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REVIEW ON HEMATOPOITIC STEM CELL TRANSPLANTATION IN RHEUMATIC AUTOIMMUNE DISEASE

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ABSTRACT

Stem cells develop in the embryo and produce a variety cells that develop to produce tissues during the organogenesis process. In addition, stem cell is characterized by an ability to indefinitely self-renew. Stem cells are broadly classified into embryonic stem cells and adult stem cells. Adult stem cells can be genetically reprogrammed to form pluripotent stem cells and exist in an Embryonic likestate. Human embryonic stem cells exist only briefly during the early stages of development. Adult stem cells are found all over the body and help to regenerate tissues after apoptosis or tissue repair. Adult stem cells called hematopoietic stem cells (HSC) produce blood and immune cells. Autoimmune responses are sustained due to the perennial persistence of tissue self-auto reactive lymphocytes. Immune reset is a process that results in the production of new self-tolerant cells after chemotherapy-induced lymphocyte destruction. Autologous HSC transplantation is based on this (HSCT). Because of complaints related transplant-related mortality and morbidity, HSCT was initially limited to refractory autoimmune rheumatic disorders (AIRD). However, with a better understanding of patient selection, conditioning, and supportive care, HSCT for AIRD has come a long way.

KEYWORDS: Hematopoietic stem cell, Transplant related mortatlity, HSCT in autoimmune rheumatic disease, Stem cell therapy.

INTRODUCTION

Stem cells originate in the embryo and differentiate into specialised cells that develop to produce tissues during the organogenesis process. Furthermore, stem cells are distinguished by their ability to self-renew indefinitely. Adult stem cells and embryonic stem cells are two types of stem cells. Adult stem cells can be genetically reprogrammed to become pluripotent stem cells and reside in a state similar to that of embryonic stem cells. Human embryonic stem cells exist only briefly during the early stages of development. Adult stem cells are found throughout the body and help to regenerate tissues after apoptosis or tissue repair. Adult stem cells called hematopoietic stem cells (HSC) generate blood and immune cells.

Embryonic stem cells have a lot of promise because they can replace every functioning cell in the human body. Teratomas are caused by the uncontrolled replication of embryonic stem cells. Ethical issues surround embryonic stem cell research.

Currently there are no Food and Drug Administration approved embryonic stem cells based therapies available for clinical use. Several clinical trials are under conducted to evaluate the use of human embryonic stem cell-based therapeutics in regenerative medicine. Adult stem cells give rise to HSC, which are blood and immune cells. HSC can be isolated from the umbilical cord, peripheral blood or the bone marrow.

Manifestations of autoimmune rheumatic diseases are heterogeneous in which the etiology is oligoclonal lymphocyte responses were triggered by genetic risks, ethnic differences, and infection. As a result of multitudes of external insult, there is interference in the signal responses that sustain immune tolerance to normal tissues. When these signals are disrupted, the effector cellular mechanism is activated, which causes self-tissue destruction to spread. The persistence of tissue auto antigens, which are frequently not removed, keeps autoimmune responses going. As a result, the treatment response is frequently nonspecific, and the majority of patients do have a relapsing and remitting history. Better understanding of mechanisms involved in immunopathogenesis and of effecter cells have lead to the acceptance of aggressive modalities of treatment namely hematopoietic stem cell transplantation which resets the host immune system. Immune reset is a process that results in the production of new self-tolerant cells after chemotherapy-induced lymphocyte elimination.

This is the basis for autologous.

PRECLINICAL DATA

Genetically determined and inducible models are used in transplant investigations in animals with Alzheimer's disease. Mice or rats with lupus-like disease, transgenic HLA-B27 expression, hyperglycemia, and IL-1Ra deficiency fall into the first category, whereas those with collagen-induced arthritis or experimental autoimmune encephalomyelitis (EAE) as models of RA and MS, respectively, go into the second. Different results were obtained in these models. Conditioning followed by pseudo autologous HSCT resulted in the cure of induced AD, but not of genetically determined AD. The outcome of autologous HSCT, and to a lesser extent allogeneic HSCT, was determined by the disease stage at the time of transplant. In inducible disease models, HSCT has both protective and therapeutic effects: in EAE-susceptible mice, both syngeneic and allogeneic HSCTs protected animals from disease when performed close to immunisation, but only allogeneic HSCT with high-grade chimerism was effective in protecting animals from EAE when the time lag was longer. HSCT avoided glial scarring and reduced disease severity after vaccination in another EAE study, but it was ineffective as a therapy for established disease. Allogeneic, but not syngeneic, HSCT reversed both acute and chronic symptoms in mice with established genetic AD, such as lupus-prone animals. Myeloablative HSCT was used in early animal studies.

In the early animal HSCT studies, myeloablative conditioning was employed prior to allogeneic HSCT to achieve full donor chimerism and eradicate autoreactive lymphocytes. Nonmyeloablative conditioning, on the other hand, has been proven to be similarly successful in producing stable chimerism while preserving efficacy in recent investigations. There was no GVHD, indicating that the potential graft-versus-autoimmunity impact and GVHD are separate phenomena. Whereas full donor chimerism was needed in the SLE and EAE models, the induction of mixed chimerism was sufficientto ameliorate chronic inflammatory arthritis in IL-1Ra-deficient mice After allogeneic HSCT, there was no significant association between arthritis score and the ratio of donor to recipient cell populations in mice with mixed chimerism.

Nonmyeloablative conditioning followed by both syngeneic and allogeneic HSCT (the latter providing a stable donor chimerism of > 95% in collagen-induced arthritis) exhibited a substantial therapeutic effect compared to conditioning alone in collagen-induced arthritis.

Allogeneic HSCT was found to be more effective than syngeneic HSCT in reducing pathogenic autoantibodies in this investigation.

CLINICAL STUDY

Autologous hematopoietic stem cell transplantation

The most common type of HSCT is autologous HSCT. It is a relatively safe technique in hemato-oncological circumstances, with a TRM of less than 3%. Sepsis, CMV infection, and haemorrhage are toxicities and transplant-related causes of death. The overall TRM for autologous HSCT in AD now is approximately 7%, although it was as high as 23% in one of the first pilot studies.

Patient-related variables of toxicity and TRM in Alzheimer's disease include diagnosis and extent of organ involvement, age, and comorbidities. TRM and toxicity also depend on the conditioning regimen and whether or not TBI is performe.

Complications from HSCT may usually be controlled in competent hands with the adaptation of eligibility criteria (for example, exclusion of patients with severe pulmonary hypertension) and adjustments of transplant regimens (for example, lung shielding with TBI). As a result, TRM has decreased. It was less than 1% for non-TBI nonmyeloablative, less than 2% for low-intensity myeloablative, and 13% for high- intensity myeloablative regimens.

In comparison to TRM, efficacy appears to be less affected by the intensity and kind of conditioning, albeit this could be complicated by the severity of the underlying disease. Nonmyeloablative conditioning demonstrated an efficacy comparable to myeloablative conditioning in SLE patients, with a significantly lower TRM of 2% versus 13%. A similar observation was made for SSc where nonmyeloablative regimens had a TRM of less than 4% in contrast to 23% for myeloablative conditioning with TBI, with similar efficacy. However, because such comparisons are not based on prospective controlled studies, they must be regarded with caution.

Mechanisms of action of hematopoietic stem cell transplantation inautoimmune disease

Conditioning with high-dose cyclophosphamide, ATG, and/or TBI kills the majority of the host's autoreactive effector cells in autologous HSCT. B and T lymphocytes, monocytes, NK cells, and DCs are among the adaptive and innate immune cells involved. At least in the short term, this intense immunosuppressive impact is thought to constitute the main effect of HSCT

on AD. The injection of autologous HSCs reduces aplasia but is unlikely to be necessary for the anti-autoimmune effect. Early inflammatory illness has a better response rate in animal studies than chronic long-term AD. The latter could be related to a greater involvement for the stromal cell compartment, difficulty in distinguishing disease activity from damage, or decreased immune system sensitivity. tolerance induction in longstanding disease.

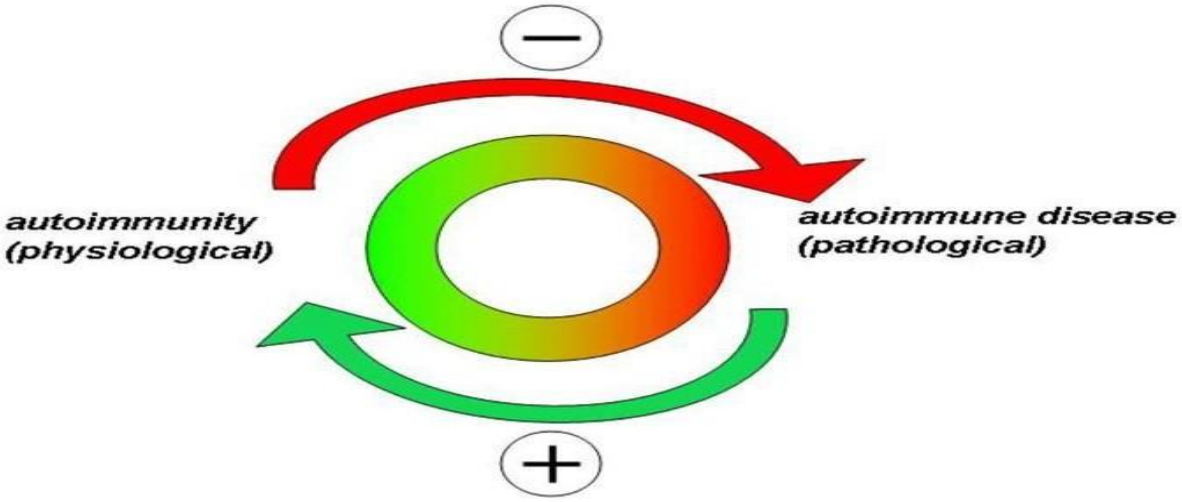
After both myeloablative and nonmyeloablative conditioning, autoreactive host cells survived with persistent autoantibody titres after autologous HSCT. Such cells may contribute to relapses. This means that there must be variables that either impede autoreactive clone development or render the host anergic in those individuals who do not relapse. Immuno ablative therapy can have both general and specific effects, such as post-transplant lymphopenia and lower levels of pathogenic autoantibodies, as well as more specific effects, such as the activation of regulatory T cells. In the proteoglycan-induced arthritis mouse model, the initial improvement after autologous HSCT corresponded to an increase in $CD4^{+}CD25^{+}$ cells. Initially, these T-regulatory cells did not express FoxP3.

However, subsequent FoxP3 expression was linked to a further stabilisation of AD. Patients with juvenile chronic arthritis have shown similar results. Autoreactive T cells altered from a proinflammatory phenotype (mRNA interferon-gamma, T-bet high) before HSCT to a tolerant phenotype after autologous HSCT (IL-10 and GATA-3 high). T-regulatory cells markedly increased after autologous HSCT. In the first period, they reconstitute through homeostatic clonal expansion; after several months, a thymic-dependent naïve $CD4^{+}CD25^{+}$ T-regulatory cell regeneration is seen. Significantly, the most of autologous HSCT relapses occurred within the first 9 months following the procedure, before the thymus-dependent recovery of naive T-regulatory cells. As a result, it's thought that a healthy thymus is required to produce a functionally active CD4+CD25+ population. Evidence for thymic reactivation after autologous HSCT has been obtained from studies showing increases in T-cell receptor excision circles and $CD31^{+}$ T cells and normalisation of new T-cell receptor repertoires.

The increased toxicity of the high dose chemotherapy or radiation employed as part of the conditioning regimem is one of the key disadvantages of HSCT for autoimmune illness.

Eradication of autoaggressive lymphocytes

Reduction of (auto)antibody production

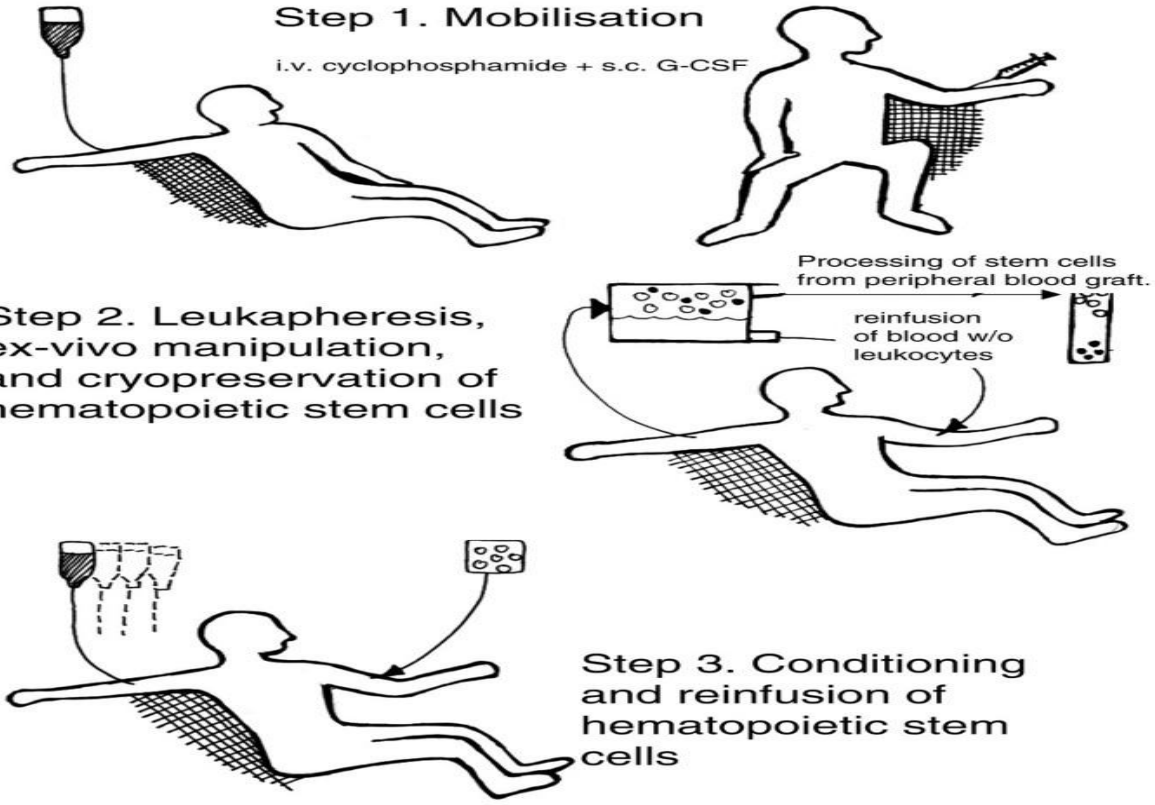


Restoration of thymic function, resulting in broadening of T cell receptor repertoire and induction of regulatory T cells

Restoration of cytokine imbalance

Induction of neoangiogenesis in skin

Resolution of skin fibrosis



HSCT OF RA

The formation of an inflammatory pannus, which erodes the synovial cartilage and surrounding bone, causes progressive joint destruction in RA. Articular symptoms like as pain and morning stiffness are common, and as the disease progresses, extra-articular signs such as lung fibrosis, vasculitis, and ocular disease may develop. With the introduction of biologics and early aggressive DMARD therapy, early disease control and remission have become possible. Some people are resistant to treatment, despite vigorous approaches. Prognostic factors for poor survival include functional limitations as measured by the Health Assessment Questionnaire (HAQ) and chronic inflammation in many joints.

HSCT in RA dates back to 1997. Pilot studies have indicated that prolonged remission responses were short-lived, extending up to 6-12 months, until DMARDs/anti-TNF medication was reintroduced. This was due to the failure of an HSCT to entirely remove the synovial T cell repertoire. However, following HSCT there was a better response to biologic and non- biologic DMARDs supporting the immune modulating effect of HSCT.

In RA, HSCT has had different levels of efficacy, but the results have not been encouraging when compared to diseases such as SSc. When compared to other AIRD, the success of HSCT is measured in terms of progression free survival and disease free survival, both of which are highest in patients with SSc and RA. Though overall survival rates for RA have been about 98 percent, the ability to maintain a prolonged ACR 70 response has been low, with just 28 percent maintaining progression-free survival after three years for such an expensive medication.

CONCLUSION

Understanding HSC biology and medical management of patients receiving HSCT has progressed significantly. Cord blood banking will allow an increasing number of patients to undergo unrelated allogeneic transplants while also providing a useful research resource. The development of RIC regimens is encouraging, as it opens up the possibility of remission for older patients who would not have been candidates for HSCT earlier. The optimization of the GvT impact while decreasing the risk of acute and chronic GvHD remains the most difficult problem. Further basic scientific study will help to define the immunological mechanisms that cause GvHD and lead to more effective medicinal treatments.

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