Reduced intensity conditioning allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation

Mohamad Mohty,[1] Myriam Labopin,[2] Reza Tabrizzi,[3] Niklas Theorin,[4] Axel A Fauser,[5] Alessandro Rambaldi,[6] Johan Maertens,[7] Shimon Slavin,[8] Ignazio Majolino,[9] Arnon Nagler,[10] Didier Blaise,[11] and Vanderson Rocha[2,12] on behalf of the Acute Leukemia Working Party

[1]Service d'Hématologie Clinique, CHU Hôtel Dieu, Université de Nantes, Nantes, France; [2]European Group for Blood and Marrow Transplantation (EBMT), Acute Leukemia Working Party, Hopital Saint-Antoine, Assistance Publique des Hôpitaux de Paris and Université de Paris 6, Pierre et Marie Curie, Paris, France; [3]Centre Hospitalo-Universitaire de Bordeaux, Hôpital Haut-Leveque, Pessac, France; [4]University Hospital, Dept. of Hematology, Linköping, Sweden; [5]Klinik fuer Knochenmarktransplantation und Haematologie/Onkologie, Idar-Oberstein, Germany; [6]Ospedale Bergamo, Divisione di Ematologia, Bergamo, Italy; [7]University Hospital Gasthuisberg, Dept. of Hematology, Leuven, Belgium; [8]Hadassah University Hospital, Department of Bone Marrow Transplantation, Jerusalem, Israel; [9]Ospedale S. Camillo-Forlanini, Dept. of Hematology and BMT, Rome, Italy; [10]Tel-Aviv University, Chaim Sheba Medical Center, Tel-Hashomer, Israel; [11]Unité de Transplantation et de Thérapie Cellulaire, Institut Paoli-Calmettes, Marseille, France and [12]Department of Hematology, Hopital Saint-Louis, Assistance Publique Hopitaux de Paris, Paris, France

ABSTRACT

This retrospective study reported the outcome of 97 adult acute lymphoblastic leukemia patients who received a reduced-intensity conditioning allogeneic stem cell transplantation. With a median follow-up of 2.8 years, two year overall-survival, leukemia-free survival and non-relapse mortality were significantly better in patients transplanted in first complete remission (CR1, 52±9%; 42±10%; and 18±7% respectively) compared with those transplanted in more advanced phase (p=0.003, p=0.002 and p=0.01 respectively). In multivariate analysis, disease status (CR1 *vs.* advanced; p=0.001) and chronic graft-vs-host disease (p=0.01) were associated with an improved overall-survival, suggesting that reduced-intensity conditioning allogeneic stem cell transplantation is feasible in patients with high risk lymphoblastic leukemia in remission at transplantation.

Key words: allogeneic SCT, acute lymphoblastic leukemia.

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Introduction

Acute lymphoblastic leukemia (ALL) accounts for approximately 15 to 20% of all adult acute leukemias.[1] Despite the fact that 80 to 90% of adult patients with ALL succeed in achieving complete remission (CR), most of them will relapse and die of their disease.[2] The poor outcome in adult ALL has been variously attributed to a greater drug resistance, less effective treatment regimens as compared with childhood ALL, but also to poorer tolerance of treatment-related toxicities. Among adults with ALL, long-term leukemia-free survival (LFS) rates of 30 to 40% have been obtained with the use of chemotherapy, as compared with 45 to 75% with the use of conventional myeloablative allogeneic stem cell transplantation (allo-SCT).[3,4] However, the median age of ALL in adults is about 65 years. Therefore, most adults with ALL are not candidates for conventional myeloablative allo-SCT. The potential use of reduced intensity conditioning (RIC) prior to allo-SCT in such patients may offer previously unavailable opportunities to obtain a graft-vs-leukemia (GVL) effect without the toxicities of intense preparative regimens.

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Correspondence: Mohamad Mohty, M.D., Ph.D., Service d'Hématologie Clinique, CHU Hôtel-Dieu, Université de Nantes, Place Alexis Ricordeau, F-44093 Nantes, France. E-mail: mohamad.mohty@univ-nantes.fr
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Experience with RIC allo-SCT for adult ALL is still very limited.[5,6] We report a retrospective analysis of 97 adult ALL patients who received RIC allo-SCT reported to the EBMT registry.

Design and Methods

Study design and data collection

This was a retrospective multicenter analysis. Data of adult ALL patients receiving RIC allo-SCT were provided by the Acute Leukemia Working Party (ALWP) of the EBMT group. The EBMT registry is a voluntary working group of more than 450 transplant centers, participants of which are required once a year to report all consecutive stem cell transplantations and follow-up.

Criteria of selection

The study included ALL patients receiving RIC allo-SCT from an HLA-identical related or unrelated donor, who (i) were aged >15 years at time of transplant; (ii) were transplanted between 1996 and 2004; (iii) had received a RIC regimen defined as the use of fludarabine associated with low-dose total body irradiation (TBI) (″4Gy.), or busulfan (total dose ″8 mg/kg), or other immunosuppressive or chemotherapeutic drugs such as melphalan or cyclophosphamide;[7] (iv) were patients whose clinical data on outcomes were adequate. Patients receiving previous conventional allo-SCT and/or autologous transplantation were not excluded from this analysis. Indication for RIC allo-SCT depended on each center's policy. Out of 260 patients who received RIC allo-SCT for ALL and were reported to the EBMT registry during the study period, a total of 97 RIC allo-SCT recipients from 47 transplant centers met these eligibility criteria.

Patients and transplant procedures

The characteristics of patients, disease, and transplants are given in Table 1. Thirty-eight percent of patients had Philadelphia-chromosome [t(9;22)] positive (Ph^+) ALL. The RIC preparative regimen included TBI in 24% of patients, and antithymocyte globulins in 39%. For GVHD prevention, 40% of patients received cyclosporine A (CsA) alone, 21% received CsA plus mycophenolate mofetil, and 27% received CsA plus methotrexate.

The majority of patients (67%) received RIC allo-SCT from an HLA-identical sibling. Only 29% of patients were transplanted in first CR (CR1; n=28), while the remaining patients were transplanted beyond CR1 (CR2, CR3) or in more advanced disease (n=69). The median follow-up was 2.8 (range, 0.4-6.3) years.

Statistical analysis

Demographic and patient characteristics considered were: recipient age, sex and CMV serology; disease characteristics (cytogenetics), donor characteristics (age, sex, CMV serology, related or unrelated), history of prior stem cell transplantation, disease characteristics at RIC allo-SCT (first CR); allo-SCT characteristics (year, RIC regimen, GVHD prophylaxis, and stem cell source). Acute and chronic GVHD were studied as time dependant variables. Cumulative incidence curves were used in a competing risks setting, death being treated as a competing event to calculate probabilities of acute and chronic GVHD, neu-

Table 1. Characteristics of patients, disease, transplant, and transplant-related events.

Characteristic	*N=97 (%)*
Recipient age (years), median (range)	38 (17-65)
Donor age (years), median (range)	39 (15-66)
Recipient gender (Male / Female)	61 (63) / 36 (37)
Female donor to a male recipient	38 (39)
Disease status at time of RIC allo-SCT[a]	
First CR (CR1)	28 (29)
Beyond CR1 (CR2/CR3)	25 (26)/5 (5)
Advanced/refractory or persistent disease	39 (40)
Cytogenetics risk group	
t(9;22)	37 (38)
t(4;11)	3 (3)
Other	42 (43)
NA/failed/missing	15 (15)
History of prior stem cell transplantation	
Conventional myeloablative allo-SCT	19 (20)
Autologous transplantation	15 (15)
Donor type	
HLA-identical sibling	65 (67)
HLA matched unrelated donor	32 (33)
Stem cell source	
G-CSF-mobilized peripheral blood stem cells	80 (82)
Bone Marrow	17 (18)
GVHD prophylaxis	
CsA alone	39 (40)
CsA and methotrexate	26 (27)
CsA and mycophenolate mofetil	20 (21)
Other	12 (12)
RIC regimen	
ATG-based regimen	37 (39)
Low dose TBI-based regimen	23 (24)
Acute GVHD	
Grade 0-1	65 (67)
Grade 2	20 (21)
Grade 3-4	12 (12)
Chronic GVHD	37 (38)
Donor lymphocyte infusions (n=21)	
For relapse/progression	14 (14)
Pre-emptive	2 (2)
Mixed chimerism	5 (5)
Causes of death (n=70)	
Relapse/disease progression	43 (61)
Infection	13 (19)
GVHD	6 (9)
Other transplant-related causes	8 (11)

CR: complete remission; RIC: reduced intensity conditioning; allo-SCT: allogeneic stem cell transplantation; NA: not available; CsA: cyclosporine A; ATG: antithymocyte globulin; TBI: total body irradiation; GVHD: graft-vs-host disease; G-CSF: granulocyte colony-stimualting factor. aThe interval from diagnosis to RIC allo-SCT was 169 (range, 73-304), 636 (range, 191-3413), and 458 (range, 132-2203) days for patients transplanted in first complete remission (CR1), beyond CR1, and advanced disease respectively.

trophil recovery, and relapse or disease progression incidence (RI). The cumulative incidence method was also used to calculate non-relapse mortality (NRM) probability. Probabilities of survival and leukemia-free survival (LFS) were calculated using the Kaplan-Meier estimate; the log rank test was used for univariate comparisons. All potential prognostic factors with a p value less than 0.20 in univariate analyses and factors known to influence outcomes (such as disease status at transplant) were included in the multivariate analyses, using Cox proportional hazards with a time dependant variable. A stepwise regression analysis with a non-restrictive p value of 0.15 was then used to find the final model.

Results and Discussion

In the total population at 2 years, the OS and LFS were 31±5% and 21±4% respectively. The overall RI was 51±5%, and the overall NRM was 28±4%. LFS, NRM and RI according to disease status at time of allo-SCT are shown in Figure 1 (*Supplemental Online*). In patients transplanted in CR1, the results were 52±9% for OS, 42±10% for LFS, 40±9% for RI, and 18±7% for NRM. In patients transplanted beyond CR1 (CR2, CR3) and in more advanced disease, the results were 27±8% and 20±7% for OS, 20±8% and 7±5% for LFS, 63±9% and 49±7% for RI, and 17±7% and 44±8% for NRM respectively. OS, LFS and NRM were significantly better in patients transplanted in CR1 as compared to those transplanted in more advanced phases (p=0.003, p=0.002 and p=0.01 respectively). RI was not statistically different between groups according to disease status at allo-SCT. Interestingly, OS, LFS, RI and NRM were not statistically different when comparing patients from the t(9;22) and t(4;11) group (n=40) to the remaining 57 patients with other cytogenetics features (26±7% *vs.* 32±7%, p=NS; 16±6% *vs.* 22±7%, p=NS; 56±8% *vs.* 46±8%, p=NS; and 2±7% *vs.* 38±8%, p=NS respectively). There were no significant differences in terms of OS, LFS, RI, and NRM when comparing patients receiving a transplant from a non-sibling donor with those receiving a transplant from a matched related donor. In multivariate analysis, disease status at transplant (first CR *vs.* more advanced) was the only risk factor associated with RI (p=0.02; RR=2.5, 95%CI, 1.2-5.3). Disease status at transplant and female donor were associated with an improved LFS (p=0.001; RR=2.7, 95%CI, 1.5-4.9; and p=0.02; RR=1.8, 95%CI, 1.1-2.9 respectively). Finally, three factors were associated with better OS: disease status at time of transplant (p=0.001; RR=3.2, 95%CI, 1.7-6.1), chronic GVHD (p=0.01; RR=0.4, 95%CI, 0.2-0.8), and a female donor (p=0.02; RR=1.8, 95%CI, 1.1-3). Notably, patients experiencing chronic GVHD had a better OS compared with patients without chronic GVHD (p=0.008; using a Cox model with GVHD as a time dependant variable in patients surviving beyond day 100 after allo-SCT).

Despite the limitations of a retrospective based registry analysis, this study comprises the greatest number of adults with ALL receiving RIC allo-SCT reported so far. This cohort is unique in several aspects. Besides being considered unfit for conventional myeloablative allo-SCT, most patients had unfavorable prognostic criteria with 38% suffering from Ph$^+$ ALL and 71% transplanted beyond CR1 and/or with uncontrolled disease at time of allo-SCT. Twenty percent of the patients had already failed a conventional myeloablative allo-SCT before undergoing salvage RIC allo-SCT, with, interestingly, history of prior autologous or allo-SCT not influencing outcome. Additionally, 33% of donors were non-family donors. With these considerations in mind, an overall NRM of 28% is not surprising. The expectations to RIC allo-SCT are that the high morbidity of high-dose radiochemotherapy could be decreased, while preserving the GVL effect, thereby extending the indications for allo-SCT to patients otherwise ineligible for allo-SCT.[8] In this study, the latter could be observed in patients transplanted in CR1, with these patients having less than Twenty percent incidence of NRM and significantly improved survival. In contrast to conventional allo-SCT data,[3,4] the high-risk Ph$^+$ ALL subgroup did not appear to benefit more from RIC allo-SCT in comparison to other cytogenetics risk subgroups. Interpretation of these findings is complicated by the criteria used to select patients for RIC allo-SCT and by other disease (i.e. white blood cell count at diagnosis) and patient-related risk factors that were not available for analysis. Also, the role of GVL in adult ALL is still controversial. Some studies report little, if any, effect of acute GVHD alone, whereas others have found a lower RI after acute or chronic GVHD, or both, than without GVHD. Classically, chronic GVHD had the strongest GVL effect.[3,9,10] Results from the current study suggest that a GVL effect can be induced after RIC allo-SCT in adult ALL. On the other hand, death from leukemia accounted for 61% of all deaths reflecting the damaging impact on survival of advanced disease stage at time of RIC allo-SCT, and raising the question as to whether the putative reduction of toxicity aimed with a RIC regimen is compatible with a sufficient reduction of tumor burden significant enough to allow for emergence of an effective GVL effect.[11] The use of preemptive DLI immediately after RIC allo-SCT may be beneficial, especially in patients with a positive residual disease.[12,13]

But this could not be assessed in this cohort. In addition, amplification of the GVL effect may be one way to reduce the rate of relapse (e.g. by IL-2 activation)[12] or using specific sensitization prior to cell infusion.[14] Post RIC allo-SCT maintenance therapy may also succeed in eradicating residual leukemic cells. Monoclonal antibodies directed against antigens expressed by leukemic cells (anti-CD20/22/33) may be less toxic and more efficient than chemotherapy.[15] Though imatinib prior to and early

after RIC allo-SCT may also have a major role in Ph+ ALL patients,[16-18] the benefit and usefulness of RIC allo-SCT itself may be questioned in the era of targeted drugs.

Altogether, we conclude that RIC allo-SCT is a feasible therapeutic option for adult ALL, especially for those patients in CR1. However, since other studies failed to prove that, when a family donor is available, allo-SCT produces a better outcome than autologous transplantation or chemotherapy both in adults and children with high-risk ALL,[19,20] well-conducted prospective trials are warranted.

Authorship and Disclosures

All authors listed in the manuscript have contributed substantially to this work. Conception and design: MM, ML, VR; financial support: VR; administrative support: MM, ML, VR; provision of study materials or patients: MM, RT, NT, AAF, AR, JM, SS, IM, AN, DB, VR; collection and assembly of data: ML; data analysis and interpretation: MM, ML, VR: manuscript writing and revisions: MM: final approval of manuscript: all co-authors. The authors reported no potential conflicts of interest.

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