

Hematopoietic Cell Transplants in Autoimmunity

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ABSTRACT: Approximately 1 in 31 people suffers from an autoimmune disease. The clinical care of patients with autoimmunity crosses multiple disciplines within pediatrics and internal medicine, including, for example, allergy-clinical immunology, rheumatology, nephrology, hematology, pulmonology and neurology. There are two major areas that are considered in the analysis of autoimmunity in human patients. The first of course is etiology and the second, and of even greater importance, is therapy. Towards that end, considerable attention has focused on the role of hematopoietic stem cell transplantation to either reverse or modulate autoimmune disease. Indeed, it is a field that has far more promise than premise based on a variety of issues, including economics, health care delivery, and obviously efficacy and safety. To put this in perspective, we have attempted to review some of the issues that pertain to this novel approach to the management of autoimmunity. Finally, we emphasize the need to incorporate basic research into therapeutic trials, a vacuum all too often present in clinical intervention.

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There has been a dramatic shift in the treatment of human autoimmunity. The paradigm for several decades has rested on the use of glucocorticoids and/or immunosuppressive agents. Indeed, the literature is replete with studies that attempt to fine tune the therapies of a variety of human immunopathologies with such agents [1-4]. This revision of the paradigm includes the introduction of biologics, something that occurred over the previous decade, first in rheumatoid arthritis and more recently in other diseases [5-10]. Unfortunately and perhaps not unexpectedly, the introduction of directed therapies to biologic mediators of inflammation or to either lymphoid populations or cell adhesion molecules has led to unique toxicities. Some of these include infection [11], while other toxicities include the development of progressive multifocal leukoencephalopathy [12,13]. Finally, there have been recent alerts regarding the increased incidence of neoplasia in autoimmunity and in autoimmune patients who receive such therapies [14]. The paradigm will

further change with improvement in hematopoietic stem cell transplantation, which is reviewed here.

STEM CELL TRANSPLANTATION AND AUTOIMMUNE DISEASES

Autologous or allogeneic stem cells transplantation from bone marrow or peripheral blood is performed to treat severe and refractory autoimmune diseases. However, this procedure is not a viable option for the general population [15]. It is expensive and there still remains the need for evidence-based research to define the optimal technology, the safety aspects, and the diseases with the most potential for remission. It is clear that some autoimmune diseases have the potential for a severe and life-threatening course – such as primary systemic vasculitis, systemic lupus erythematosus, primary antiphospholipid syndrome, bullous disorders of the skin, multiple sclerosis, juvenile idiopathic arthritis and systemic sclerosis – and these disorders seem to be ideal candidates for ASCT. With these comments in mind, hematopoietic stem cell transplantation has provided realistic data on multiple sclerosis, and in some cases recovery with long-term disease stability may be observed. Interestingly, magnetic resonance imaging studies demonstrated that the inflammation in the central nervous system resolved and gadolinium-enhancing lesions were decreased or totally eliminated after ASCT. However, it is important to emphasize that ASCT is reserved for patients who do not respond to standard treatment and worsen quickly. Another neurological disease for which ASCT could be potentially used but has a limited experience is chronic inflammatory demyelinating polyradiculoneuropathy, in which 25% of the patients with this disorder do not respond adequately to conventional treatment [15]. Regarding systemic sclerosis, Farge et al. [16] reviewed the short and long-term reports from the various phase I-II studies, showing that ASCT in patients with severe diffuse cutaneous systemic sclerosis results in continued improvement of skin thickening and stabilization of organ function for up to 7 years after transplantation.

There are also limited data in juvenile rheumatoid arthritis. For example, there is a report of four juvenile arthritis patients with a 4–5 year favorable long-term outcome who received ASCT [17]. The experience of ASCT in adult RA

ASCT = allogeneic stem cells transplantation
RA = rheumatoid arthritis

patients demonstrates a limited therapeutic potential in rare patients with this disease refractory to modern therapy and sufficient conditions for the procedure. Systemic lupus erythematosus is another disease for which ASCT has been implemented. More than 150 lupus patients received ASCT until 2008, with a mortality rate of 7%. A remarkably good outcome was observed in some subjects, although this procedure was also used in the early stages of patently aggressive disease [18]. ASCT remains the only treatment with the capacity to reverse type 1 diabetes in humans. In a preliminary study of ASCT in 19 newly diagnosed patients with type 1 non-ketoacidotic diabetes, this procedure led to the discontinuation of insulin use in 18 of these patients and 14 patients have maintained this status after a median follow-up of about 2 years [19].

RATIONALE FOR HSCT

As previously described, it is not surprising that the first case reports of remission of autoimmune disease following HSCT were noted in patients who underwent transplantation for an underlying malignancy but also suffered from an autoimmune disease [20-22]. Indeed, graft types can be allogeneic, autologous and embryonic. Allogeneic, of course, implies a non-

identical donor. Autologous refers to self as a donor. Embryonic is defined as a related or unrelated pluripotent embryonic cell. The types of protocol used in such transplantation have been both myeloablative and lymphoablative. Of these, the myeloablative is directed at progenitor and circulating effector cells. The lymphoablative is directed only at circulating effector cells. The general principal is that patients suffer from a genetic predisposition that leads to regulatory escape and subsequent self-reactivity.

The concept of using hematopoietic precursors is based on the fact that transplanted patients will develop a new repertoire. In other words, the clinician attempts an immune 'reset' of a patient who has lost tolerance [23].

EXAMPLES OF HSCT IN AUTOIMMUNITY

This article will not review the numerous trials that have been conducted for diseases such as dermatomyositis, autoimmune cytopenia, Behçet disease, celiac disease, chronic inflammatory demyelinating polyneuropathy, Crohn's disease, Evans' syndrome, juvenile idiopathic arthritis, multiple sclerosis, pemphigus foliaceus, polymyositis, rheumatoid arthritis, small-vessel vasculitis, systemic sclerosis, systemic lupus erythematosus, systemic vasculitis, Takayasu's arteritis, Wegener's granulomatosis, antiphospholipid syndrome, type 1 diabetes mellitus, and inflammatory bowel disease. Instead, we refer to

Hematopoietic cell transplantation is a procedure used for the treatment of severe and refractory autoimmune diseases that failed to conventional therapy with conventional immunosuppressive agents

HSCT = hematopoietic stem cell transplantation

Table 1. Autoimmune diseases treated with ASCT

Disease	N	Type of ASCT	Initial response (%)	Sustained improvement (%)	Failure (%)	Mortality (%)
Amyopathic dermatomyositis	1	Autologous	100	100	0	0
Autoimmune cytopenia	47	Autologous, allogeneic	57-86	35-72	14-43	12-14
Behcet disease	1	Autologous	100	0	0	0
Celiac disease	7	Autologous	100	43	14	0
Chronic inflammatory demyelinating polyneuropathy	2	Autologous, allogeneic	100	100	0	0
Crohn's disease	15	Autologous	100	0-100	0-8	0
Type 1 diabetes	15	Autologous	0-100	0-93	0-100	0
Evan's syndrome	3	Allogeneic	100	100	0	0
Juvenile idiopathic arthritis	56	Autologous	68-71	40-53	21-32	9
Systemic lupus erythematosus	147	Autologous	71-100	0-82	8-100	0-12
Multiple sclerosis	249	Autologous	24-100	5-100	0-76	0-5.3
Pemphigus foliaceus	1	Autologous	100	100	0	0
Polymyositis	2	Autologous	100	0-100	0	0
Rheumatoid arthritis	74	Autologous, allogeneic	67-100	32-100	0-16	0-2
Systemic sclerosis	109	Autologous, allogeneic	89-100	22-100	0-48	0-50
Systemic vasculitis	27	Autologous, allogeneic	75-100	47-100	0-25	0

Adapted with permission from Deane et al. [15].

the recent literature and a symposium on this subject [15,22-29] and emphasize that these protocols, while encouraging, have made little or no attempt at standardization and often studied patients who have end-stage disease with little likelihood of reversibility. Table 1 presents a summary of ASCT in autoimmune diseases. Despite these reservations, there is no question that many of the data are very encouraging.

ECONOMIC COSTS

ASCT is a very expensive procedure, ranging from US\$ 30,000 for an uncomplicated ASCT to US\$ 200,000 for an allogeneic stem cell transplantation using an unconnected donor [30]. Few people can afford ASCT as an out-of-pocket expense. Even for insured persons, the high costs may limit access to this procedure because of coverage denial, high deductibles, or a life time spent paying it off. Consequently, identifying factors associated with the high cost of ASCT and determining methods for reducing those costs without compromising clinical outcomes are of substantial importance. Previous studies have identified a variety of possible cost factors: experience of transplant center, the health care system, year of transplantation, conditioning regimen, graft versus host disease prophylaxis, changes in diagnostic tools, clinical outcome, disease status, donor characteristics, source of the graft, the age and health status of recipients, governmental economic policies, and others [31,32]. There have been some noteworthy advances in ASCT technology, and as a result, patients who previously would have undergone risky ASCT because of disease indications may instead be receiving ASCT with reduced intensity regimens.

FUTURE DIRECTIONS

Clearly, if hematopoietic stem cell transplantation is to become a viable option for patients, it will be necessary for clinical investigators to develop consensus guidelines. Indeed, autoimmunity has been coined a mosaic of medicine because of the myriad presentations and the large number of seemingly different autoimmune diseases [33]. The experimental protocols should become reasonably standardized and an international registry should be developed. We have already emphasized the need for basic science issues. Although close to 100 studies on stem cell transplantation in autoimmunity have been published, relatively few address these complex relationships. Indeed, we would emphasize issues such as transcriptional regulation of cytokines following transplantation, the relationship between infections and the development of a restored immune repertoire, a better understanding of the changes in signal processing following transplantation, the appearance of so-called predictive autoantibodies over

time, the response following vaccinations in such patients and, of course, a vigorous study of the kinetics of phenotype and function of mononuclear cell subpopulations, both following transplantation and over time [34-40].

Furthermore, and perhaps of even greater importance, it is essential that such observations be long term and that all data be centrally reported so that investigators will be able to evaluate such therapies in real time. Finally, we also strongly encourage the use of immunological evaluations so that the data will be more than clinical observations but rather will provide insight on the mechanisms involved in loss of tolerance, reemergence of disease, and/or changes in the immune repertoire. We believe that with this type of mechanistic evaluation, the cost will decrease and more importantly we can expect a higher degree of success.

Type 1 diabetes, systemic lupus erythematosus, multiple sclerosis, systemic sclerosis, autoimmune cytopenia and systemic vasculitis are some of the autoimmune diseases for which hematopoietic transplantation is a therapeutic option

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