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Hemopoietic stem cell transplantation in rheumatic diseases—an update

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Abstract

Hematopoietic stem cell transplant (HSCT) for autoimmune diseases has been recognized as a potential treatment for patients who have failed conventional therapy. Autologous (self) donor cells have been preferred over allogeneic (HLA-matched) cells for rescue after high dose immunotherapy, given the previous higher rates of mortality, graft versus host disease (GVHD), and the need for more intense myeloablation associated with the latter. The European Group for bone Marrow Transplantation in Basel Switzerland (EBMT) and various groups within the US funded by the NIH (including the Autologous Blood and Marrow Transplant Registry (ABMTR)) have been pivotal in maintaining registries on patients transplanted as well as promoting homogeneity for future studies including Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE) and Systemic Sclerosis (SSc). Although, patients transplanted for RA show initial success, relapse of the disease is common. In many, however, a second positive result can be obtained with the addition of DMARD therapy to which they were previously unresponsive, suggesting a "debulking" of disease by HSCT. SLE patients also have a high rate of success after HSCT, although current mortality rates appear high. Transplant in SSc patients has offered durable responses with improving transplant-related mortality related to careful patient selection.

Keywords: Hematopoietic stem cell transplant; Systemic sclerosis; Rheumatoid arthritis; Systemic lupus erythematosus; Autologous

Contents

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Since 1995, over 500 patients reported to the European Group for bone Marrow Transplantation (EMBT) registry have undergone HSCT for the treatment of autoimmune diseases [1]. The initial success in both experimental animal models and HSCT in patients with malignancy and concomitant autoimmune disease provided the initial motivation for the Phase I/II trials in selected diseases. Although successful outcomes in many autoimmune diseases have been attributed to HSCT, recent large analyses on RA, SLE, and SSc have been published and are herein reviewed. The pivotal trials are summarized in Table 1.

1. Rheumatoid Arthritis (RA)

An estimated 25% of RA patients do not respond to established DMARD therapy despite the introduction of tumor necrosis factor-alpha (TNF-a) antagonist treatment [2]. Autologous HSCT offers promise to refractory patients, but given the expense and potential morbidity, patient selection is crucial, and guidelines for candidates have been established by EMBT/EULAR based on predictors of poor outcome such as DMARD failures including TNF-a antagonist therapy [3].

In 2004, Snowden published an analysis of the worldwide experience for autologous HSCT in RA including 73 patients from the European and US registries [4]. HSCT regimens varied, however the majority of patients received granulocyte colony stimulating factor (G-CSF 5–12 μg/kg once or twice a day) and cyclophosphamide (CYC 2–4 g/m^2) for mobilization of progenitor cells (CD34$^+$) from the bone marrow to the peripheral blood for collection. After stem cell collection, cyclophosphamide 200 mg/kg was typically administered as the conditioning phase of the procedure for immunosuppression. Based on an early study in RA patients, the dose of 200 mg/kg was chosen over 100 mg/kg as it prolonged the time of remission without added toxicity (details of the study in Table 1) [5]. Other agents, including more myeloablative therapy such as busulfan, antithymocyte globulin, and total body irradiation were also used.

Stem cell rescue was preceded in most cases by graft manipulation, a process of ex-vivo selection of CD34$^+$ progenitor cells, or selective elimination of T cells with antibodies. The procedure is expensive, can increase the time of immunosuppression and graft failure, but is supported by consensus guidelines as a necessary step in reducing the theoretical risk of re-infusing autoreactive cells [6]. The largest study included in Snowden's analysis was by Moore et al. in 33 RA patients undergoing HSCT. They evaluated the importance of graft manipulation in two RA cohorts: one cohort received CD34$^+$ selected stem cells while another cohort received unmanipulated stem cells. Although the numbers are not powered for significance, American College of Rheumatology (ACR) responses were equally favorable in both groups and the relapse rate between cohorts was not significant (details in Table 1) [6].

The efficacy measures used after HSCT in 73 RA patients in Snowden's analysis included best overall ACR response, 6–12 month follow-up data, relapse rate, and mortality. Among 73 patients who underwent autologous HSCT, best ACR overall response included 3 (4%) in remission, 33 (45%) achieving an ACR 20% response, 13 (17.8%) achieving an ACR 50% response, and 12 (16%) with an ACR 70% response. Twelve patients (16%) did not respond, including 1 death due to sepsis (Transplant Related Mortality (TRM) was 1.4%). Relapse with disease activity requiring the re-institution of DMARDs occurred in 92% of evaluable patients. In evaluable patients (n=43) who restarted DMARDs, 21/43 (49%) were described as doing better than prior to transplant, and 22/43 (51%) were the same or worse. The results suggest HSCT may "debulk" the burden of the disease, allowing DMARDs to become effective in many. The Dutch group also supported this theory in their evaluation of 12 patients undergoing HSCT for RA, where 6 patients with a sustained response were