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Research paper

Association of recipient and donor hypercholesterolemia prior allogeneic stem cell transplantation and graft-versus-host disease

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ABSTRACT

Few authors have reported a decreased frequency of acute graft-versus-host disease (aGVHD) using statins, as these medications have anti-inflammatory effects, however, to date, the direct association between high cholesterol and GVHD has not been reported. The aim of his study was to investigate the association of recipient and donor hypercholesterolemia with the incidence of aGVHD. A retrospective analysis was performed identifying allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients and donors at the National Institute of Medical Sciences and Nutrition in Mexico City between May 1999 and August 2017. The final cohort included 113 consecutive patients undergoing allo-HSCT and 110 donors with complete data. Acute GVHD was present in 24% patients. A statistically significant increase in the frequency of aGVHD associated with hypercholesterolemia in the recipients or donors ($p = 0.03$ and $p = 0.008$, respectively). Hypercholesterolemia in both, donor and recipient, was also associated with increased aGVHD compared to either patient or donor having hypercholesterolemia or neither ($p = 0.002$). No statistical significance was observed for other variables. To date, this is the first study associating hypercholesterolemia with aGVHD. According to our results we conclude that hypercholesterolemia in the donor, or in both, the patient and donor, is an independent factor for the development of aGVHD, however, further prospective and larger studies are needed as our results are preliminary.

1. Introduction

Hypercholesterolemia leads to cholesterol accumulation in macrophages and other immune cells, promoting inflammatory responses. Also, signaling from toll-like receptors (TLRs) results in further cholesterol accumulation and increased inflammatory responses as a result of diminished cholesterol efflux, exacerbating chronic metabolic inflammation [1]. Although the links between cholesterol and inflammation are best exemplified by atherosclerosis, similar mechanisms may also contribute to other metabolic disorders such as obesity [2] or to autoimmune diseases. In this context, acute graft-versus-host disease (aGVHD) is an immunological syndrome that involves tissue damage mediated by donor lymphocytes, resulting from an imbalance between the effector and regulatory arms of the immune system that can affect the outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT) [3–5]. Moreover, prior T cell activation, the innate immune system is an important component of the induction of aGVHD. Also, pre HSCT conditioning regimens damage the intestinal epithelium leading to enhanced stimulation of TLRs which results in an increased cytokine production and T-cell activation [6]. It is known that among patients undergoing allo-HSCT, some factors might determine the occurrence of aGVHD and its severity [7,8]. For instance, the presence of certain HLA alleles [9], types and properties of the transplanted T cells [10,11], immune cells signaling, induction of proinflammatory cytokines [12], among others, have been described. On the other hand, the role of the statins, which are inhibitors of HMG-CoA reductase and are widely used for the treatment of dyslipidemia, includes inhibition of this enzyme leading to decreased rates of DNA synthesis in lymphocytes [13,14] and more importantly, anti-inflammatory activity [15]. Therefore, some authors have reported a decreased frequency of aGVHD with the usage of these medications [16–20]. Nonetheless, as hypercholesterolemia is coupled with inflammation and represents an unspecific marker of low grade chronic diseases, it might trigger immunological responses such as aGVHD, however, to date, the direct association between high cholesterol and the latter has not been reported. The aim of this study was to investigate the association of hypercholesterolemia in both, allo-HSCT recipients and donors and the incidence of aGVHD in a referral center in Mexico City.

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2. Patients and methods

2.1. Data

A retrospective analysis was performed identifying 121 patients receiving allo-HSCT at the National Institute of Medical Sciences and Nutrition in Mexico City between May 1999 and August 2017. Exclusion criteria included incomplete laboratory information of the recipient, cord blood transplants, engraftment failure or 30-day mortality. The final cohort included 113 consecutive patients undergoing allo-HSCT and 110 donors with complete data. Data such as demographic and clinical characteristics were obtained from a prospectively created institutional HSCT database or retrospectively from the Institutional medical records.

2.2. HSCT procedure

For steady-state (SS-BM) and G-CSF-primed bone marrow (G-BM), HSCs were collected from donors by multiple aspirations of the iliac crests, in an operating room, under spinal anesthesia, G-CSF (10 μg/kg/day) was administered 3 days (every 8 h) prior the procedure for the latter. For PBSC, HSCs were collected by apheresis with prior administration of G-CSF for 3 days. Most patients with hematological malignancies received reduced BUCY2 (busulfan 12 mg/kg, ORAL and cyclophosphamide 80 mg/kg, IV) [16] which is a reduced intensity conditioning regimen (RIC), the rest received other myeloablative regimens (MAC). Patients with aplastic anemia received antithymocyte globulin (ATG) and/or cyclophosphamide based conditioning regimens. Methotrexate (MTX) and cyclosporine A (CSA) were given for GVHD prophylaxis. MTX was administered IV, 15 mg/m^2 day +3, and 10 mg/m^2 during days +6 and +11. None of the patients received MTX on day +1 [17]. CSA was administered IV, 1.5 mg/kg/12 h, during day -1 and adjusting according to serum levels (200–300 ng/μl) until 2005; afterwards CSA was administered orally (IV presentation was withdrawn from the market), 10 mg/kg during day -1, and 5 mg/kg starting day 0, adjusting according to therapeutic monitoring. CsA was maintained for 4 months post-transplant (8 months in aplastic anemia), and was subsequently reduced weekly (10%), until suspended, unless development of GVHD. Antimicrobial prophylaxis and supportive therapy were given according to Institutional guidelines. Patients were discharged when engraftment occurred and in the absence of infections or complications and follow-up was performed in the out-patient clinic.

2.3. Definition of endpoints

NIH criteria was used to diagnose and evaluate severity of acute GVHD [21]. Total cholesterol in the recipient and the donor was documented approximately 1 month prior performing HSCT as part of the pre-transplant workup. High cholesterol was considered as total cholesterol ≥ 200 mg/dL, according to international guidelines [22].

2.4. Statistical analysis

Patient and HSCT characteristics and demographics were reported using descriptive statistics. Variables with normal distribution were compared with independent t-test or one-way ANOVA. Categorical variables were compared with the chi-square or Fisher's exact test. For aGVHD, death and relapse without aGVHD were considered competing risks. Patients at risk to develop aGVHD excluded those with a 30-day mortality. For multivariate analysis, Cox regression was used. A p-value of < 0.05 was considered significant. SPSS v.21 (IBM, Chicago, IL) was used.

3. Results

One hundred and thirteen patients were included. Most patients were males (n = 63, 56%). The median age was 31 years (range, 16–62). The underlying diseases were the following: acute lymphoblastic leukemia (n = 27, 24%), aplastic anemia (n = 24, 21%), myelodysplastic syndrome (n = 18, 16%), acute myeloblastic leukemia (n = 14, 12%), lymphomas (n = 6, 5%), chronic lymphocytic leukemia (n = 13, 12%), and others (n = 11, 10%). Most patients had a matched related donor (n = 108, 96%) and gender disparity was observed in 51%. Most patients received RIC or MAC (n = 86, 76%). The most frequent used stem cell source was G-BM (n = 62, 55%), followed by SS-BM (n = 29, 26%). Twenty five patients (22%) had total cholesterol

Table 1
Patient, Donor, and HSCT Demographics.

Characteristic	n (%)
Patient gender	63 (56)
Male	50 (44)
Female	
Median age (range)	31 (16-62)
Underlying disease	24 (21)
AA	27 (24)
ALL	14 (12)
AML	13 (12)
CML	3 (2.5)
HL	3 (2.5)
NHL	18 (16)
MDS	11 (10)
Others	1
ADLD	4
PNH	1
EPP	1
MPN	2
MF	2
FA	
Disease Risk Index	14 (12)
Low	47 (42)
Intermediate	18 (16)
High	2 (2)
Very high	32 (28)
Not applicable (benign)	
Median infused CD34+ cell x 10^6/kg (range)	2.00 (0.65-8.26)
HLA matched donor	108 (96)
Related	5 (4)
Unrelated (8/8 matched)	
Gender disparity	58 (51)
Yes	49 (44)
No	6 (5)
Unknown	
Conditioning regimen	86 (76)
MAC/RIC	27 (24)
NMA	
Stem cell source	62 (55)
G-BM	29 (26)
SS-BM	22 (19)
PBSC	
Cholesterol (mg/dL) prior HSCT	88 (78)
Patient	25 (22)
< 200	83 (76)
≥ 200	27 (24)
Donor	65 (58)
< 200	8 (7)
≥ 200	40 (35)
Both	
< 200	
≥ 200	
Other	

Abbreviations: AA: Aplastic anemia; ADLD: Adrenoleukodystrophy; ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; EPP: Erythropoietic Protoporphyria; FA: Fanconi anemia; G-BM: G-CSF-primed bone marrow; HL: Hodgkin lymphoma; MAC: Myeloablative conditioning regimen; MDS: Myelodysplastic syndrome; MF: Myelofibrosis; MPN: Myeloproliferative Neoplasm; NMA: Non-myeloablative conditioning regimen; PBSC: Peripheral blood stem cells; PNH: Paroxysmal nocturnal hemoglobinuria; RIC: Reduced intensity conditioning regimen; SS-BM: Steady-state bone marrow.