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Co-transplantation of multipotent mesenchymal stromal cells in allogeneic hematopoietic stem cell transplantation: A systematic review and meta-analysis

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Abstract

Background aims. Allogeneic hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment option for patients with hematological malignancies. Co-transplantation of multipotent mesenchymal stromal cells (MSCs) during allogeneic HSCT has been explored to enhance engraftment and decrease the risk of graft-versus-host disease (GVHD). We aimed to identify, evaluate and summarize the findings of all relevant controlled clinical studies to determine the potential benefits of MSC infusion during allogeneic HSCT, with regard to the outcomes engraftment, GVHD, post-transplant relapse and survival. *Methods.* We conducted a systematic search of electronic databases for relevant controlled clinical studies. Studies included patients of all ages with hematological malignancies receiving allogeneic HSCT with or without infusion of MSCs within a 24-h time frame of transplantation. *Results.* Nine studies met our inclusion criteria, including three randomized, one non-randomized and five historically controlled trials, representing a total of 309 patients. Our meta-analyses did not reveal any statistically significant differences in donor engraftment or GVHD. A review of data regarding relapse and overall survival may result in a positive attitude toward intervention with MSCs, but due to heterogeneous reporting, it is difficult to draw any strict conclusions. None of the studies had overall serious risks of bias, but the quality of the evidence is low. *Conclusions.* Meta-analysis did not reveal any statistically significant effects of MSC co-transplantation, but the results must be interpreted with caution because of the weak study design and small study populations. We discuss further needs to explore the potential effects of MSCs in a HSCT setting.

Key Words: *Allogeneic hematopoietic stem cell transplantation, Engraftment, Evidence-based practice, Graft-versus-host disease, Multipotent mesenchymal stromal cells, Systematic review*

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is an established curative treatment modality for patients with severe malignant and non-malignant hematological diseases. The patients are prepared with a high dose of chemo- and/or radiotherapy, followed by intravenous infusion of hematopoietic stem cells (HSCs) [1]. Shortly after infusion, the HSCs will leave circulation and home to extravascular spaces to engraft in the patient's bone marrow (BM). During a successful engraftment, the HSCs repopulate and reconstitute hematopoiesis in the BM. The engraftment of HSCs depends on several factors including: (i) the intensity of the preparative regimen, (ii) the transplanted stem cell dose, (iii) the degree of histocompatibility mismatch between donor and recipient, (iv) the T-cell content in the graft and (v) the intensity of post-transplant immunosuppression [1].

A common major complication in patients undergoing allogeneic HSCT is immune-mediated graft-versus-host disease (GVHD), which may occur as acute GVHD (aGVHD) or chronic GVHD (cGVHD). Grading systems have been developed to define the severity of GVHD; patients with grade III and grade IV aGVHD have estimated 5-year survival rates of 25% and 5%, respectively [2], and increasing severity of cGVHD is associated with increased treatment-related mortality [3]. Other major causes of death include relapse (approximately 30% of deaths) and infections (10% of deaths) where most deaths occur within the first 2 years after allogeneic HSCT [4,5].

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Several therapeutic approaches are being explored to reduce the development of GVHD and the incidence of relapse, including the use of multipotent mesenchymal stromal cells (MSCs) as a cell-based therapeutic approach.

The term "multipotent mesenchymal stromal cells" has been defined by he International Society for Cellular Therapy and describes cells that are self-renewing, adhere to plastic, express specific surface antigens and have multilineage potential *in vitro* to differentiate to cell types of mesodermal origin [6,7]. MSCs can be derived from several sources such as adult BM, adipose tissue and several fetal tissues [6,7], however, BM and umbilical cord blood (UCB) are the most commonly used sources to obtain MSCs for clinical use. Interest in MSCs has risen dramatically over the past decade due to MSCs self-renewal potential, vast differentiation capacity and immune modulating properties. A vast amount of studies have explored the use of MSCs as cellular therapy in a broad range of fields, including as a therapeutic approach during or after HSCT [8]. Preclinical animal studies have shown improved engraftment of HSCs and decreased risk of GVHD after co-transplantation of *ex vivo* expanded human MSCs and HSCs [9–12], and this has encouraged further investigations into the clinical usage of MSC therapy aiming to improve transplantation outcomes after allogeneic HSCT in patients with hematological malignancies. However, although several preclinical and clinical studies with MSCs have been conducted, the results have been mixed and the efficacy of MSCs in a transplantation setting is so far unclear.

In this systematic review, we focus on the potential effects of MSCs co-transplanted with allogeneic HSCs for patients with severe hematological malignancies. Favourable outcomes for patients undergoing HSCT are (i) improved engraftment and avoidance of graft failure, (ii) reduced serious complications such as GVHD, (iii) reduced incidence of post-transplant relapse and (iv) improved survival, and we have used these outcomes in our evaluation of the clinical studies. We have evaluated the evidence from clinical randomized and non-randomized controlled studies robustly for effectiveness, and performed a meta-analysis for the outcomes where available data made this possible. For outcomes not found suitable for meta-analysis, the results are represented in tables with narrative review.

Methods

Search strategy

An extensive and systematic search for relevant studies without language restriction was conducted in the databases MEDLINE (Ovid), Embase (Ovid), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and the Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley), Web of Science (Thomson Reuters) and Inspec (Thomson Reuters); all databases were searched from their inception until May 27, 2015. The search strategies included the subject headings "Hematologic Diseases," "Mesenchymal Stem Cell Transplantation" and "Hematopoietic Stem Cell Transplantation"; the complete search strategy is available in Supplementary Table S1. The abstracts and titles identified in the searches were screened independently by two reviewers and full texts were retrieved if one or both selected the item as relevant to the study. Duplicates were eliminated electronically. The reference lists in the retrieved full text review articles were also screened for any additional relevant studies. Corresponding authors of the included studies were contacted and asked if they were aware of any other published or ongoing studies that could meet our inclusion criteria.

Eligibility criteria

We sought to include randomized or non-randomized controlled trials (RCTs or NRCTs, respectively) in which the majority of the study participants had a malignant hematological disease. Studies included patients of all ages receiving an allogeneic HSCT with administration of MSCs within a ± 24-h time frame. All sources of stem cells as well as different donor relations (related and unrelated, matched and unmatched), of both MSCs and HSCs, could be applied. Eligible comparator interventions were patients receiving HSCT alone, alternatively HSCT plus placebo, whereas studies using MSCs in other settings or in combination with other experimental cells and/or treatments were excluded. To be included, the studies had to report one or more of the following outcomes: (i) neutrophil engraftment, (ii) GVHD, (iii) relapse and/or (iv) survival. Finally, only studies published as full articles in English or Scandinavian languages were included. On the basis of title and abstract, the studies were reviewed manually, and inclusion was agreed on by two authors independently. The inclusion criteria were then applied to the studies retrieved in full text and any differences in opinion on whether a study should be included were resolved through discussion.

Data extraction and quality assessment

Data extraction was conducted by two authors independently using a standardized data extraction form according to the guidelines proposed by the Cochrane Collaboration [13], consisting of study characteristics, participant information, intervention characteristics and outcomes. The extraction form was