Ther Adv Hematol

2025, Vol. 16: 1–3

DOI: 10.1177/20406207251314612

Total body irradiation-based myeloablative conditioning for acute lymphoblastic leukaemia patients undergoing allogeneic haematopoietic stem cell transplantation: the best way to prevent relapse in a real-world scenario

Mario Delia, Vito Pier Gagliardi, Francesco Tarantini, Corinne Contento, Daniela Di Gennaro, Olga Battisti, Camilla Presicce, Immacolata Attolico, Paola Carluccio, Francesco Albano and Pellegrino Musto

Keywords: ALL, allotransplant, TBI

To the Editor,

For patients affected by Philadelphia chromosome-negative (PH−) acute lymphoblastic leukaemia (ALL) with diagnostic high-risk (HR) features and for those with minimal residual disease (MRD) persistency during paediatric-inspired therapeutic approaches, the best outcome success depends on the subsequent allogeneic haematopoietic stem cell transplantation (allo-HSCT),[1] while in PH+ ALL-patients, the benefit from allo-HSCT seems doubtful in case of MRD negativity.[2] For what concern the optimal conditioning regimen, the total body irradiation (TBI)-driven efficiency benefit has been not clearly demonstrated when allo-HSCT was performed in ALL-patients with diagnostic standard-risk features and in first complete remission (CR1) using lower than 12 Gy-TBI dose.[3] It was also recently reported that high-dose TBI (12 Gy) was associated with better survival and lower relapse rate if compared with busulfan-based conditioning regimen.[4] However, the latter evidence[3,4] comes from two large prospective randomized clinical trials with different study populations (adult ALL-patients allotransplanted in CR1[3] and paediatric ALL-patients allotransplanted not only in CR1[4]). Therefore, in a real-world scenario, we retrospectively collected data from allotransplanted ALL-patients comparing those who performed a high dose (i.e. 12 Gy) TBI-based allo-HSCT, with those who underwent a TBI-free myeloablative conditioning to investigate the TBI-impact on adult ALL allotransplanted patients' outcomes.

Post-allotransplantation outcomes have been reported in Table 1. The patient characteristics and Cox-regression analyses of factors with impact on overall survival (OS), relapse and transplant-related mortality (TRM) have been detailed in Supplemental Table S1 and S2, respectively. See also Supplemental Materials for details about myeloablative conditioning regimens and Statistics.

As already reported,[5] in our study population the OS lack of benefit by TBI doesn't seem due to the excess of TRM (Supplemental Table S2), but to the consistent number of subsequent to second CR-patients at allotransplant (18%). In fact, when analysing only TBI-based allotransplants, CR1 showed a trend in favour of better OS-outcome (5-year OS: 57% (CR1) vs 41% (CR≥2), Table 1) thus confirming the exclusive OS-benefit from CR1 when the conditioning regimen was a TBI-based one. As expected,[6] in multivariate analysis, relapse-risk was lower in patients undergoing TBI-based approach (HR = 0.349, Supplemental Table S2). Of note,

Correspondence to:
Mario Delia
Hematology and Stem Cell Transplantation Unit, Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Piazza G. Cesare, 11, Bari 70120, Italy
mario.delia@policlinico.ba.it

Vito Pier Gagliardi
Francesco Tarantini
Immacolata Attolico
Paola Carluccio
Hematology and Stem Cell Transplantation Unit, Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy

Corinne Contento
Daniela Di Gennaro
Olga Battisti
Camilla Presicce
Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), 'Aldo Moro' University of Bari School of Medicine, Bari, Italy

Francesco Albano
Pellegrino Musto
Hematology and Stem Cell Transplantation Unit, Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari, Bari, Italy

Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), 'Aldo Moro' University of Bari School of Medicine, Bari, Italy

Table 1. Post-allotransplant outcomes in ALL-patients according to complete remission (1 vs ⩾2) at transplant.

Study population	No. patients	5-Year OS (%)			5-Year CIR (%)			1-Year TRM (%)		
		CR1	CR⩾2	*p*	CR1	CR⩾2	*p*	CR1	CR⩾2	*p*
Whole group	60	55	32	**0.006**	34	70	**0.025**	11	19	ns
TBI-based	26	57	41	0.097	12	52	**0.036**	13	9	ns
Bu-based	34	39	30	ns	47	80	**0.005**	9	23	ns

ALL, acute lymphoblastic leukaemia; Bu, busulfan; CIR, cumulative incidence of relapse; CR1, first complete remission; CR⩾2, second or subsequent CR; OS, overall survival; TBI, total body irradiation; TRM, transplant-related mortality.
Bold values denote statistical significance at the $p<0.05$ level.

in our study population, TBI-based conditioning regimen was TBI-Cy in 100% of the cases; consequently, in accordance with recently published data reporting a protective effect against relapse by TBI-Cy,[7] the prevalent TBI-impact on relapse (rather than on OS) was expected. The contribution of TBI on cumulative incidence of relapse (CIR) seemed to equal the CR1 achievement before allotransplant, being the 5-year CIR 47% (in CR1) and 52% (in CR⩾2) in non-TBI and in TBI-based conditioning regimen (Table 1), respectively, Therefore, our data confirm that CR1 hierarchically remains the treatment goal to impact OS, while TBI appears crucial to maximize the prevention of relapse (5-year CIR rate of 12%) in a real-world scenario.

However, we must recognize that the flow cytometry-MRD negativity CR1 achievement (47% of our transplants, see Supplemental Materials) at the time of allotransplant inevitably could have impacted the choice to or not to transplant those ALL-patients if they had been followed according to an MRD-driven curative strategy (i.e. not HR patients by diagnostic features).[1] In fact, the sequential chemo-immune antineoplastic approach has demonstrated the most promising outcomes in MRD persistency,[8] paving the way to a long-term survival even without allo-HSCT[8,9] for MRD negative ALL-patients without adverse diagnostic features.[1] On the other hand, the crucial role of TBI-based myeloablative conditioning in CR1 remains[10] thus suggesting how the choice to adopt a TBI-sparing approach in curing ALL-patients should depend on a careful evaluation of the balance between TRM and relapse-risk.

Declaration

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Mario Delia: Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

Vito Pier Gagliardi: Data curation.

Francesco Tarantini: Data curation.

Corinne Contento: Data curation.

Daniela Di Gennaro: Data curation.

Olga Battisti: Data curation.

Camilla Presicce: Data curation.

Immacolata Attolico: Data curation.

Paola Carluccio: Data curation.

Francesco Albano: Data curation.

Pellegrino Musto: Writing – review & editing.

Acknowledgement
The authors greatly thank Donata Grazia Coladonato for her support to the final draft of the paper.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets generated and analysed during the current study are available from the corresponding author upon request.

ORCID iD

Mario Delia https://orcid.org/0000-0002-6486-8912

Supplemental material

Supplemental material for this article is available online.

References

1. Bassan R, Chiaretti S, Della Starza I, et al. Pegaspargase-modified risk-oriented program for adult acute lymphoblastic leukemia: results of the GIMEMA LAL1913 trial. *Blood Adv* 2023; 7(16): 4448–4461.
2. Ghobadi A, Slade M, Kantarjian H, et al. The role of allogeneic transplant for adult Ph+ ALL in CR1 with complete molecular remission: a retrospective analysis. *Blood* 2022; 140(20): 2101–2112.
3. Zhang H, Fan Z, Huang F, et al. Busulfan plus cyclophosphamide versus total body irradiation plus cyclophosphamide for adults acute B lymphoblastic leukemia: an open-label, multicenter, phase III trial. *J Clin Oncol* 2023; 41(2): 343–353.
4. Peters C, Dalle JH, Locatelli F, et al. Total body irradiation or chemotherapy conditioning in childhood ALL: a multinational, randomized phase III study. *J Clin Oncol* 2021; 39: 295–307.
5. Kebriaei P, Anasetti C, Zhang MJ, et al. Intravenous busulfan compared with total body irradiation pretransplant conditioning for adults with acute lymphoblastic leukemia. *Biol Blood Marrow Transplant* 2018; 24(4): 726–733.
6. Khimani F, Dutta M, Faramand R, et al. Impact of total body irradiation-based myeloablative conditioning regimens in patients with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation: systematic review and meta-analysis. *Transplant Cell Ther* 2021; 27(7): 620.e1–620.e9.
7. Giebel S, Labopin M, Socié G, et al. Fludarabine or cyclophosphamide in combination with total body irradiation as myeloablative conditioning prior to allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia: an analysis by the Acute Leukemia Working Party of the EBMT. *Bone Marrow Transplant* 2023; 58: 506–513.
8. Jabbour E, Short NJ, Jain N, et al. Blinatumomab is associated with favorable outcomes in patients with B-cell lineage acute lymphoblastic leukemia and positive measurable residual disease at a threshold of 10^{-4} and higher. *Am J Hematol* 2022; 97: 1135–1141.
9. Gokbuget N, Zugmaier G, Dombret H, et al. Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia. *Leuk Lymphoma* 2020; 61(11): 2665–2673.
10. Pavlů J, Labopin M, Niittyvuopio R, et al. Measurable residual disease at myeloablative allogeneic transplantation in adults with acute lymphoblastic leukemia: a retrospective registry study on 2780 patients from the acute leukemia working party of the EBMT. *J Hematol Oncol* 2019; 12: 108.