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IRTIS DE OLIVEIRA FERNANDES JUNIOR

TRANSPLANTE DE CÉLULAS HEMATOPOIÉTICAS MIELOABLATIVO OU DE INTENSIDADE REDUZIDA/NÃO MIELOABLATIVO PARA LEUCEMIA LINFOBLÁSTICA AGUDA PHILADELPHIA POSITIVO EM ADULTOS COM MAIS DE 40 ANOS DE IDADE:

UMA ANÁLISE SECUNDÁRIA DE UM BANCO DE DADOS CIBMTR

Rio de Janeiro
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Trabalho de Conclusão de Curso apresentado ao Instituto Nacional de Câncer como requisito parcial para a conclusão do Programa de Residência Médica em Transplante de Medula Óssea

Orientadora: Profª Dra. Marta Colares Nogueira

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RESUMO

FERNANDES JR., Irtis de Oliveira. **Transplante de células hematopoiéticas mieloablativo ou de intensidade reduzida/não mieloablativo para leucemia linfoblástica aguda Philadelphia positivo em adultos com mais de 40 anos de idade:** uma análise secundária de um banco de dados CIBMTR. Trabalho de Conclusão de Curso (Residência Médica em Transplante de Medula Óssea) — Instituto Nacional de Câncer (INCA), Rio de Janeiro, 2023.

Poucos estudos abordaram o papel dos regimes de condicionamento de intensidade reduzida (RIC) e não mieloablativos (NMA) em idosos com leucemia linfoblástica aguda Philadelphia positivo (Ph+ ALL). O objetivo deste estudo atual foi comparar os resultados de regimes RIC/NMA versus regimes mieloablativos, baseados na Irradiação Corporal Total (TBI) com condicionamento mieloablativo (MAC) em pacientes Ph+ ALL com mais de 40 anos de idade submetidos a transplante de células hematopoiéticas em primeira remissão completa (CR1). Utilizamos um banco de dados disponível gratuitamente no CIBMTR. Os transplantes foram realizados entre 2013 e 2017. Com seguimento médio de 37,6 meses, incluímos 629 pacientes. Usamos a ponderação do escore de propensão. As taxas de sobrevida total em três anos foram de 64% no grupo TBI-MAC e 66% no grupo RIC/NMA. A sobrevida não foi diferente (HR = 0,92; $p = 0,69$). As incidências de recaída em três anos foram de 21,6% e 27,6% nos grupos TBI-MAC e RIC/NMA. RIC/NMA não foi associado a um aumento na taxa de recidiva (HR 1,02; $p = 0,91$). As taxas de mortalidade sem recidiva (NRM) em três anos foram de 24,3% no grupo TBI-MAC e 20,3% no grupo RIC/NMA. RIC/NMA não foi associado a NRM superior (HR 0,88; $p = 0,57$). Em resumo, mostramos que os regimes RIC / NMA alcançam resultados comparáveis ao MAC baseado em TBI em pacientes idosos com LLA Ph+ em CR1 que podem tolerar um regime MAC baseado em TBI.

Palavras-chave: leucemia linfoblástica aguda; transplante de células hematopoiéticas, condicionamento pré-transplante reduzido; transplante de células hematopoiéticas, condicionamento pré-transplante mieloablativo; CIBMTR.

ABSTRACT

FERNANDES JUNIOR, Irtis de Oliveira. **Myeloablative or reduced-intensity/ non-myeloablative hematopoietic cell transplantation for Philadelphia-positive acute lymphoblastic leukemia in adults older than 40 years old — a secondary analysis of a CIBMTR database.** Final paper (Medical Residency in Bone Marrow Transplantation) — Brazilian National Cancer Institute (INCA), Rio de Janeiro, 2023.

Few studies have addressed the role of reduced-intensity conditioning (RIC) and non-myeloablative (NMA) regimens in older adults with Philadelphia acute lymphoblastic leukemia (Ph+ ALL). The objective of this current study was to compare the outcomes of RIC/NMA versus TBI-based myeloablative (MAC) regimens in Ph+ ALL patients older than 40 years old who underwent hematopoietic cell transplantation (HCT) in first complete remission (CR1). We used a freely available database from the CIBMTR. Transplants were performed between 2013 and 2017. With a median follow-up of 37.6 months, we have included 629 patients. We used propensity score weighting. Three-year Overall Survival (OS) were 64% in the TBI-MAC group and 66% in the RIC/NMA group. OS was not different (HR = 0.92; p = 0.69). Three-year relapse incidences were 21.6% and 27.6% in the TBI-MAC and RIC/NMA groups. RIC/NMA was not associated with an increase in relapse rate (HR 1.02; p = 0.91). Three-year non relapse mortality (NRM) were 24.3% in the TBI-MAC group and 20.3% in the RIC/NMA group. RIC/NMA was not associated with superior NRM (HR 0.88; p = 0.57). In summary, we have shown that RIC/NMA regimens achieve outcomes comparable to TBI-based MAC in Ph+ ALL older patients in CR1 who may tolerate a TBI-based MAC regimen.

Keywords: acute lymphoblastic leukemia; Philadelphia-positive acute lymphoblastic leukemia; reduced-intensity conditioning regimen; myeloablative conditioning regimen; allogeneic hematopoietic cell transplantation; CIBMTR.

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ORIGINAL ARTICLE

Myeloablative or reduced-intensity/non-myeloablative hematopoietic cell transplantation for Philadelphia-positive acute lymphoblastic leukemia in adults older than 40 years old — a secondary analysis of a CIBMTR database

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Abstract
Few studies have addressed the role of reduced-intensity conditioning (RIC) and non-myeloablative (NMA) regimens in older adults with Philadelphia acute lymphoblastic leukemia (Ph + ALL). The objective of this current study was to compare the outcomes of RIC/NMA versus TBI-based myeloablative (MAC) regimens in Ph + ALL patients older than 40 years old who underwent hematopoietic cell transplantation (HCT) in CR1. We used a freely available database from the CIBMTR. Transplants were performed between 2013 and 2017. With a median follow-up of 37.6 months, we have included 629 patients. We used propensity score weighting. Three-year OSs were 64% in the TBI-MAC group and 66% in the RIC/NMA group. OS was not different (HR = 0.92; $p = 0.69$). Three-year relapse incidences were 21.6% and 27.6% in the TBI-MAC and RIC/NMA groups. RIC/NMA was not associated with an increase in relapse rate (HR 1.02; $p = 0.91$). Three-year NRMs were 24.3% in the TBI-MAC group and 20.3% in the RIC/NMA group. RIC/NMA was not associated with superior NRM (HR 0.88; $p = 0.57$). In summary, we have shown that RIC/NMA regimens achieve outcomes comparable to TBI-based MAC in Ph+ ALL older patients in CR1 who may tolerate a TBI-based MAC regimen.

Keywords Acute lymphoblastic leukemia · Philadelphia-positive acute lymphoblastic leukemia · Reduced-intensity conditioning regimen · Myeloablative conditioning regimen · Allogeneic hematopoietic cell transplantation · CIBMTR

Introduction

Philadelphia, or BCR-ABL, acute lymphoblastic leukemia (Ph + ALL) used to carry a very poor prognosis until the release of the first tyrosine kinase inhibitor (TKI), imatinib [1]. Since then, the survival of Ph + ALL has dramatically increased, but adults with Ph + ALL are still often referred for hematopoietic cell transplantation (HCT) in first complete remission (CR1) [2].

Ph + ALL increases with age [3] which makes treatment even more challenging because those patients may not be suitable for HCT with a myeloablative conditioning (MAC) regimen. For those, reduced-intensity conditioning (RIC) and non-myeloablative conditioning (NMA) regimens are the available options, but so far, only a few studies have addressed the role of RIC and NMA regimens in older adults with Ph + ALL [4, 5].

The objective of this current study was to compare the outcomes of RIC/NMA versus TBI-based MAC (TBI-MAC) regimens in Ph + ALL patients older than 40 years old who underwent HCT in CR1.

Methods

We used the CIBMTR database used by Wieduwilt et al. [6]. The CIBMTR (Center for International Blood and Marrow Transplant Research) is a research collaboration between

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the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. It comprises a voluntary working group of > 330 participating centers worldwide that contribute detailed data on cellular therapies.

In brief, from that database, we selected Ph + ALL patients, older than 40 years old, which underwent haploidentical, matched-sibling, or unrelated donor HCT in CR1 and received either a TBI-based MAC regimen, or a RIC or an NMA regimen, and we compared the results of TBI-based MAC with RIC/NMA regimens. Transplants were performed between 2013 and 2017. The CIBMTR definition of RIC/NMA included regimens containing melphalan ≤ 150 mg/m^2, busulfan ≤ 7.2 mg/kg IV, TBI ≤ 5 Gy (single dose), or ≤ 8 Gy (fractionated). Detailed definition of regimen intensity can be found in CIBMTR manual (https://www.manula.com/manuals/cibmtr/fim/1/en/topic/q155-315-pre-hct-preparative-regimen-conditioning). MRD testing methods were as reported from CIBMTR sites. MRD testing methods included flow cytometry, molecular methods, cytogenetics, or missing, with some patients being evaluated with more than 1 method. We analyzed overall survival (OS), relapse-free survival (RFS), relapse incidence (RI), and non-relapse mortality (NRM). Univariable analyses were performed comparing survival or cumulative incidence curves, as appropriate, with the log rank or Gray tests. Propensity score (PS) weighting was used with Cox models. Inverse probability of treatment weighting (IPTW) was used to estimate the average treatment effect. Variables included in the PS estimation are those included in Table 1, except for sex. TBI-MAC is the reference category throughout the manuscript. All analyses were performed with R, version 4.2.1.

Table 1 Patients characteristics

	MAC-TBI	RIC/NMA	Total	*p* value
Total	351	278	629	
Age				< 0.001
Median (IQR)	48.5 (44.8,54.1)	60.5 (53.8,65.2)	53.3 (46.5,61)	
Sex				0.417
Male	202 (57.5)	151 (54.3)	353 (56.1)	
Female	149 (42.5)	127 (45.7)	276 (43.9)	
KPS				0.395
< 90%	149 (42.5)	132 (47.5)	281 (44.7)	
90–100%	200 (57)	144 (51.8)	344 (54.7)	
Missing	2 (0.6)	2 (0.7)	4 (0.6)	
MRD				0.635
MRD −	233 (66.4)	182 (65.5)	415 (66)	
MRD +	115 (32.8)	91 (32.7)	206 (32.8)	
Unknown	3 (0.9)	5 (1.8)	8 (1.3)	
Donor				< 0.001
MSD	167 (47.6)	87 (31.3)	254 (40.4)	
Haplo	15 (4.3)	52 (18.7)	67 (10.7)	
MUD 8/8	150 (42.7)	125 (45)	275 (43.7)	
MMUD 7/8	19 (5.4)	14 (5)	33 (5.2)	
Sex match				0.541
F- > M	62 (17.7)	44 (15.8)	106 (16.9)	
Others	289 (82.3)	234 (84.2)	523 (83.1)	
Graft				0.093
BM	45 (12.8)	49 (17.6)	94 (14.9)	
PBSC	306 (87.2)	229 (82.4)	535 (85.1)	
Time to HCT				0.006
0–5 months	250 (71.2)	166 (59.7)	416 (66.1)	
6–11 months	91 (25.9)	96 (34.5)	187 (29.7)	
12 + months	10 (2.8)	16 (5.8)	26 (4.1)	

IQR interquartile range, *KPS* Karnofsky performance status, *MSD* matched-sibling donor, *Haplo* haploidentical, *MUD* matched unrelated donor, *MMUD* mismatched unrelated donor, *F- > M* female donor and male recipient, *BM* bone marrow, *PBSC* peripheral blood stem cells, *HCT* hematopoietic cell transplantation

Results

With a median follow-up of 37.6 months, we have included 629 patients, 351 and 278 who received TBI-MAC and RIC/NMA regimens, respectively. Patients' characteristics (Table 1) were different for the type of donor — 47.6% matched-sibling donor (MSD) in the TBI-MAC arm, against 31.3% in the RIC/NMA arm — and for time to transplant (71.2% up to 6 months in the TBI-MAC arm and 59.7% in the RIC/NMA arm). Age was higher in the RIC/NMA group (60.5 versus 48.5 in the TBI-MAC and RIC/NMA groups, respectively, $p < 0.001$).

Three-year OSs were 64% (95CI 59–70%) in the TBI-MAC group and 66% (95CI 60–72%, Fig. 1A) in the RIC/NMA group. OS was not different (HR = 0.92; 95CI 0.63–1.37; $p = 0.69$). Three-year RFSs were 54% (49–60%) and 52% (46–59%, Fig. 1B) in the TBI-MAC and RIC/NMA groups. RFS was not different either (HR = 0.96; 95CI 0.67–1.36; 0.81).

Three-year relapse incidences were 21.6% (95CI 27.6–26.6%) and 27.6% (95CI 22.6–33.7%, Fig. 1C) in the TBI-MAC and RIC/NMA groups, respectively. In the Cox model with PS weighting, RI was not different (HR 1.02; 95CI 1.59–1.80; $p = 0.91$). Three-year NRMs were 24.3% (95CI 20.1–29.5%) in the TBI-MAC group and 20.3% (95CI 16.0–25.8%, Fig. 1D) in the RIC/NMA group. RIC/NMA was not associated with better NRM (HR 0.88; 95CI 0.56–1.38; $p = 0.57$).

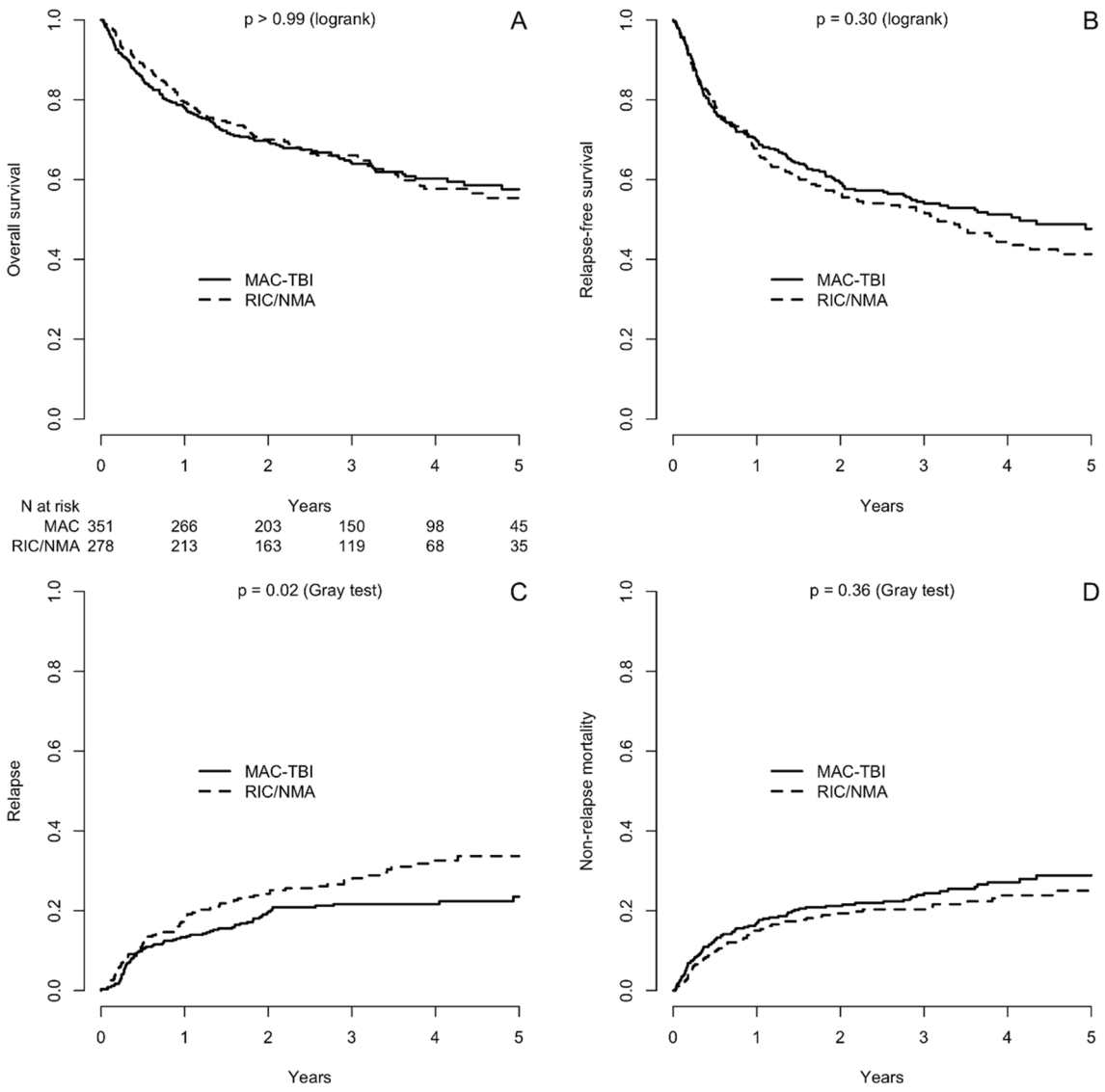

Fig. 1 Overall survival, relapse-free survival, relapse, and non-relapse mortality. **A** Overall survival, **B** relapse-free survival, **C** relapse, **D** non-relapse mortality. For relapse, death in remission was the competing event. For non-relapse mortality, relapse was the competing event

Discussion

Our results show comparable results between TBI-MAC and RIC/NMA regimens in terms of OS (HR = 0.92; 95CI 0.63–1.37; $p = 0.69$), HR = 0.96; 95CI 0.67–1.36; 0.81), and NRM (HR 0.88; 95CI 0.56–1.38; $p = 0.57$). Relapse was not higher with RIC/NMA regimens (HR 1.02; 95CI 1.59–1.80; $p = 0.91$).

Relapse in the RIC/NMA regimens (27.6%) was numerically lower compared with a previous CIBMTR analysis [8], which showed 49% relapse incidence, which included patients from 2000 to 2009 (in our study, transplants were performed between 2013 and 2017). This may reflect differential posttransplant TKI maintenance strategies [9], but this is speculative.

High 3-year OS rates were achieved with both TBI-MAC and RIC/NMA regimens. This might reflect the fact that posttransplant relapse prognosis has been increasing in the latest years, mainly due to more effective posttransplant salvage with newer generation TKI [10]. Akahoshi et al. [4], in a study that included 226 patients, did not find any difference between MAC and RIC regimens in any outcome in Ph + ALL patients older than 50 years old who were MRD negative at transplant, although the HR for relapse was numerically high (1.97) with a wide confidence interval. In Akahoshi's study, almost 80% of the RIC patients received a melphalan-based regimen whereas around 40% of the MAC patients received a chemotherapy-based conditioning regimen. Yoon [5], in a study with 195 patients, also compared MAC with RIC in Ph + ALL in CR1 and found comparable outcomes. Their RIC regimen was uniformly based on melphalan 140 mg/m^2, and the MAC regimen was TBI-based. In our study, RIC regimens might have been heterogeneous (this data was not available in the database) while all MAC regimens were TBI-based.

We have not found any advantage of RIC/NMA regimens in terms of NRM. One hypothesis is that frailer patients may have been selected for RIC/NMA regimens, which is supported by the older age in the RIC/NMA group. However, performance status was not different between the groups, and propensity score weighting should have removed this confounding. Improvement in supportive care may also have played a role.

Our study has several limitations. As already pointed out, RIC regimen specification was not available. However, the main finding — that older patients with Ph + ALL achieve good OS with NMA or RIC regimens — remains. Although MRD data was available for the great majority of the patients, MRD positivity was not prognostic for relapse (HR = 0.78, $p = 0.16$, in univariate analysis), in contrast to recently published data [11]. The pattern of posttransplant TKI use and/or immunosuppressive management may have been different. Another hypothesis is that MRD simply is not prognostic when some kind of posttransplant maintenance with a TKI is planned. The main strength of our paper is the high number of patients (as far as we are concerned, this is the study in older adults with Ph + ALL with the largest number of patients) and, consequently, the narrow confidence intervals.

In summary, we have shown that both TBI-based MAC HCT and RIC/NMA achieve excellent outcomes in patients with Ph + ALL in CR1. Randomized trials in this older population are warranted.

Acknowledgements We used the freely available CIBMTR database.

Author contribution IOFJ and LJA designed the study and wrote the manuscript. LJA did all analyses.

Data availability The database is already available in the CIBMTR website.

Declarations

Competing interests The authors declare no competing interests.

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