.	0.10	Ref.	0.08
	Male	1.38 (0.92 2.07)		1.4 (0.93 2.10)		1.37 (0.94 2.01)		1.41 (0.96 2.07)	
aGvHD	No	Ref.	0.53			Ref.	0.63		
	Yes	1.13 (0.77 1.64)				0.92 (0.65 1.30)			
cGvHD	No	Ref.	0.03		0.04	Ref.	0.04	Ref.	**0.06**
	Yes	0.63 (0.42 0.95)		0.65 (0.42 0.98)		0.67 (0.46 0.98)		0.69 (0.47 1.01)	
Donor Sex	Female	Ref.	0.34			Ref.	0.76		
	Male	1.20 (0.82 1.76)				1.06 (0.74 1.50)			
Time to WBC engraftment		1.00 (0.92 1.09)	0.91			0.99 (0.92 1.07)	0.86		
Time to Platelet engraftment		0.98 (0.91 1.05)	0.59			0.99 (0.92 1.06)	0.74		
Time between diagnosis and HSCT		0.998 (0.997 0.999)	0.020	0.998 (0.997 1.00)	0.156	0.998 (0.997 0.999)	0.017	(0.99 1.00)	0.06
Risk	Standard	Ref.	0.83			Ref.	0.97		
	High	1.05 (0.69 1.59)				1.01 (0.68 1.49)			
Treatment	Standard Induction	Ref.	0.035		0.506	Ref.	0.12	Ref.	0.97
	Cyto-reduction Induction	1.56 (1.03 2.35)		1.19 (0.71 1.99)		1.37 (0.92 2.04)		0.99 (0.61 1.61)	

aGvHD: acute graft-versus-host disease; **cGvHD:** chronic graft-versus-host disease; **OS:** overall survival; **DFS:** disease-free survival; **CI:** confidence interval; HR: hazard ratio

Table 3. Univariate and multivariate cox regression model for OS (Landmark Modeling)

		OS (0-2 Landmark)				**OS (**(2-end Landmark)**)**			
		Univariate		**Multivariate**		**Univariate**		**Multivariate**	
		HR (CI %)	**P**	**HR (CI %)**	**P**	**HR (CI %)**	**P**	**HR (CI %)**	**P**
Age		1.00 (0.98 1.03)	0.63			0.98 (0.94 1.03	0.49		
Sex	Female	Ref.	0.09	Ref.	0.083	Ref.	0.91		
	Male	1.50 (0.94 2.40)		1.51 (.95 2.44)		1.05 (.45 2.42)			
aGvHD	No	Ref.	0.31			Ref.	0.56		
	Yes	1.24 (0.81 1.90)				0.78 (0.34 1.77)			
cGvHD	No	Ref.	0.03	Ref.	**0.007**	Ref.	0.26		
	Yes	0.47 (0.28 0.77)		0.50 (.30 0.83)		1.60 (0.71 3.63)			
Donor Sex	Female	Ref.	0.15	Ref.	0.425	Ref.	0.49		
	Male	1.37 (0.89 2.12)		1.20 (0.77 1.86)		0.75 (.33 1.71)			
Time to WBC engraftment		1.02 (0.93 1.12)	0.62			0.91 (0.74 1.13)	0.44		
Time to Platelet engraftment		1.00 (0.94 1.09)	0.81			0.84 (0.70 1.004)	0.06	0.88 (0.73 1.05)	0.147
Time between diagnosis and HSCT		0.998 (0.99 1.00)	0.053	0.998 (0.99 1.00)	0.089	0.998 (0.99 1.00)	0.187	1.00 (0.997 1.00)	0.63
Risk	standard	Ref.	0.56			Ref.	0.50		
	High	1.15 (0.71 1.86)				0.73 (0.30 1.80)			
Treatment	Standard Induction	Ref.	0.38	Ref.	0.64	Ref.	0.004	Ref.	**0.035**
	Cyto-reduction Induction	1.24 (0.77 2.01)		0.87 (0.48 1.57)		3.34 (1.46 7.62)		3.43 (1.09 10.79)	

Table 4. Univariate and multivariate Fine and Gray regression model for Relapse Incidence and Non-relapse Mortality Incidence (NRM)

		Relapse Incidence				NRM Incidence			
		Univariate		Multivariate		Univariate		Multivariate	
		SHR (CI %)	P	SHR (CI %)	P	SHR (CI %)	P	SHR (CI %)	P
Age		1.01 (.99 1.02)	0.126	1.00 (0.99 1.02)	0.544	0.99 (.98 1.02)	0.83		
Sex	Female	Ref.	0.012	Ref.	**0.003**		0.73		
	Male	1.52 (1.10 2.12)		1.70 (1.19 2.39)		0.92 (.58 1.46)			
aGvHD	No	Ref.	0.028	Ref.	**0.001**		0.11	Ref.	0.08
	Yes	0.72 (0.54 0.97)		0.58 (0.42 0.80)		1.44 (.92 2.27)		1.54 (0.95 2.51)	
cGvHD	No	Ref.	0.15	Ref.	0.103		0.19	Ref.	0.34
	Yes	0.80 (0.59 1.09)		0.76 (0.55 1.05)		0.72 (0.45 1.17)		0.78 (0.47 1.29)	
Donor Sex	Female	Ref.	0.49				0.13	Ref.	0.49
	Male	0.90 (0.67 1.21)				1.43 (0.90 2.26)		1.18 (0.73 1.91)	
Time to WBC engraftment		1.03 (0.96 1.10)	0.39			0.92 (0.83 1.04)	0.21		
Time to Platelet engraftment		0.99 (0.94 1.06)	0.95			0.97 (0.89 1.06)	0.57		
Time between diagnosis and HSCT		0.998 (0.997 0.999)	<0.0001	0.997 (.996 .998)	**<0.0001**	1.00 (0.998 1.001)	0.78		
Risk	standard	Ref.	0.27				0.12	Ref.	0.12
	High	0.83 0.61 1.15)				1.55 (0.88 2.71)		1.55 (0.89 2.71)	
Treatment	Standard Induction	Ref.	0.35	Ref.	**0.246**		0.15	Ref.	0.24
	Cyto-reduction Induction	1.17 (.84 1.65)		0.78 (0.51 1.19)		1.44 (0.88 2.37)		1.37 (0.81 2.32)	

DISCUSSION

Relatively high prevalence of ALL and its high mortality substantiates the necessity to find the suitable and effective treatment. Regarding recent reports of superior outcomes of HSCT in ALL and availability and relatively low cost of stem cell transplantation in our country, we hypothesized that an induction regimen with adequate capability to decrease tumor cell burden and also lower toxicity and complications ,which allows its administration even in emergency ward, can be used in ALL patients .Afterwards, a rapid HSCT following induction therapy may result favorable outcomes thorough more eradication of malignant cells by the conditioning regimen of transplantation as well as graft-versus-leukemia effect. In our depth review of literature, no similar study in adults was found.

A review of literature showed that the use of vincristine and prednisone as induction chemotherapy in children with ALL had resulted in 90% complete remission(CR)[19] and studies on adult patients are rare due to introduction of new chemotherapy drugs. In 1976, Scavino et al. used this relatively nontoxic combination in 14 adult patients and 13 attained complete remission with lower complications and duration of hospitalization[20]. Later studies revealed lower CR rate as 61% (11 from 18 patients) [21]. Sixty-six percent of adults (total n=43) obtained complete remission in the study of Hess and Zirkle[19].The CR rate was age dependent in their study. Comparing to our case-control study, all of 49 patients of our cyto-reduction group which received dexamethasone and vincristine for induction therapy achieved complete remission. As noticed, data about administration of glucocorticoid plus vincristine in induction of adult ALL patients are very few and except one small study of Scavino, this complete remission rate is not reported elsewhere. The major difference between our study and theirs is the use of dexamethasone instead of prednisone, which could

be the cause of our high rate of complete remission. This finding corroborates studies showing more cytotoxicity of dexamethasone to leukemia cells in comparison to prednisone[28,29]. Early mortality of 2 %(one patient) was seen in cyto-reduction group which is obviously better than the 11% [27] early death from standard regimen which is reported in the literature. Because some of patients of our control group were referral patients that had received standard induction regimen in other centers, no data about their early mortality was available in our study.

One disadvantage of prednisone plus vincristine as induction regimen has been high rate of early relapse. The median duration of CR in Hess and Zirkle study was 8.3 months[19].To overcome this problem, all patients of cytoreduction group underwent conditioning and HSCT within maximum two months after induction to decrease the chance of early relapse. Although we found a 22% decrease in the chance of relapse in the cytoreduction group, this decrease was not statistically significant. On the other hand, cytoreduction regimen increased hazard of death 3.4 times than the standard therapy after the second year post-HSCT(Table-3) and most of deaths were due to relapse. During this period, eighty percent of deaths due to relapse happened in the cytoreduction group, while only 61.45% occurred in standard group. It seems that lower depth of response in induction therapy could increase the chance of death due to relapse even after allo- HSCT and graft versus leukemia effect cannot compensate it. It is necessary to increase depth of response by using multiple agents in induction therapy of ALL patients undergoing allo-HSCT. It is compatible with the results of a recent meta-analysis on the influence of pre-transplant minimal residual disease (MRD) on prognosis after Allo-HSCT for patients with acute lymphoblastic leukemia. They figured out that patients with positive MRD prior to allogeneic stem cell transplantation had a significantly higher rate of relapse compared with those with negative MRD (HR = 3.26; $P < 0.05$). Pre-transplantation positive MRD was also a significant negative predictor of RFS and OS in their study [30].

As predicted, the time between diagnosis and HSCT was shorter in case group than the controls. Adjustment of variables in multivariate cox regression test was done to assess effects of this variable on transplantation outcomes. Although time to transplantation had no significant effect on OS (HR=0.99, P= 0.15, Table-2), the multivariate model of relapse incidence showed that every one day lag between diagnosis and HSCT decreased the risk of relapse about 0.3 percent (Table-4). It means that a patient with a lag time of more than 100 days between diagnosis and HSCT compared to a patient with other same characteristics has a lower risk of relapse (30%). Presumably, exclusion of poor prognosis patients from transplantation due to mortality from initial standard induction therapy or its complications have resulted in special selection of patients, but this natural selection did not happen in case group.

Although several studies have concluded that HSCT is more beneficial in high risk patients in first complete remission[9-12], and stem cell transplantation in standard risk patients is a controversial issue, there are reports from favorable and significantly good outcomes of allo-HSCT in standard risk patients too[31,32]. Our study findings revealed no difference between OS and DFS of high risk and standard risk patients undergoing HSCT in their first complete remission. Perhaps factors other than these routine criteria of risk assessment are effective on results.

CONCLUSION

Overall, it seems despite achieving complete remission in induction therapy, depth of response is a critical predictor for long-term outcomes of HSCT in ALL patients and use of multiple agents may be necessary to decrease tumor cell burden and MRD.

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