Transfusion Medicine Reviews xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: www.tmreviews.com

Adverse Events Associated With Infusion of Hematopoietic Stem Cell Products: A Prospective and Multicenter Surveillance Study

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ARTICLE INFO

Available online xxxx

Keywords:
Adverse events
Infusion
Hematopoietic stem cell product
Hematopoietic stem cell transplantation
Hemovigilance

ABSTRACT

Adverse events (AEs) associated with blood transfusions, including component-specific red cell, platelet, and plasma products, have been extensively surveyed. In contrast, surveillance of AEs associated with hematopoietic stem cell (HSC) products in HSC transplantation (HSCT) has been less rigorous, even though HSC products include a diversity of immature and mature hematopoietic cells, substantial plasma, and dimethyl sulfoxide (DMSO) in the case of cryopreserved HSC products. HSC infusion-related AEs have been attributed to DMSO toxicity, but AEs associated with the infusion of noncryopreserved HSC products are not uncommon. To quantify the frequencies, types, and risk factors of HSC infusion-related AEs, we implemented national surveillance for AEs observed within 24 hours after infusion. Herein we report on 1125 HSCTs, including 570 peripheral blood stem cell transplantations (PBSCTs) (290 autologous [auto-] and 280 allogeneic [allo-]), 332 allo-bone marrow transplantations (allo-BMTs) and 223 allo-cord blood transplantations (allo-CBTs). Unexpectedly, incidences of grade ≥ 2 AEs were most frequent in allo-BMTs (37.7%) with no DMSO in any product compared with auto-/allo-PBSCTs (20.9%, $P < .001$) and allo-CBTs (19.3%, $P < .001$) typically cryopreserved with DMSO. Hypertension was most often noted in BMTs, whereas nausea/vomiting, fever, and allergic reactions were most frequent in allo-PBSCTs. In a multivariate analysis, a history of transfusion reactions was a risk factor for overall AEs in all HSCTs (odds ratio [OR] = 1.459, $P = .045$). For grade ≥ 2 AEs in allo-HSCTs, a history of transfusion reactions (OR = 1.551, $P = .044$) for overall AEs, and high infusion volume (OR = 7.544, $P = .005$) and allo-PBSCTs (versus BMTs, OR = 9.948, $P = .002$) for allergic reactions were identified as risk factors. These findings suggest that some factors unrelated to DMSO, such as allo-antigens, contribute to HSC infusion-related AEs. As severe AEs, a total of 117 grade ≥ 3 AEs were reported in 1125 HSCTs, including life-threatening complications in 3 (0.3%) HSCTs: 1 allo-CBT (anaphylaxis) and 2 allo-PBSCTs (hypoxia, kidney injury) with cryopreserved product. Our data show that HSC infusion risks vary by product, can be severe, and should be monitored with the same rigor as modern transfusion hemovigilance programs.

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https://doi.org/10.1016/j.tmrv.2018.05.005
0887-7963/

Please cite this article as: Ikeda K, et al, Adverse Events Associated With Infusion of Hematopoietic Stem Cell Products: A Prospective and Multicenter Surveillance Study, Transfus Med Rev (2018), https://doi.org/10.1016/j.tmrv.2018.05.005

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This study was supported by funding from the Japan Society of Transfusion Medicine and Cell Therapy to HO, and a research grant from the Ministry of Health, Labor, and Welfare and funding from the Japan Agency for Medical Research and Development to RT.

Hematopoietic stem cell (HSC) transplantations (HSCTs), including peripheral blood stem cell (PBSC) transplantation (PBSCT), bone marrow (BM) transplantation (BMT), and cord blood (CB) transplantation (CBT), are a powerful strategy to potentially cure various hematologic malignancies but often cause severe complications such as conditioning regimen-related toxicities to the lungs, kidneys, cardiovascular system, and various other organs; veno-occlusive disease/sinusoidal obstruction syndrome; infections; and graft-vs-host disease [1, 2]. PBSC is used as a source for both autologous (auto-) and allogeneic (allo-) transplantations. For auto-PBSCT, the product is always cryopreserved, whereas either cryopreserved or noncryopreserved product is used for allo-PBSCT. Noncryopreserved BM is used as an allo-transplantation source. CB is routinely cryopreserved and used for allo-transplantation. In the HSCTs, around the timing of HSC infusion when acute regimen-related toxicities often occur, HSC infusion itself is also known to lead to adverse events (AEs), such as flushing, nausea/vomiting, malodor, hypotension, hypertension, allergic reactions, arrhythmia, encephalopathy, and respiratory distress [3]. Notably, very severe or even fatal HSC infusion-related AEs have been reported [4-9]. Thus, it may be important to recognize HSC infusion-related AEs as well as regimen-related toxicities around the timing of HSC infusion.

The HSC infusion-related AEs have been attributed to the toxicity of dimethyl sulfoxide (DMSO) and dead cells in patients who undergo HSCT with the cryopreserved HSC product [3, 10-13]. However, patients' age and disease correlate with the incidences of HSC infusion-related AEs, and DMSO removal shows a limited effect on reducing AEs [3]. Moreover, infusions of noncryopreserved HSC products also cause AEs [5, 14]. These findings indicate that not only DMSO but also other components contribute to HSC infusion-related AEs.

AEs associated with blood transfusions, in which component-specific, differentiated red blood cells (RBCs), platelets, or plasma are infused as products, have been routinely and systemically surveyed through hemovigilance programs [15, 16]. Transfusion reactions are the most frequent AEs associated with infusion of allo-blood products but only occur in less than 1% of blood transfusions. Compared with the products for blood transfusions, HSC products contain cruder components such as immature and mature hematopoietic cells, plasma components, and DMSO. However, AEs associated with the infusion of HSC products in HSCT have been poorly investigated. In previous retrospective studies, which have focused on the toxicities of DMSO rather than other components, the frequencies of HSC infusion-related AEs have widely ranged [14]. In addition, differences among HSC sources and between cryopreserved and noncryopreserved products or auto- and allo-products have not been sufficiently addressed.

Here, we prospectively investigated the frequency and severity of AEs associated with infusion of HSC products among HSC sources and cryopreservation status in more than 1000 auto- and allo-HSCTs performed in several Japanese hospitals. This study clarified the infusion risks of HSC products, varying among the types of HSCTs, and identified risk factors for HSC infusion-related AEs.

Materials and Methods

Study Design

This is a nationwide prospective surveillance study which was carried out under the leadership of the Cell Therapy Committee in the Japan Society of Transfusion Medicine and Cell Therapy (JSTMCT) and registered at http://www.umin.ac.jp/ctr/index.htm as #UMIN000012095. We surveyed AEs that occurred within 24 hours after starting the infusions of HSC products in all HSCT procedures performed in 16 hospitals certified for HSCTs in Japan from September 1, 2013, to July 31, 2016, targeting 1000 recipients. This study was approved by the Ethics Review Boards of the JSTMCT and all attending institutions, which are guided by local policy, national law, and the Declaration of Helsinki.

Preparations and Infusions of HSC Products

All the products, including grafts for CBT, were derived from a single donor. Total BM cells were collected from the iliac crest, mixed with

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