Allogeneic Hematopoietic Cell Transplantation for Primary Refractory Acute Lymphoblastic Leukemia - a Report from the ALWP of the EBMT

Running title: Allografting in primary refractory ALL

Jiri Pavlu[1], Myriam Labopin[2], Anna K. Zoellner[3], Ioanna Sakellari[4], Matthias Stelljes[5], Jurgen Finke[6], Renato Fanin[7], Gernot Stuhler[8], Boris V Afanasyev[9], Adrian Bloor[10], Achilles Anagnostopoulos[4], Mohamad Mohty[2], Sebastian Giebel[11] and Arnon Nagler[12]

1. Centre for Haematology, Imperial College London at Hammersmith Hospital, London, United Kingdom;

2. Department of Haematology, EBMT Paris study office / CEREST-TC / Saint Antoine Hospital, Paris, France;

3. Ludwig-Maximilians-University Hospital of Munich-Grosshadern, Department of Internal Medicine III, Hematopoietic Cell Transplantation, Munich, Germany;

4. Haematology - BMT Unit, George Papanicolaou General Hospital, Thessaloniki, Greece;

5. Department of Medicine A, University Hospital of Muenster, Muenster, Germany;

6. Hematology/Oncology, University Medical Center Freiburg, Freiburg, Germany;

7. Division of Hematology and BMT, Department of Experimental and Clinical Medical Sciences, Azienda Ospedaliero-Universitaria di Udine, Udine, Italy;

8. Zentrum für Blutstammzell und Knochenmarktransplantation, DKD Helios Klinik Wiesbaden, Wiesbaden, Germany;

9. First Pavlov State Medical University of Saint-Petersburg, Saint-Petersburg, Russia;

10. The Christie NHS Foundation Trust, Manchester, United Kingdom;

11. Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland;

12. Division of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer and Sackler School of Medicine, Ramat Gan, Israel

Corresponding author:

Jiri Pavlu, Centre for Haematology, Imperial College London at Hammersmith Hospital, Du Cane Road, London, W12 0HS, United Kingdom;
telephone: +44(0)-20-3313-8117, fax +44(0)-20-3313-3965,
email: jiri@pavlu.co.uk

Number of pages:18, tables: 2, figures:1

Funding sources:

The study was supported in part by National Institute for Health Research Biomedical Research Centre based at Imperial College London.

Conflicts of interest:

The authors declare that they have no conflicts of interest.

Author contributions:

JP, ML, MM, and SG designed the study. ML and AN performed the statistical analysis. JP wrote the manuscript. AKZ, IS, MS, JF, RF, GS, BVA, AB, AA, and MM provided cases for the study. All authors edited and approved the manuscript.

Precis for use in Table of Contents:

The aim of the study was to establish outcomes of allogeneic hematopoietic transplantation in patients with primary refractory acute lymphoblastic leukaemia and to identify factors potentially influencing these outcomes. With a median follow-up of 106 months, the probability of survival was 36% at 2 years and 23% at 5 years with superior survival in patients who received total body irradiation and in male patients receiving cells from female donors.

Abstract:

Background:

Patients with primary refractory acute lymphoblastic leukemia (PREF ALL) who fail to achieve complete remission (CR) after two or more courses of chemotherapy have a dismal prognosis without allogeneic hematopoietic cell transplantation (HCT). There are currently no data on factors influencing transplantation outcomes.

Methods:

We retrospectively studied outcomes of transplantation for PREF ALL reported to EBMT registry. Eligibility criteria for this analysis included adult patients who underwent their first HCT for PREF ALL between 2000 and 2012. PREF disease was defined as failure to achieve a morphological CR after two or more courses of induction chemotherapy.

Results:

Data on 86 adult patients were analyzed. With a median follow-up of 106 months, the probability of survival was 36% at 2 years and 23% at 5 years. The probability of LFS was 28% and 17% and probability of NRM was 20% and 29% at 2 and 5 years respectively. For 66 patients (76%) achieving CR, the survival at 2 and 5 years was 36% and 29%. In multivariate analysis, use of total body irradiation (TBI) was associated with improved survival. TBI and infusion of female hematopoietic cells into male recipient was associated with improved LFS. These were incorporated into a scoring system that identified

three groups (two, one or no prognostic factors) with survival rates of 57%, 22% and 8% respectively.

Conclusions:

Although overall these patients would clearly benefit from introduction of novel anti-leukemic therapies, our data support the use of allogeneic HCT in selected patients with PREF ALL.

Keywords:

acute lymphoblastic leukemia (ALL), refractory disease, stem cell transplantation, allogeneic transplantation, conditioning regimen, total body irradiation.

Introduction

Patients with acute leukemia who are refractory to initial and re-induction chemotherapy have dismal prognosis unless they undergo hematopoietic cell transplantation (HCT) [1,2]. Studies have been undertaken to assess outcomes of transplantation for primary refractory (PREF) acute myeloid leukemia (AML) [3,4,5], but in acute lymphoblastic leukemia (ALL) considerable skepticism remains as to whether transplantation can result in long-term survival in patients who are not in complete remission (CR) at the time of transplantation.

Due to a lack of studies looking specifically into PREF ALL there are no known factors potentially influencing transplantation outcomes in these patients. Therefore decisions regarding whether to proceed into transplantation or not cannot be evidence based. We believe that identifying these factors and clarifying outcomes of HCT in PREF ALL is particularly important at the time of introduction of novel therapies for chemo-refractory ALL.

Methods

Study design and data collection

This was a retrospective multicenter analysis performed by the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT promotes all activity aiming to improve stem cell transplantation or cellular therapy, which includes

registering all the activity relating to stem cell transplants. Data are entered, managed, and maintained in a central database with internet access; each EBMT center is represented in this database. Quality control measures included several independent systems: confirmation of validity of the entered data by the reporting team, selective comparison of the survey data with minimum essential data A (MED-A) data sets in the EBMT registry database, cross-checking with the National Registries, and regular in-house and external data audits. Since 1990, patients have provided informed consent authorizing the use of their personal information for research purposes. Eligibility criteria for this analysis included adult patients who underwent their first HCT for PREF ALL from 2000 and 2012. PREF disease was defined as failure to achieve a morphological CR (<5% of blasts in the bone marrow) after two or more courses of induction chemotherapy. Patients younger then 18 years and those with lymphoblastic lymphoma were excluded.

Statistical methods

Long-term follow-up data are available on all patients. The main endpoints of the study were survival defined as time to death from any cause, CR rate, leukemia free survival (LFS), and non-relapse mortality (NRM). All outcomes were measured from the time of stem cell infusion. LFS was defined as survival in CR. NRM was defined as death without previous relapse/progression. Acute and chronic GVHD were graded according to standard criteria. All patients were considered assessable for acute GVHD after day +1. The presence of chronic GVHD was evaluated among patients who demonstrated sustained engraftment from day +100 post transplant.

The probabilities of OS and LFS were calculated by using the Kaplan-Meier estimator [6]. The probabilities of CR, NRM, acute and chronic GVHD were calculated by using the cumulative incidence estimator to accommodate for competing risks [7]. For NRM, disease progression was the competing risk, and NRM was the competing risk for progression. For acute and chronic GVHD, death without the event was the competing risk. A Cox proportional hazards model was used for multivariate regression. Factors with $P < 0.10$ in univariate analysis were entered into the multivariate analysis. Results were expressed as hazard ratio (HR) with 95% confidence interval (CI). Proportions hazards assumptions were checked systematically for all proposed models using the Grambsch-Therneau residual-based test. All tests were two-sided. The type-1 error rate was fixed at 0.05 for determination of factors associated with time to event outcomes. Statistical analyses were performed with IBM SPSS Statistics 22.0 and R version 3.1.2 (R Development Core Team, Vienna, Austria) software packages.

Results

Demographics and transplant details

Details of patients' and transplant characteristics are summarized in Table 1. Out of 86 patients included in the analysis, 70 individuals were transplanted using a myeloablative conditioning regimen, of whom 52 received a total body irradiation (TBI)-based regimen (median dose 12 Gy; range: 8-14); 16 patients were transplanted using a reduced-intensity conditioning (RIC) regimen, as defined by the EBMT criteria [8]. In 6 patients, the RIC regimen incorporated

TBI at a dose of 6 Gy or less. In vivo T-cell depletion was used in 28 (33%) patients (anti-thymocyte globulin was used in all but 6 who received alemtuzumab). No patients included in this study received blinatumomab or inotuzumab at any point during their disease course.

Engraftment, early response and graft-versus-host disease

A total of 76 (89%) patients demonstrated neutrophil engraftment at a median of 18 days (9–87) post transplant and 9 (11%) patients experienced primary graft failure. In all, 66 (79%) patients achieved CR after transplant at a median time of 31 days (28 – 147 days); 18 (21%) patients failed to achieve CR. Grade II or greater acute GVHD was documented in 28 (34%) patients, while 14 (17%) patients experienced grade III/IV acute GVHD. Chronic GVHD of any severity developed in 27 (32%) patients of those surviving more than 100 days.

Long-term outcomes

With a median follow-up of 106 months (range 9–181 months), 20 patients were alive and free of leukemia. The probability of survival (Figure 1a) for the whole group was 36% (95% confidence interval (CI): 25 – 46) at 2 years and 23% (95% CI: 13 – 32) at 5 years. The probabilities of LFS and NRM at 2 and 5 years were 28% (95% CI: 18 – 38) and 17% (95% CI: 8 – 25) and 20% (95% CI: 12 – 29) and 29% (95% CI: 19 – 39), respectively. Causes of death for the whole cohort were: original disease in 40 (61%), GVHD in 11 (17%), infection in 7 (11%), and hemorrhage in 2 (3%) patients. Six patients died of other rare transplant related causes. For patients achieving a CR, the survival

was 36% (95% CI: 25 – 46) and 29% (95% CI: 18 – 41) and relapse incidence was 51% (95% CI: 38 – 63) and 54% (95% CI: 41 – 66) at 2 and 5 years, respectively.

Donor lymphocytes were used in 14 patients; in 4 preemptively and in 10 after the relapse. One patient who received preemptive lymphocytes is alive at 122 months after the infusion (126 months after the HCT). Two patients who received donor lymphocyte infusions as treatment for disease relapse are alive 97 and 115 months after the infusion (118 and 123 months post transplant). The second patient also underwent a second HCT one month after the donor lymphocyte infusion. In total eleven patients had a second allogeneic HCT for relapse at a median of 8 months (range 2–57) after their original transplant for PREF ALL. Only 2 patients are alive after a second allograft at 54 and 96 months after the second HCT (61 and 123 months after first HCT).

Prognostic factors

The results of the univariate analysis are shown in Table 2. In multivariate analysis, use of TBI was associated with improved survival (Hazard Ratio (HR): 0.53; 95% CI: 0.29–0.973; P=0.04), (Figure 1b). The following factors were associated with improved LFS: use of TBI (HR: 0.44; 95% CI: 0.24–0.82; P=0.01) and infusion of female hematopoietic cells into male recipient (HR: 0.45; 95% CI: 0.23–0.90; P=0.01). Presence of extra-medullary disease was associated with increased NRM (HR: 4.92; 95% CI: 1.85–13.02; P=0.001). Conditioning intensity was not associated with the studied outcomes in this

population.

We developed a score based on the summation of the number of prognostic factors found to be significant for LFS by multivariate analysis: use of TBI and infusion of female hematopoietic cells into male recipient. This allows delineation of three prognostic groups as follows: score 2 (both prognostic factors present): (N=14), 5 year survival: 57% (95% CI 31 – 83) and 5 year LFS: 50% (95% CI 24 – 76); score 1 (only 1 prognostic factor): (N=45), 5 year survival: 22% (95% CI 9 – 34); and 5 year LFS 12% (95% CI 2 – 22); score 0 (no prognostic factor): (N=24), 5 year survival and LFS: 8 (95% CI 0 – 19) (Figure 1c).

Discussion

This study demonstrated that HCT can induce long-term survival in patients with PREF ALL as 29% of these patients were alive 5 years after transplantation. The LFS was 17% and NRM 29% at 5 years in this cohort transplanted between 2000 and 2012. Naturally, the population of patients we have studied represent a selected subgroup, who were judged fit enough to proceed to transplant and had an available donor.

In comparison to early results of transplantation in PREF ALL [2] our current data speak for improved NRM with similar LFS: 38 patients transplanted between 1982 and 1989 had LFS of 23% and NRM of 44% at 3 years. A more recent study included ALL patients transplanted between 1995 and 2004 while not in CR due to both relapsed and PREF disease. Their probability of

survival at 3 years was 16% for the whole cohort. The survival of the PREF subgroup was not published, but they had significantly better outcomes compared to patients with relapse [9]. Clinicians accepting usefulness of allogeneic HCT in PREF AML should not be skeptical about its use in PREF ALL as our results compare well to results allografting in AML [5,9,10].

Outcomes of HCT within our cohort varied according to pre-transplantation variables, and this allowed for the development of a predictive scoring system. Higher-risk patients had a 5-year survival of only 6%, whereas 5-year survival for lower-risk patients was 57%, which is almost comparable to the outcomes seen in patients transplanted in CR. Although this scoring system requires validation, it provides a basis for future studies. Two clinically important factors predicting long-term survival were defined: the use of conditioning regimens containing TBI and use of female donor in a male recipient. Interestingly these are potentially modifiable factors: use of TBI is possible in many patients and often is clinician's choice. In addition, for some male patients it is possible to select a female donor.

There is still uncertainty about the optimal conditioning regimen in patients with ALL. Our observation is in keeping with results of a number of published trials suggesting superiority of TBI containing regimens [11,12,13]. Although in the most recent of these studies intravenous busulfan was the most common chemotherapy only regimen [11], some doubts remain whether the intravenous administration could eliminate this survival advantages of TBI in ALL as seems to be the case in PREF AML [10].

Also improved LFS in male recipients of female cells has been previously described in a number of hematological malignancies. It is explained by presence of female donor T-cells specific for recipient minor histocompatibility antigens encoded by Y chromosome genes [14,15,16]. Clinically this results in increased graft versus leukemia effect, which is particularly important in patients not in remission at the time of transplantation.

Maintenance therapy is rarely used other than in Philadelphia positive ALL patients after transplantation [17], mainly because its effects would potentially interfere with graft-versus-leukemia effects of transplantation. This applies to most currently used anti-leukemic drugs except for blinatumomab [18]. Although an attractive therapeutic strategy, none of the patients in this study received blinatumomab. A trial testing its use following allogeneic HCT is underway [19].

Being a registry based our study suffers from some limitations including missing data such as TKI administration to the 13 patients with Philadelphia chromosome positive disease. However as all patients in the current study had refractory ALL and none of the patients entered transplantation in complete remission it is reasonable to assume that TKI therapy had no major biological impact on patients outcome.

In conclusion, our data support use of allogeneic HCT in selected patients with PREF ALL who cannot reach complete remission. It also shows the need for introduction of modern therapies capable of improving anti-leukemic control prior to transplantation.

Acknowledgments

We thank all European Group for Blood and Marrow Transplantation (EBMT) centers and national registries for contributing patients to the study and data mangers for their superb work. Supplementary information is available at the EBMT Web site. The list of institutions reporting data included in this study is available in the Online Supplementary Appendix.

References

1. Forman SJ, Schmidt GM, Nademanee AP, Amylon MD, Chao NJ, Fahey JL et al. Allogeneic bone marrow transplantation as therapy for primary induction failure for patients with acute leukemia. *J Clin Oncol*. 1991;9:1570-1574.
2. Biggs JC, Horowitz MM, Gale RP, Ash RC, Atkinson K, Helbig W et al. Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy. *Blood.* 1992;80:1090-1093.
3. Fung HC, Stein A, Slovak M l, O'donnell MR, Snyder DS, Cohen S et al. A long-term follow-up report on allogeneic stem cell transplantation for patients with primary refractory acute myelogenous leukemia: impact of cytogenetic characteristics on transplantation outcome. *Biol Blood Marrow Transplant.* 2003;9:766-771.
4. Michallet M, Thomas X, Vernant JP, Kuentz M, Socié G, Espérou-Bourdeau H et al. Long-term outcome after allogeneic hematopoietic

stem cell transplantation for advanced stage acute myeloblastic leukemia: a retrospective study of 379 patients reported to the Société Française de Greffe de Moelle (SFGM). *Bone Marrow Transplant.* 2000;26:1157-1163.

5. Craddock C, Labopin M, Pillai S, Finke J, Bunjes D, Greinix H et al. Factors predicting outcome after unrelated donor stem cell transplantation in primary refractory acute myeloid leukaemia. *Leukemia.* 2011;25:808-813.
6. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *J Am Stat Assoc.* 1958;53:457-481.
7. Klein JP, Rizzo JD, Zhang MJ, Keiding N. Statistical methods for the analysis and presentation of the results of bone marrow transplants. Part I: unadjusted analysis. *Bone Marrow Transplant*. 2001;28:909-915.
8. Aoudjhane M, Labopin M, Gorin NC, Shimoni A, Ruutu T, Kolb H-J et al. Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European group for Blood and Marrow Transplantation (EBMT). *Leukemia.* 2005;19:2304-2312.
9. Duval M, Klein JP, He W, Cahn J-Y, Cairo M, Camitta BM et al. Hematopoietic Stem-Cell Transplantation for Acute Leukemia in Relapse or Primary Induction Failure. *J Clin Oncol.* 2010;28:3730-3738.
10. Nagler A, Savani BN, Labopin M, Polge E, Passweg J, Finke J et al. Outcomes after use of two standard ablative regimens in patients with

refractory acute myeloid leukaemia: a retrospective, multicentre, registry analysis. *Lancet Haematol.* 2015; doi:10.1016/S2352-3026(15)00146-5.

11. Cahu X, Labopin M, Giebel S, Aljurf M, Kyrcz-Krzemien S, Socié G et al. Impact of conditioning with TBI in adult patients with T-cell ALL who receive a myeloablative allogeneic stem cell transplantation: a report from the acute leukemia working party of EBMT. *Bone Marrow Transplant.* 2016;51:351-357.
12. Granados E, de La Cámara R, Madero L, Díaz MA, Martín-Regueira P, Steegmann JL et al. Hematopoietic cell transplantation in acute lymphoblastic leukemia: better long term event-free survival with conditioning regimens containing total body irradiation. *Haematologica*. 2000;85:1060-1067.
13. Eroglu C, Pala C, Kaynar L, Yaray K, Aksozen MT, Bankir M et al. Comparison of total body irradiation plus cyclophosphamide with busulfan plus cyclophosphamide as conditioning regimens in patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplant. *Leuk Lymphoma*. 2013;54:2474-2479.
14. Gahrton G, Iacobelli S, Apperley J, Bandini G, Björkstrand B, Bladé J et al. The impact of donor gender on outcome of allogeneic hematopoietic stem cell transplantation for multiple myeloma: reduced relapse risk in female to male transplants. *Bone Marrow Transplant.* 2005;35:609-617.
15. Gratwohl A, Hermans J, Niederwieser D, van Biezen A, van Houwelingen HC, Apperley J et al. Female donors influence transplant-related mortality and relapse incidence in male recipients of sibling blood and marrow transplants. *Hematol J.* 2001;2:363-370.

16. Randolph SSB. Female donors contribute to a selective graft-versus-leukemia effect in male recipients of HLA-matched, related hematopoietic stem cell transplants. *Blood.* 2004;103:347-352.

17. Giebel S, Czyz A, Ottmann O, Baron F, Brissot E, Ciceri F, et al. Use of tyrosine kinase inhibitors to prevent relapse after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: A position statement of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Cancer*. 2016;122:2941-51.

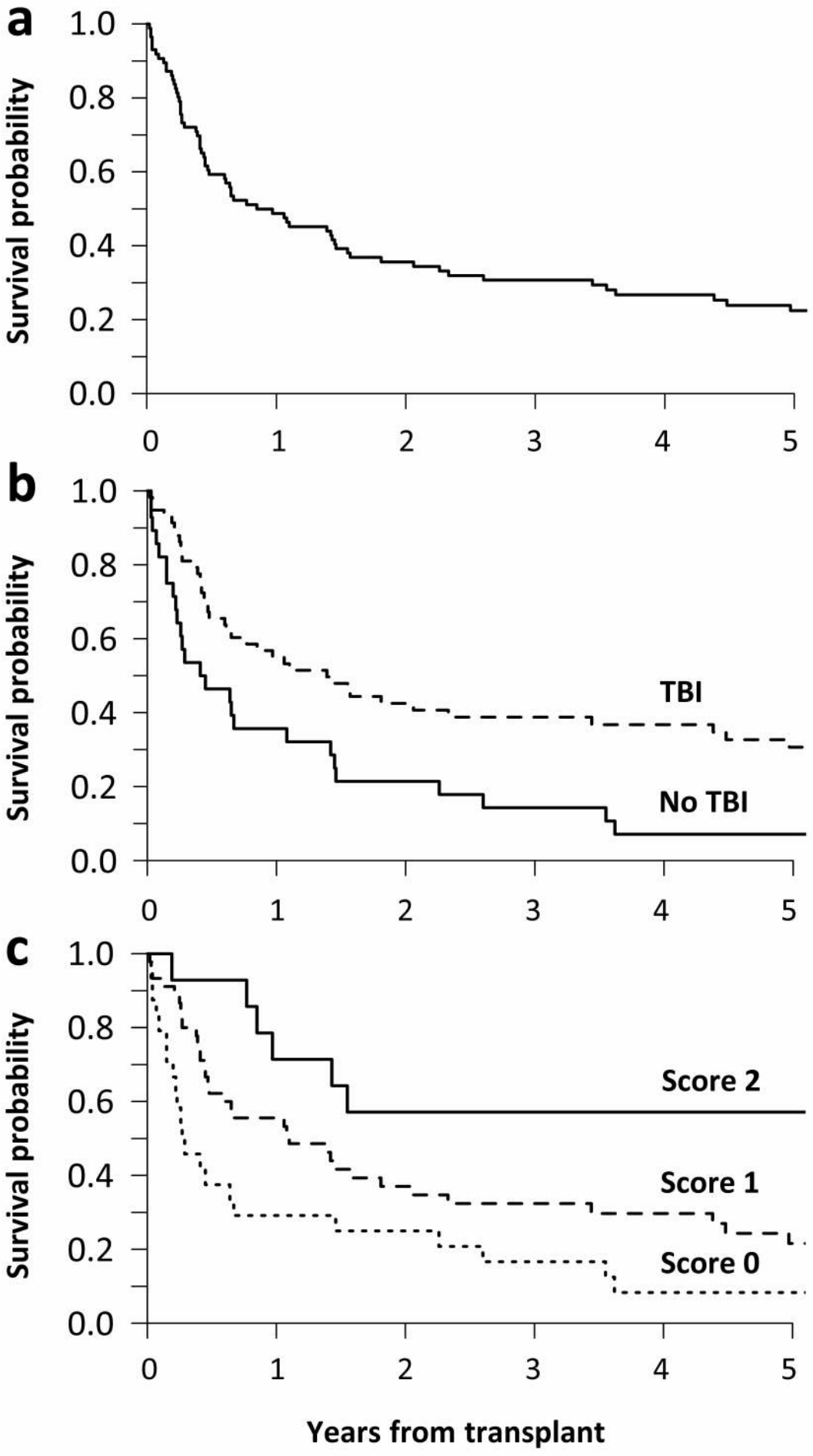
18. Alcharakh M, Yun S, Dong Y, Vincelette ND, Daud M, Manzoor S, et al. Blinatumomab-induced donor T-cell activation for post-stem cell transplant-relapsed acute CD19-positive biphenotypic leukemia. *Immunotherapy.* 2016;8:847-52

19. M.D. Anderson Cancer Center; Amgen. Blinatumomab Maintenance Following Allogeneic Hematopoietic Cell Transplantation for Patients With Acute Lymphoblastic Leukemia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2016 Dec 19]. Available from: https://clinicaltrials.gov/ct2/show/NCT02807883?term=blinatumomab&rank=3

Figure Legend

Figure 1.

a Survival 86 patients with primary refractory acute lymphoblastic leukemia after hematopoietic cell transplantation. **b** Survival of the study population according to the use of total body irradiation (TBI). **c** Survival of study population according to scoring system: one point assigned to patients who had received total body irradiation (TBI), one point assigned to male patients with female donors.


a
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
b
Survival probability
TBI
No TBI
c
Survival probability
Score 2
Score 1
Score 0
Years from transplant

Tables

Table 1.

Demographics and transplant details of 86 patients who underwent hematopoietic cell transplantation for primary refractory acute lymphoblastic leukemia. Abbreviations: ATG, anti-thymocyte globulin; BM, bone marrow; CMV, cytomegalovirus.

Characteristic	Data available N	N (%)
Median age - years (range)	86	33 (18 – 66)
Peripheral blood blasts	64	
Present		36(56%)
Absent		28(44%)
BM blasts - median - range	69	68% (5 – 100)
Cytogenetics	74	
Philadelphia negative		61 (82%)
Philadelphia positive		13 (18%)
Extramedullary disease	79	
present		19(24.05)
absent		60(75.95)
Number of induction courses	86	
Two		24 (28%)
Three		23 (27%)
Four		25 (29%)
More than four		14(16%)
Donor type	86	

Matched related		40 (47%)
Unrelated		36 (42%)
Haploidentical		7 (8%)
Umbilical cord blood		3 (3%)
Sex of the recipient	86	
Male		55 (64%)
Female		31 (36%)
Sex mismatch	83	
Female to male		65 (78%)
Other		18 (22%)
Patient CMV serology	82	
Negative		25 (30%)
Positive		57 (70%)
Donor CMV serology status	76	
Negative		32 (42%)
Positive		44 (58%)
Conditioning regimen	86	
Myeloablative		70 (81%)
Reduced intensity		16 (19%)
T-cell depletion	86	
Replete		58 (67%)
In vivo ATG		22 (26%)
In vivo alemtuzumab		6 (7%)

Table 2.

Univariate analysis of factors determining 5-year OS and LFS of 86 patients who underwent hematopoietic cell transplantation for primary refractory acute lymphoblastic leukemia. Abbreviations: ATG, anti-thymocyte globulin; BM,

bone marrow; CMV, cytomegalovirus.

Characteristic	Survival at 5 years	P-value	LFS at 5 years	P-value
Age				
≤ median (33 years)	23%	0.516	14%	0.054
> median (33 years)	23%		20%	
Peripheral blood blasts				
Present	33%	0.213	21%	0.603
Absent	23%		17%	
BM blasts				
	24%	0.272	18%	0.193
	21%		12%	
Cytogenetics				
Philadelphia negative	26%	0.714	19%	0.630
Philadelphia positive	21%		12%	
Extramedullary disease				
…present	31%	0.004	23%	0.045
…absent	5%		5.3%	
No. of induction courses				
Two	36%	0.047	28%	0.109
> two	17%		12%	
Donor type				
Matched related	18%	0.878	16%	0.961
Other	27%		17%	
Sex of the recipient				
Male	29%	0.038	21%	0.085
Female	13%		10%	

Sex mismatch				
Female to male	44%	0.022	41%	0.009
Other	18%		11%	
Patient CMV serology				
Negative	27%	0.958	19%	0.99
Positive	22%		17%	
Conditioning regimen				
Myeloablative	22%	0.645	15%	0.877
Reduced intensity	25%		25%	
Conditioning containing body				
Chemotherapy only	7%	0.003	7%	0.002
Total body irradiation	31%		22%	
T-cell depletion				
Replete	18%	0.250	14%	0.530
ATG or alemtuzumab	34%		23%	