Mediterranean Journal of Hematology and Infectious Diseases

Scientific Letter

High Tuberculosis Density Incidence Rate in Matched Unrelated Allogeneic Stem Cell Transplantation Recipients in the State of São Paulo, Brazil

Keywords: Tuberculosis; Tuberculosis prevalence; Hematopoietic stem cell transplantation (HSCT); Retrospective cohort; Density incidence rate.

Published: July 1, 2023 **Received: January 5, 2023** **Accepted: June 2, 2023**

Citation: Litvoc M.N., Leal F.E., Ferreira D.B., Ferreira Lopes M.I.B., Capuani L., Rocha V.G., Costa S.F. High tuberculosis density incidence rate in matched unrelated allogeneic stem cell transplantation recipients in the state of São Paulo, Brazil. Mediterr J Hematol Infect Dis 2023, 15(1): e2023037, DOI: http://dx.doi.org/10.4084/MJHID.2023.037

To the editor.

There is limited data regarding tuberculosis in hematopoietic stem cell transplantation (HSCT), especially in endemic countries. We conducted a retrospective cohort study including all patients who underwent matched unrelated allo-HSCT from 2007-2016 in the state of São Paulo, Brazil. Tuberculosis in this population was identified by record linkage between the national HSCT database (REREME) and the São Paulo State Tuberculosis Control Program database. Five tuberculosis cases (3 males) were identified and described among 1,223 allo-HSCT. The mean age was 25, and the mean time between HSCT and Tuberculosis diagnosis was 376 days. Density incidence rate and standardized incidence ratios (SIR) were compared between matched unrelated donor allo-HSCT and the São Paulo state Tuberculosis database (172,925 cases). Considering 2,718 patients/year, the density incidence rate in the allo-HSCT population was 183 cases/100.000 patients/year (SIR:4.9 and 95% CI 1.8-11:), much higher than the average rate for the whole population in the state of São Paulo for the same period: 38.8/100.000 inhabitants. In our study, allo-HSCT patients are highly vulnerable to tuberculosis disease, almost five times higher than in the general population.

Tuberculosis incidence in hematopoietic stem cell transplant (HSCT) recipients seems to be related to the prevalence in the country.[1,2] In HSCT patients, the risk of tuberculosis is higher in allogeneic stem cell transplantation (allo-HSCT). Tuberculosis incidence among allo-HSCT has been reported from 0.014% to 16.0%.[3] Data regarding Tuberculosis among HSCT is scarce even in endemic countries such as Brazil, one of the 30 most high-burden tuberculosis countries in the world.[4]

We aimed to describe tuberculosis's density incidence rate and standard incidence ratios (SIR) in matched unrelated allo-HSCT.

Methods. This retrospective cohort study includes all matched unrelated allo-HSCT patients in the São Paulo state from 2007 to 2016. We collected data from the São Paulo State Tuberculosis Control Program and the national allo-HSCT database from REREME at the National Institute of Cancer (INCA.,2021).[5]

REREME collects data from all matched unrelated donors allo-HSCT in the country. Probabilistic record linkage compares similarities between databases applying mathematical functions. Data were reviewed to correct errors and to standardize the content of the key variables – name, surname, and date of birth. Those fields are recorded in a Soundex code through parsing, substring, and transforming the text into a phonetic code to make the linkage between misrecorded information.[6] Record pairs are formed to be compared and classified into true pairs, non-pairs, and doubtful pairs and then manually reviewed to accept or reject the cases.

Available clinical, demographic, and epidemiological data of patients with tuberculosis were compared to the entire allo-HSCT patient cohort. During the study period, fluoroquinolones were recommended as bacterial prophylaxis in Brazil during the neutropenia until the engraftment. Microbiologic and molecular tests to diagnose tuberculosis are available in all centers. However, the decision to perform bronchoalveolar lavage (BAL) was of the clinical physician of each Hospital.

In order to calculate the incidence density rate of tuberculosis, we consider the contribution time from each patient, from the transplant date until death or until December 31st, 2016, the final follow-up date. Long-term follow-up was characterized by death (outcome) or tuberculosis diagnosis. No autopsy cases data were available.

The study was approved by the institutional review board of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

Statistical Analysis. Density incidence rate and standard incidence ratios (SIR) were calculated to compare the incidence of tuberculosis in matched unrelated donor allo-HSCT and the general population in São Paulo during the study period. Nominal and ordinal variables were described as frequency and percentage; quantitative data, in median and range. All calculations were performed with Epi-Info 7.2.

Results. In the state of Sao Paulo, from 2007 until 2016, 1,223 matched unrelated donor allo-HSCTs were performed. Among those, 1172 were new transplants, 39 were second-time transplant recipients, and 12 patients did the first transplant before the beginning of the study. Most patients were males (713 cases-60%), and the mean age at the onset of allo-HSCT was 25 years old. Acute Lymphoblastic Leukemia was the most common diagnosis (359 patients), followed by Acute Myeloid Leukemia and Chronic Myeloid Leukemia (**Table 1**).

Table 1. Allo-HSCT recipients from REREME 2007-2016 in São Paulo state, Brazil.

	Alo-HSCT with tuberculosis	**Alo-HSCT without tuberculosis**
	(N=5)	**(N=1218)**
Male sex (%)	3 (60)	713 (58)
Age at transplant (mean; years)	31.2	25
Death rate (%)	40	35.9
Survival (mean; days)	590	224
Transplants (%)		
1	4(80)	1133 (92)
2	1(20)	90 (7,5)
Acute Lymphoblastic Leukemia	1	359
Acute Myeloid Leukemia	1	335
Chronic Myeloid Leukemia	1	96
Non-Hodgkin Lymphoma	1	23
Hodgkin Disease	1	9
Chronic Monocytic Leukemia	0	5
Chronic Lymphocytic Leukemia	0	4
Others leukemias	0	36
Acute Myelomonocytic Leukemia	0	9
Aplastic anemia	0	119
Other anemias	0	18
Immunodeficiency	0	34
Others causes	0	149
Non specified	0	27
Total	5	1218

One patient was confirmed by microbiological criteria (culture); radiological and clinical criteria were used to diagnose the other cases.

After transplantation, 440 patients have not survived, with a death rate of 35.9% and an average survival time until the death of 182.7 days; 172,925 cases were identified in the São Paulo State Tuberculosis Control Program database during the study period. Record linkage found 60 record pairs from two databases. After manual checking, 23 tuberculosis cases were identified among allo-HSCT patients. Five tuberculosis cases were diagnosed after, and 17 cases were diagnosed before the HSCT (**Table 1** and **supplementary material**). The period without TB of all HSCT patients ranged from 11 days to 9 years. Post-transplantation cases were diagnosed in four different hospitals (2 public and 2 private) in the state of São Paulo. All new cases were pulmonary forms of tuberculosis except one neurological manifestation. The mean days between HSCT and Tuberculosis diagnosis were 376 days (ranging from 61 days until 1048 days). Four patients were cured after treatment with four drugs (RIPE); one case abandoned the treatment (**Table 2**). The incidence rate was 183 cases per 100.000 patients/year, and the SIR(4,9-95%CI:1.8-11.0). None of the 17 patients with previously treated Tuberculosis before HSCT reactivated during the follow-up period. The mean age of patients with previous tuberculosis was 19.3 years old. The mean time of diagnosis of active tuberculosis was 439.2 days before HSCT. The RIPE regimen was the most used in 10 cases (58.0%). The indication for HSCT was: Acute myeloid leukemia (AML) 8 (47.0%), Combined immunodeficiency 3 (17.0%), unspecified

Table 2. Density incidence rate and SIR of new tuberculosis cases diagnosed after allo-HSCT in the state of São Paulo from 2007 to 2016.

Sourse	REREME-SP
Total records	1223
Tuberculosis cases	5
Frequency (%)	0,40
Patients′ year	2718
Density Incidence rate	183/100,000 patients/year
SIR (IC95%)	4.9 (1.8 - 11)

neutrophil functional disorder 3 (17.0%), Unspecified immunodeficiency 1 (5.8%) and other combined deficiencies 01 (5.8%). The clinical form of tuberculosis was pulmonary in 7 cases (41.1%), disseminated in 4 cases (23.5%), lymph node in 2 cases (11.7%), unspecified in 2 cases (11.7%), bone in 1 case (11.7%) and "extrapulmonary," without other definitions, in 1 case (11.7%).

Discussion. Our study is the first attempt to improve epidemiological data about Tuberculosis in HSCT in Brazil. Incidence of Tuberculosis matched unrelated allo-HSCT (183 cases/100,000 patients/year) was 4.9 times higher than the average rate for the population in the state of São Paulo (38.8/100,000 inhabitants). A Spanish mathematical modeling study has estimated an incidence rate of 135.6 cases per 100,000 inhabitants after allo-HSCT.[2] A recent Brazilian study reported a cumulative tuberculosis incidence of 3% among allo-HSCT.[7] Other authors observed a higher Tuberculosis incidence rate compared with our study. In Korea, a retrospective study examined 845 matched unrelated allo-HSCT and reported a Tuberculosis incidence of 654.2 /100,000 patients/year.[8]

Our study has limitations as most cases were treated based on clinical and radiological findings. However, a relevant finding was the number of patients, 17 with previously treated tuberculosis, that underwent HSCT and did not reactivate during the follow-up period. Another limitation of the study was that the susceptible testing was not available. However, four of the five patients that developed TB after HSCT were cured after treatment with four drugs, and one case abandoned the treatment. Thus, there was probably no tuberculosis resistance among the cases.

Conclusions. tuberculosis remains a healthcare concern in endemic countries. It should be addressed in immunosuppressive conditions like allo-HSCT since its incidence could be almost five times higher than in the general population.

Marcelo Nóbrega Litvoc[1], Fabio Eudes Leal[2], Diogo Boldim Ferreira[3], Max Igor Banks Ferreira Lopes[1], Ligia Capuani[4], Vanderson Geraldo Rocha[5] and Silvia Figueiredo Costa[1,4].

[1] Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, SP, Brazil.
[2] Instituto Nacional de Câncer, Rio de Janeiro, Brazil.
[3] Hospital São Paulo, Escola Paulista de Medicina da Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil.
[4] Departamento de Doenças Infecciosas e Parasitárias, Laboratório de Investigação Médica em Protozoologia, Bacteriologia e Resistência Antimicrobiana (LIM 49), Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, SP, Brazil.
[5] Haematology Department, NHS BT, Oxford University, Oxford, UK.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Marcelo Nóbrega Litvoc, MD. Av. Dr. Enéas de Carvalho Aguiar 255-Cerqueira César. São Paulo, SP CEP 05403-000, Brazil. E-mail: malitvoc@gmail.com Orcid: 0000-0002-5144-5451

References:

1. Cordonnier C, Martino R, Trabasso P, Held TK, Akan H, Ward MS, et al; European Blood and Marrow Transplant Group Infectious Disease Working Party. Mycobacterial infection: a difficult and late diagnosis in stem cell transplant recipients. Clin Infect Dis 2004;38(9):1229-36. https://doi.org/10.1086/383307 PMid:15127333
2. De la Cámara R, Martino R, Granados E, Rodriguez-Salvanés FJ, Rovira M, Cabrera R, et al. Tuberculosis after hematopoietic stem cell transplantation: incidence, clinical characteristics and outcome. Spanish Group on Infectious Complications in Hematopoietic Transplantation. Bone Marrow Transplant 2000;26(3):291-8. https://doi.org/10.1038/sj.bmt.1702506 PMid:10967568
3. Russo RL, Dulley FL, Suganuma L, França IL, Yasuda MA, Costa SF. Tuberculosis in hematopoietic stem cell transplant patients: case report and review of the literature. Int J Infect Dis 2010;14 Suppl 3:e187-91. https://doi.org/10.1016/j.ijid.2009.08.001 PMid:19819176
4. Ministério da Saúde. Tuberculose - 2021. Boletim Epidemiológico. 2021;3(1):44.
5. INCA (Instituto Nacional de Câncer José Alencar Gomes da Silva) REDOME | REDOME - Registro Nacional de Doadores de Medula Óssea - Site Oficial [Internet]. 2021 [acesso em: 2021 10 set 10]. Disponível em: http://redome.inca.gov.br/o-redome/conheca-o-redome/
6. Oliveira GP, Bierrenbach AL, Camargo KR Júnior, Coeli CM, Pinheiro RS. Accuracy of probabilistic and deterministic record linkage: the case of tuberculosis. Rev Saude Publica 2016;50:49. https://doi.org/10.1590/S1518-8787.2016050006327 PMid:27556963 PMCid:PMC4988803
7. De Oliveira MR, de Almeida Testa LH, Dos Santos ACF, Zanetti LP, da Silva Ruiz L, de Souza MP, et al. Latent and active tuberculosis infection in allogeneic hematopoietic stem cell transplant recipients: a prospective cohort study. Bone Marrow Transplant 2021;56(9):2241-7. https://doi.org/10.1038/s41409-021-01329-3 PMid:33966056
8. Lee HJ, Lee DG, Choi SM, Park SH, Cho SY, Choi JK, et al, Min WS, Jung JI. The demanding attention of tuberculosis in allogeneic

hematopoietic stem cell transplantation recipients: High incidence compared with general population. PLoS One 2017;12(3):e0173250. https://doi.org/10.1371/journal.pone.0173250 PMid:28278166 PMCid:PMC5344370