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Stem cell therapy for autoimmune disease: overview of concepts from the Snowbird 2002 tolerance and tissue regeneration meeting

RK Burt[1], R Arnold[2], R Emmons[3], Y Oyama[1] and A Marmont[4]

[1]*Northwestern University Medical Center, Chicago IL, USA;* [2]*University Hospital Charite, Berlin, Germany;* [3]*University of Massachusetts, USA; and* [4]*Bone Marrow and Blood Transplantation Center, S Martino's Hospital, Genoa, Italy*

Summary:

Hematopoietic stem cell transplantation as a treatment for autoimmune disease began in 1996 and has subsequently spread worldwide. In Europe phase III trials have opened, while in America phase III trials are being designed and funded by the National Institutes of Health. On 6 June 2002, clinicians and scientists from around the world met at Snowbird, Utah to discuss the results and future directions of stem cell therapy for autoimmune diseases. What follows are general concepts from chairpersons of this meeting.
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Philosophy of autologous HSCT for autoimmune diseases: immune ablation *vs* immune balance

There are two slightly different philosophical ideas behind development of autologous hematopoietic stem cell transplantation (HSCT) for autoimmune disease. One notion is to ablate all autoreactive immune cells with the conditioning regimen. Advocates of this position use the terminology high-dose immune suppressive therapy (HDIT).[1] It is a notion borrowed from the field of malignancies in which every single viable malignant cell is pathologic. For malignancies, conditioning regimens for autologous HSCT are designed to maximally reduce or hopefully eliminate malignant clones. While this approach towards autoimmune diseases can achieve intense immune suppression, elimination of the last resting memory lymphocyte with high-dose chemotherapy or chemoradiotherapy is in practice not feasible. As learned from autologous HSCT for most malignancies, chemoradiotherapy can reduce by several logs but not completely eliminate all tumor cells. In many cases cure is only possible by an allogeneic HSCT with adoptive transfer of the donor's lymphocytes mediating an immunotherapeutic antitumor effect termed graft-versus-leukemia (GVL).[2,3] Similarly, complete immune ablation, the philosophical goal of HDIT and autologous HSC support, would probably require the graft-versus-auto-immune (GVA) effect of an allogeneic HSCT to be realized.[4,5]

A second or alternative concept is one of immune 'reset' or immune 'balance'.[6] In this notion, autoreactive cells unlike a malignant cell are 'normal'. During development, T cells that bind self with high avidity undergo apoptosis.[7–9] However, T cells that fail to recognize a self-epitope also undergo apoptosis.[7–9] Therefore, circulating T-cells in a healthy person normally posseses a T-cell receptor repertoire selected to self. Immune cells unlike malignant cells are not intrinsically bad but rather in a dynamic equilibrium that maintains steady state by constantly fluctuating between tolerance and immunity. This dynamic state is best demonstrated by the intermittent clinical course of some autoimmune diseases such as relapsing-remitting multiple sclerosis that flares and remits spontaneously even without treatment. Using the notion of immune balance, the conditioning regimen is not intended to destroy every immune cell but rather be sufficient enough to restore immune 'balance'.

In practice, the philosophy of HDIT leads to maximal immune suppressive regimens that have been accompanied by infection-related as well as regimen-related mortality.[10] In comparison, the notion of immune balance leads to less intense regimens that are more easily tolerated and have less infection-related risk. Whether one concept or the other is correct remains unclear. There are currently no data to support more intense regimens over less toxic regimens in terms of disease remission or relapse rate. The appropriate regimen intensity may vary by disease. For example, cyclophosphamide +/− ATG appears inadequate for complete responses or sustained untreated partial responses in rheumatoid arthritis.[11] Yet this same regimen appears highly effective in systemic lupus erythematosus.[12] Whatever the most appropriate concept for a given disease, it is probably prudent to determine outcome with less intense regimens before testing more intense and potentially more toxic conditioning regimens.

Correspondence: Dr RK Burt, Northwestern University Medical Center, 320 East Superior, Searle, Room 3-489 Chicago, IL 60611, USA.
E-mail: rburt@nwu.edu

Autoimmune diseases likely to respond to autologous HSCT

For malignancies, autologous HSCT is generally appropriate if the disease is chemotherapy responsive. The concept is to dose escalate disease responsive drugs to myeloablation followed by rescue with autologous hematopoietic stem cells (HSC). A chemotherapy nonresponsive cancer such as pancreatic cancer or squamous cell lung cancer would not be appropriate for consideration of autologous HSCT. Similarly, autoimmune diseases that are responsive to immunosuppressive therapy appear to be responsive to dose escalation and autologous HSCT. Examples of immune responsive diseases are systemic lupus erythematosus (SLE), Crohn's disease, pemphigus, relapsing-polychondritis, relapsing-remitting multiple sclerosis (MS), rheumatoid arthritis, and juvenile idiopathic arthritis. Response does not seem to be dependent on cytokine profile since Lupus and Crohn's disease that are Th2 and Th1 skewed, respectively, seem to respond equally well. Traditional immune nonresponsive diseases such as primary progressive MS and late secondary progressive MS show little or no improvement following autologous HSCT. However, marginally immune responsive diseases such as scleroderma have generally demonstrated improved skin flexibility and quality of life but little improvement in visceral function. Therefore, autoimmune diseases that traditionally respond to standard dose immune suppression appear to be the best candidates for dose escalation of immune suppression with autologous HSC support.

Selection of conditioning regimen agents

In malignancies, selection of a conditioning regimen agent is based on dose escalation of a drug effective at standard doses. Dose escalation of a noneffective drug would not be included in the regimen since it would result in increased toxicity without efficacy. Ideally, selection of autoimmune conditioning agents should be based on dose escalation of effective agents given at standard doses. SLE is highly responsive to cyclophosphamide, and dose escalation of cyclophosphamide as a conditioning agent has achieved impressive responses.[12] Systemic sclerosis, a disease unresponsive to virtually all therapies, is marginally responsive to cyclophosphamide. Skin scores and quality of life improved to transplant doses of cyclophosphamide. Radiation has never been demonstrated to benefit systemic sclerosis and in fact can cause disease exacerbation. A study using total lymphoid irradiation (TLI), despite profound immune suppression and despite avoiding radiation to the lung, exacerbated scleroderma pulmonary disease and caused a gastrointestinal scleroderma-related death.[13] In breast cancer patients who also have scleroderma, localized breast radiation is considered a relative contraindication.[14] Using total body irradiation (TBI) in the transplant regimen for scleroderma, 2 patients died from an acute pulmonary death, and despite subsequent lung shielding, pulmonary function tests declined acutely in the other patients.[2] Designing conditioning regimens utilizing disease-exacerbating agents seems like a singularly inconsistent idea.

Allogeneic HSCT

Allogeneic HSCT from an HLA-matched sibling offers the potential to replace completely the immune system with that of a healthy sibling, transferring numerous non-HLA autoimmune disease-resistant genes to the donor. The donor's lymphocytes would also eliminate residual host hematopoietic and immune cells. As mentioned for malignancies, donor lymphocyte induced recipient hematopoietic aplasia is termed GVL while the same phenomena in autoimmune diseases is termed graft-versus-autoimmunity (GVA).[3–6] For autoimmune diseases, this approach would have to be modified to diminish the risk of donor lymphocyte mediated graft-versus-host disease (GVHD). Diseases and patient selection should initially focus on patients at high risk of disease-related mortality such as diffuse systemic sclerosis. For systemic sclerosis, which is generally not responsive to immune suppression, and is associated with a vasculopathy, allogeneic HSCT may allow replacement of endothelial cells and fibroblasts from a disease-resistant donor's hematopoietic stem cell compartment.[15]

Tissue regeneration

Embryonic stem cells (ESC) that have been derived from the inner cell mass of the preimplantation embryo may be maintained in culture indefinitely, cryopreserved and recultured, and differentiated into all cell lineages when returned to the embryonic inner cell mass of another embryo. When taken from culture and injected into an adult, ESC either die or differentiate into a disorganized teratoma. On the other hand, adult stem cells, such as HSC, when injected into an adult, respond in a physiologic manner to regenerate both the stem cell pool and differentiated adult tissues. It had been dogma that adult stem cells are lineage specific. Recent data in both animals and humans suggest that HSC may differentiate into other tissues such as liver, gut, skin, cardiac muscle, and perhaps neuronal cells.[16–20] A variety of explanations are possible for lineage plasticity of HSC including transdifferentiation, retrodifferentiation (dedifferentiation to an earlier stage before differentiation along another lineage), cell fusion, contamination, and existence of a totipotent or semi-totipotent adult stem cell. Lineage switch of an adult stem cell (ASC) is probably best demonstrated by single cell cloning as performed by Krause *et al*.[20] Fusion of donor hematopoietic cells with cells in recipient tissues results in tetraploidy.[21] Most reports of HSC lineage plasticity lack evidence for tetraploidy. Contamination arises when a nonhematopoietic ASC such as a liver stem cell contaminates the marrow or peripheral blood mobilized stem cells. This may happen because there is no unique identifiable phenotype for adult stem cells. It is even theoretically possible that a primitive ASC with embryonic-like characteristics (ie totipotent or semitotipotent) is the source for all ASC compartments including HSC. Whether tissue regeneration from ASC is clinically feasible, occurring with a clinically relevant frequency of functional cells, is unknown. However, it appears that regeneration from ASC may occur using either marrow or cytokine mobilized peripheral

blood cells and is facilitated within an organ by acute tissue injury.

Conclusions

Stem cell therapy has virtually unlimited promise towards overcoming obstacles that hinder traditional surgical, radiation, and pharmaceutical treatments. The Snowbird 2002 meeting provided an avenue for international experts from around the globe to discuss advancements that transcend traditional departmental, divisional, clinical, and research barriers. Due to page constraints, this supplement publishes only a few clinically relevant lectures. The chairs are in debt to the numerous outstanding research and clinical lectures that could not be incorporated into the supplement.

Snowbird 2002 speakers

Renate Arnold (Berlin, Germany), Rosa Bacchetta (Milan, Italy), Walter Barr (Chicago, IL, USA), Carl Bjartmar (Cleveland, OH, USA), Richard Burt (Chicago, IL, USA), Ewa Carrier (San Diego, CL, USA), Richard Champlin (Houston, TX, USA), Diana Clarke (Cambridge, MA, USA), Bruce Cohen (Chicago, IL, USA), Robert Craig (Chicago, IL, USA), Robert Emmons (Worcester, MA, USA) Keiichi Fukuda (Tokyo, Japan), Charles Hackett (Bethesda, MD, USA), Falk Heipe (Berlin, Germany), Susumu Ikehara (Osaka, Japan), Stephen Miller (Chicago, IL, USA), John Moore (Sydney, Australia), Tomas Kozak (Prague, Czeck Republic), Charles Link (Des Moines, IA, USA), Alberto Marmont (Genoa, Italy), Paolo Muraro (Bethesda, MA, USA), Steve Paveltic (Bethesda, MA, USA), Richard Nash (Seattle, WA, USA), Yu Oyama (Chicago, IL, USA), Jonathan Powell (Baltimore, MA, USA), Darwin Prockop (New Orleans, LA, USA), Peter Quesenberry (Providence, RI, USA), Byron Petersen (Gainesville, FL, USA), Robert Rosa (Chicago, IL, USA), Robert Rubin (Albuquerque, NM, USA), Riccard Saccardi (Florence, Italy), John Snowden (Sheffield, England), Andreas Thiel (Berlin, Germany), George Tsokas (Washington, DC, USA), Ann Traynor (Chicago, IL, USA), Julio Voltarelli (San Paolo, Brazil), Dirk van Bekkum (Leiden, The Netherlands), Nico Wulffraat (Utrecht, The Netherlands), Henry Young (Macon, GA, USA), Lixin Zheng (Bethesda, MA, USA). The chairs wish to thank the sponsors: Cumming Foundation, Leucadia National Foundation, Miltenyi Biotec, Pharmacia and Sangstat.

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