



Review

Hematopoietic stem cell transplantation for autoimmune diseases: What have we learned?

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Abstract

Numerous individuals and institutions throughout the world have contributed to the development of hematopoietic stem cell transplantation (HSCT) for autoimmune diseases. In this review, we will summarize what we have learned at our own institution (Northwestern University), and how it has guided our therapy. An emphasis will be placed on both the scientific basis for the development of autologous hematopoietic stem cell transplantation and a summary of the data in a variety of human diseases.

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1. Animal models

Autologous hematopoietic stem cell transplantation (HSCT) for autoimmune diseases is based on the rationale of using chemotherapy for ablation of an aberrant or “self-reactive” immune system and regeneration of a new and hopefully self-tolerant immune system from hematopoietic stem cells (HSC). Pre-clinical data to support this rationale was derived from animal models of autoimmune diseases. In some cases, the disease is predominately a genetically pre-ordained HSC defect that arises spontaneously and in other examples requires environmental stimuli such as immunization with self-peptides or adjuvant. Examples of the former include type I diabetes in NOD (non-obese diabetic) mice, while the latter includes EAE (experimental autoimmune encephalomyelitis) a demyelinating multiple sclerosis like disease induced by immunization with myelin peptides. Animal autoimmune diseases that arise spontaneously require an allogeneic stem cell transplant using a disease resistant donor for cure. In comparison,

environmentally induced autoimmune diseases may be cured with syngeneic (the animal analogy for autologous) HSCT.

In our experience at Northwestern University, performing HSCT in EAE, an environmentally induced autoimmune disease, and in NOD mice, a spontaneous onset autoimmune diabetes, we have gleaned some insights that may also be applicable to humans. While animal HSC are collected by flushing bone marrow cells from a surgically amputated femur, most human HSCT utilize peripheral blood stem cells (PBSC) mobilized into the blood with a growth factor/cytokine and collected by leukopheresis. It is standard practice to use a growth factor such as neupogen (G-CSF) to mobilize hematopoietic stem cells (HSC) in normal donors and in patients with cancer. These growth factors may, depending on the disease, exacerbate or flare an autoimmune disease. We, therefore, evaluated the effect of various cytokines on disease severity in EAE, the animal model for multiple sclerosis [1]. Most cytokines including G-CSF caused irreversibly deterioration in neurologic function and some such as flt-3L caused lethal disease exacerbation [1]. A notable exception was thrombopoietin (TPO) that mobilizes stem cells without flaring EAE [1].

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While EAE, an animal model of multiple sclerosis, enters durable remission following syngeneic HSCT, we found that auto-reactive myelin-specific T cell clones remain *in vivo* after transplantation [2]. These clones proliferate *ex vivo* to the disease initiating protein as well as spread epitopes of myelin [2], and disease may recur with re-immunization to myelin peptides. Self-reactive T cells persisted or recurred *in vivo* despite utilizing an intense myeloablative total body irradiation (TBI) conditioning regimen. This implies that autologous HSCT achieves immune reset and disease remission but does not eliminate autoreactive repertoires that may, under appropriate conditions, reactivate disease, either because these repertoires are normal and regenerate after the transplant, albeit are initially self-tolerant, are reintroduced with the graft, or are memory T cells that survive the conditioning regimen even after intense myeloablative TBI. We also demonstrated that for EAE, an immune-mediated demyelinating disease, neurologic improvement after autologous HSCT depends on disease stage at the time of transplant [2]. Neurologic disability markedly improves when syngeneic HSCT is performed during the early acute phase of disease but has no discernable beneficial clinical effect in chronic EAE [2]. In other words, autologous HSCT is effective for the inflammatory but not degenerative stages of disease.

In contrast to environmentally induced autoimmune diseases, spontaneous onset autoimmune diseases require an allogeneic HSCT for sustained disease remission. The immune suppressive conditioning regimen not only allows for immune reset but facilitates engraftment of allogeneic HSC and regeneration of a new immune system from a genetically distinct and hopefully disease resistant stem cell compartment that should prevent disease recurrence. The phenomena by which engrafted allogeneic HSC prevent autoimmune disease recurrence has been termed graft versus autoimmunity (GVA) [3,4].

Allogeneic lymphocytes facilitate full donor engraftment by eliminating residual host hematopoiesis, but also cause graft versus host disease (GVHD), a potentially lethal immune-mediated disorder. In malignancies, the benefit from lymphocyte depletion of the allograft in terms of less GVHD is obscured by recurrence of leukemia from residual host hematopoiesis. In autoimmune diabetes, we have demonstrated in NOD mice that diabetes may be prevented and islet cell tolerance induced, that is a GVA phenomena may occur, without GVHD by using embryonic stem cell-derived HSC that are completely devoid, by virtue of *ex vivo* production, of any contaminating lymphocytes [5]. Thus allogeneic mixed chimerism, that is co-existence of both donor and host hematopoiesis, appears to be sufficient to achieve and maintain remission of autoimmune diseases without GVHD.

In summary, depending on the disease, growth factors used for mobilization may flare symptoms. Since, TPO is not commercially available for clinical usage in America, depending upon disease, a therapeutic mobilization using cyclophosphamide (2 g/m²) prior to G-CSF to ameliorate disease activity during mobilization should be considered. Second, an autologous HSCT, even when using an intense myeloablative regimen, does not completely eliminate all self-reactive T cells

but does allow an immune reset that induces disease remission. Therefore, the rationale for using intense and more toxic myeloablative regimens that is based on the supposition of completely ablating autoreactive repertoires is suspect. Thus, our approach, knowing that complete immune ablation cannot be achieved, is to achieve immune reconstitution and thus “immune reset” by designing optimal autologous non-myeloablative immune-specific regimens. Third, allogeneic HSCT should be designed to minimize the risk of GVHD by utilizing *in vivo* or *ex vivo* lymphocyte depletion which despite achieving only low level donor mixed chimerism can, in animal models, induce self tolerance without GVHD.

2. Human trials

At Northwestern University, we have performed 200 HSCT for immune-mediated diseases. The most common indications for HSCT at our center are systemic lupus erythematosus, multiple sclerosis, systemic sclerosis, and Crohn’s disease. Other indications have included chronic inflammatory demyelinating polyneuropathy, myasthenia gravis, rheumatoid arthritis, polymyositis, autoimmune related retinitis and optic neuritis (ARRON syndrome), vasculitis (Behçet’s, Sjögren’s, Wegner’s), and sarcoidosis. Through this experience we have drawn several general conclusions.

- (1) Treatment-related mortality needs to be very low for non-malignant diseases. To minimize mortality, the regimens we generally utilized for autologous HSCT of autoimmune diseases are non-myeloablative. Non-myeloablative regimens are safer than myeloablative regimens. The rationale of an autologous HSCT for immune-mediated disorders is maximal suppression of the immune system without irreversible ablation of the entire bone marrow compartment [6]. Following a non-myeloablative regimen, hematopoietic recovery *will* occur without infusion of HSC; however autologous HSC provide support and shorten the duration of chemotherapy induced neutropenia. White blood cell and platelet engraftment is more rapid following a non-myeloablative regimen compared to a TBI containing myeloablative regimen [7]. It is probable that the longer the duration of disease, the more organ systems damaged, and the longer accumulated duration of prior therapies, the higher the risk differential between myeloablative and non-myeloablative regimens. Myeloablative regimens used to treat breast cancer had 2% TRM in patients generally not immune suppressed and with otherwise normal organ function. In comparison, initial experience in autologous HSCT for autoimmune diseases in the EBMT registry was 11% TRM [8] and most recently with more experience and more careful patient selection TRM is 7% with higher TRM from more intense, i.e. myeloablative regimens [9]. TRM has fluctuated widely between centers and regimens. In one American study using a TBI containing myeloablative regimen for scleroderma, TRM was reported to be 23% (8 of 34 patients) [10]. At

Northwestern University, the TRM using non-myeloablative regimens is 1.6% (3 of 180 patients).

- (2) Although it is possible that a percentage of patients may be cured, until and unless proven otherwise, autologous HSCT for autoimmune diseases should not be viewed as a cure but rather as changing the natural history of the disease. Investigators should consider this more realistic expectation in justifying mortality endpoints from myeloablative versus non-myeloablative regimens. In fact, similar to syngeneic HSCT in animal models, autologous HSCT, even when using aggressive myeloablative regimens containing TBI, does not completely eliminate serologic markers or clonal repertoires. Autologous HSCT achieves an immune reset and immune regeneration after HSCT [11,12], and the new immune system's default is to regenerate self-tolerance. However, true immune ablation with elimination of all autoreactive memory cells does not occur even with aggressive TBI containing myeloablative regimens.
- (3) Depending on disease, growth factor alone or therapeutic mobilization utilizing cyclophosphamide (2 g/m²) and G-CSF may be used to collect HSC. Therapeutic mobilizations may be associated with infectious complications but tend to ameliorate autoimmune disease activity and has been reported to decrease relapse compared to PBSC mobilization with growth factor alone [9].
- (4) Avoid conditioning agents that will further damage already injured organs. Unlike what happens in cancer, in which visceral organ dysfunction is a contraindication for HSCT, in immune-mediated diseases some organ damage often provides the indication for HSCT. Similarly, avoid late toxicities of the conditioning regimen such as life-threatening malignancies that occur years later. Immune-mediated diseases, may, despite significant morbidity, spontaneously remit or "burn out". While probability of bad outcome can be determined for a given population, individual patients who will remit spontaneously cannot be excluded *a priori*. It is not appropriate to expose a subset of patients who will remit without HSCT to agents such as total body irradiation that cause a relatively high incidence of a more lethal disease, i.e. myelodysplastic syndrome (MDS)/leukemia. The incidence of second malignancies in follicular (low grade) lymphomas treated with autologous HSCT is currently the best analogy for anticipated transplant induced malignancies in autoimmune diseases. Using a TBI regimen for low grade lymphomas, one study reported a 28% incidence of secondary malignancies, 10% due to MDS (leukemia) [13]. Another study compared TBI to non-TBI autologous HSCT regimens for low grade lymphomas with a 8.5% incidence of MDS/leukemia following a TBI regimen compared to 1.7% for non-TBI regimens [14]. Treatment of systemic sclerosis and multiple sclerosis with TBI containing regimens has already been reported to be complicated by MDS/leukemia [10,15]. Of 34 patients with systemic sclerosis treated with a myeloablative TBI containing regimen, 8 died from treatment, 4 died from disease progression, and 2 of the surviving 22 patients (10%) developed MDS [10]. A TBI regimen used for autologous HSCT of multiple sclerosis was complicated by 1 of 14 patients developing MDS/leukemia [15]. The incidence of MDS, leukemia, and secondary cancer in autoimmune diseases treated with myeloablative TBI containing conditioning agents is probably being under-estimated since most initial publications do not have long term follow-up. Secondary malignancies from different conditioning regimens, correlated with prior long-term exposure to cyclophosphamide and chronic immune suppressive agents, needs to be evaluated and reported from registry data.
- (5) Limit HSCT to the inflammatory stage of the disease. Degenerative non-inflammatory stages of the disease will probably not respond. The outcome of myeloablative TBI containing regimens in late secondary progressive multiple sclerosis, which is predominately an axonal degenerative disease, is similar to syngeneic HSCT in chronic EAE, that is of no benefit [16]. In contrast for systemic sclerosis, depending on type of graft, fibrosis may reverse following HSCT. There is some data that an allogeneic HSCT can reverse dermal fibrosis [17] and may reverse pulmonary fibrosis and lower pulmonary artery pressure [18].
- (6) Treating earlier in the disease course while the disease is still inflammatory, before organ dysfunction, and before exposure to long term immunosuppression will likely improve safety and efficacy for both myeloablative and non-myeloablative regimens.
- (7) Manipulation or CD34 selection of the graft will increase infections [19] and to date has not been demonstrated to improve efficacy. The only publication comparing selected to unselected grafts suggests that this maneuver may even shorten remission duration [20]. However, the conditioning regimen and method of mobilizing PBSC may affect the need for CD34 selection. For example, it is conceivable that CD34 selection may decrease relapse if therapeutic mobilization with cyclophosphamide which has an *in vivo* purging effect is not used to collect HSC, and if antibodies such as antithymocyte globulin that lymphocyte deplete the reinfused graft *in vivo* are not utilized in the regimen. There currently exists virtually no firm data on the benefit of CD34 selection, that is lymphocyte depletion, of the autograft.
- (8) Secondary autoimmune disorders may arise from the conditioning regimen itself. Our standard non-myeloablative regimen of cyclophosphamide (200 mg/kg) and rabbit antithymocyte globulin (rATG) was well tolerated. Our second generation regimen utilized cyclophosphamide and a broader and longer acting agent, alemtuzumab, instead of rATG. Secondary immune-mediated cytopenias including idiopathic thrombocytopenic purpura, neutropenia, and autoimmune hemolytic anemia occurred from 2 to 18 months after HSCT, necessitating discontinuation of that regimen [21]. Our current third generation non-myeloablative regimen is termed "rituximab sandwich" in which one dose of rituximab (500 mg) is given before and after cyclophosphamide (200 mg/kg) and rATG (6.0 mg/kg). To date this regimen has been well tolerated.

(9) Besides the above experience in autologous HSCT for autoimmune diseases, we have initiated non-myeloablative allogeneic HSCT protocols for selected patients with HLA matched siblings. The number of patients treated is too small for definitive conclusions, but a potent GVA affect, similar to our animal experiments, with stable mixed chimerism and disease remission including serologic remissions have occurred without any GVHD [18,22]. Either CD34⁺ selection and/or inclusion of alemtuzumab in the conditioning regimen for *in vivo* donor lymphocyte depletion are used to prevent GVHD. After allogeneic HSCT, we maintain patients on cyclosporine for 1 month and cellcept for 9 months to minimize host versus graft disease, i.e. to prevent graft rejection.

3. Summary

In America there are two philosophically divergent approaches towards autologous HSCT for autoimmune diseases. One group advocates aggressive myeloablative regimens that contains total body irradiation which they believe may be more effective than non-myeloablative regimens [6,10]. We, on the other hand, advocate non-myeloablative regimens that do not have radiation [6,23–25]. It is our concern that myeloablative regimens are too toxic and their risk benefit is not justified for autoimmune diseases. While patient selection, e.g. treating very early after disease onset, with limited organ dysfunction, and before therapy with other immune suppressive agents will certainly diminish the transplant morbidity of any conditioning regimen, there remains an undetermined but possibly significant late risk of MDS/leukemia and solid tumors from TBI. It is also our bias from animal models and clinical experience that autologous HSCT, no matter what the regimen, does not cause complete *in vivo* lymphodepletion. Autoreactive memory cells survive and autoantibodies, while significantly diminished, generally remain positive. In terms of risk benefit, autologous HSCT should be viewed as changing the natural history of disease rather than a cure.

On the other hand, allogeneic HSCT by altering genetic predisposition is more likely to “cure” autoimmune diseases. Again, in America, there are two divergent philosophical approaches to allogeneic HSCT for autoimmune diseases. One group utilizes an unmanipulated allograft which has resulted in GVHD-related mortality [17]. In contrast, it is our bias that GVHD is an unacceptable risk for autoimmune diseases. We, therefore, advocate either an *in vivo* or *ex vivo* lymphocyte depleted allograft [18,22]. In animal models GVA may occur without GVHD despite relatively low level (5–10%) donor engraftment. The safety and superiority of these different approaches for both autologous and allogeneic HSCT, and the “optimal” conditioning regimen and graft composition will only be clarified with time and may perhaps require randomized comparative trials. More additional information on hematopoietic stem cell transplantation is provided in other papers in this special issue of the *Journal of Autoimmunity* [26–36]. We have not attempted to focus on mechanisms of

autoimmunity or related papers on various autoimmune diseases but refer to recent literature published in this journal [37–57].

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