Developments in Hematopoietic Stem-Cell Transplantation in the Treatment of Autoimmune Diseases

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Abstract

Intractable forms of autoimmune diseases follow a rapid course, with a significantly shortened life expectancy sometimes comparable to that of malignant diseases. Immunoablative therapy, including high dose cytotoxic agents and hematopoietic autologous stem-cell rescue, was recently introduced as an aggressive approach to treat autoimmune diseases that have a rapid course and are resistant to conventional therapy. The most frequent indication for this type of treatment is multiple sclerosis, seconded by systemic sclerosis. The results of immunoablative treatment with documented responses in both diseases are encouraging. The data are mature enough to begin comparative randomized studies of immunoablative versus conventional treatment to validate the benefit of the aggressive approach. A randomized trial involving SSc was recently launched (ASTIS) and a trial involving MS is in preparation. Considerably less experience with immunoablative treatment has been gained in systemic lupus erythematosus, rheumatoid arthritis, and other disorders with an autoimmune pathophysiology. Autologous hematopoietic stem cell transplantation in humans offers more long-lasting immunosuppression than reeducation of lymphocytes. In fact, allogeneic transplantation may replace the whole immune system. However, this attractive approach is still associated with considerable morbidity and mortality and is not yet justified for treatment of automimmune diseases. Non-myeloablative allogeneic transplantation and sub-myeloblative high dose cyclophosphamide without stem cell support are alternative approaches that could be explored in pilot studies.

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The autoimmune etiology of diseases was first described as "horror autotoxicus" by Ehrlich and Morgenroth 100 years ago. Today, 3% of the world's population suffers from some kind of autoimmune disease according to Witbesky's postulates.

Different lymphocytic subpopulations are involved in the pathogenesis of autoimmune diseases, with T lymphocytes playing an essential role in most of them. Therefore, treatment of autoimmune disease is based either on suppression or modulation of lymphocytic activity. Conventional immunosuppressive or immunomodulatory therapy can control most cases with autoimmune disease, but not all. These intractable forms of disease follow a rapid course, with a significantly shortened life expectancy. In these cases, immunoablative therapy with hematopoietic stem-cell support could be considered as a new therapeutic option in clinical trials. This method is based on maximal dose escalation of cytotoxic immunosuppressive agents (conditioning regimen) involving chemotherapy and/or total body irradiation. In most cases this treatment is not only immunoablative but also myeloablative. However, in the case of allogeneic stem-cell transplantation or reinfusion of previously stored autologous stem-cells, damaged bone marrow is rescued by the infusion of new hematopoietic stem cells. Previously known as bone marrow transplantation, this method is now called hematopoietic stem cell transplantation as peripheral blood is used more and more as a source of stem cells.

The rationale for use of HSCT in autoimmune disease is based on: a) experiments in animal models of human autoimmune disease, b) the effect of HSCT on concomitant autoimmune disease in patients treated for hematologic malignancies, and c) results of phase I/II clinical studies with HSCT specifically for autoimmune disease.

Rationale for HSCT in human autoimmune disease

Allogeneic HSCT from a resistant strain led to remission in murine SLE, a model of genetically linked, spontaneous autoimmune disease. Models closer to human autoimmune disease are antigen-induced animal autoimmune disease; examples of models are adjuvant arthritis for rheumatoid arthritis and experimental allergic encephalomyelitis for multiple sclerosis. Adjuvant arthritis induced in sensitive mice and rats can enter remission after TBI and allogeneic HSCT from resistant strains. Surprisingly, the same effect is seen in syngeneic and autologous transplantation. In EAE, allogeneic, syngeneic or autologous HSCT arrested the disease and

SSc = systemic sclerosis
MS = multiple sclerosis

HSCT = hematopoietic stem-cell transplantation
SLE = systemic lupus erythematosus
TBI = total body irradiation
EAE = experimental allergic encephalomyelitis

induced tolerance. However, the effect of allogeneic transplantation was superior [1,2].

In the case of allogeneic transplantation the whole immune system is replaced by that of the donor, which eliminates the remaining original autoreactive lymphocyte clones. This situation is sometimes called "graft-versus-autoimmunity effect." Autologous HSCT is effective predominantly through long-lasting quantitative suppression of autoreactive lymphocytes, and theoretically through self-tolerance induction by recapitulation of lymphocyte ontogeny. In a human autologous setting, ontogeny recapitulation was shown in B lymphocytes but not confirmed in T lymphocytes [3]. Therefore, in human autologous HSCT for autoimmune disease, long-term immunosuppression as a treatment mechanism is more realistic than self-tolerance induction by lymphocyte ontogeny recapitulation.

After bone marrow transplantation was introduced to clinical practice, reports began to appear regarding its effect on concomitant autoimmune disease in patients with hematologic malignancies. Most of the patients were transplanted for gold-induced severe aplastic anemia following treatment for rheumatoid arthritis. Following allogeneic HSCT, all of the patients entered remission of their RA. However, one patient, despite full chimerism, relapsed 2 years later with a clinically attenuated disease [4]. Six patients with Crohns disease were treated with allogeneic HSCT for hematologic malignancies, and all of them entered remission of Crohn's; one patient with partial chimerism relapsed 18 months later [5]. Progression of multiple sclerosis was arrested in two patients after allogeneic HSCT, but deteriorated in another [6].

In the autologous setting, remission of SLE after HSCT for non-Hodgkin's lymphoma and chronic myelogenous leukemia was reported [7,8]. Negative reports also appeared. The most notable involved Euler's series of four patients whose autoimmune disease relapsed shortly after unmanipulated autologous HSCT for malignancy. From the results mentioned above it is apparent that allogeneic HSCT is more active in the treatment of autoimmune disease. However, it does not prevent relapse, as documented in the case of RA.

The major objection to the allogeneic approach compared to the autologous setting is the significant risk of treatment-related morbidity and mortality (15–35%). Allogeneic transplantation is not justified for the treatment of autoimmune disease at this point. The most frequent causes of mortality are infection and graft-versus-host disease. In most centers practicing autologous HSCT for malignant diseases, the treatment-related mortality is below 5% and is decreasing even further with the use of peripheral blood hematopoietic stem cells. For this reason, first pilot phase I/II clinical trials and first phase III randomized studies with immunoablative treatment of autoimmune disease involve autologous HSCT.

Initial clinical experience with HSCT in autoimmune disease

Since the mid-1990s several teams have attempted to introduce systematically immunoablative therapy in the treatment of intractable autoimmune disease. The European Group for Blood and Marrow Transplantation (EBMT) and the European League against Rheumatism (EULAR) formed the EBMT/EULAR Autoimmune Disease Stem Cell Project, which included a registry of patients primarily transplanted for autoimmune disease. The most recent registry data were presented at the last EULAR meeting in Prague 2001, where the first randomized phase III clinical study on systemic sclerosis (ASTIS) involving high dose immunoablative therapy was introduced [9]. Reported to the registry were 334 transplants (327 autologous) specifically for autoimmune disease: 102 for multiple sclerosis, 70 for systemic sclerosis, 41 for rheumatoid arthritis, 35 for juvenile idiopathic arthritis, 25 for SLE, 6 for dermatomyositis, and others.

Experience with autologous HSCT in multiple sclerosis

Intractable forms of multiple sclerosis are the most frequent indications for immunoablative therapy with autologous HSCT support. Experience gained from phase I/II clinical trials was published in the late 1990s [10,11]. The most frequent type of MS transplanted was secondary progressive with severe disability not responding to any salvage conventional treatment. Different conditioning regimens were used. However the BEAM regimen (BCNU, etoposide, ARA-C and melphalan) was the most common. All trials confirmed the feasibility of this approach, with its promising effect on disease course. Summarized data from the EBMT/EULAR registry were presented at the EBMT meeting in 2001. This included 85 patients with a wide range of EDSS score (4.5–8.5, median 6.5, and a median follow-up of 16 months (range 2–60). The conditioning regimen included combination chemotherapy with or without anti-lymphocyte antibodies or with or without TBI. More than half of the patients were transplanted with *in vitro* lymph-depleted grafts.

Seven patients (9%) died: two due to disease progression and five due to procedure-related causes. The majority of patients at least stabilized their disease; moreover, neurologic improvement on EDSS 1.0 point was observed in 18 patients (21%). Progression-free survival at 3 years was 68($\pm$14)%, being higher in patients with non-primary progressive MS: 74($\pm$15)%. Magnetic resonance imaging data showed marked decrease of disease activity in a majority of evaluable patients [12]. The data are promising in terms of stabilization of otherwise intractable progressive MS, with some patients even improving. The mortality risk so far is somewhat higher than for patients undergoing autologous HSCT for lymphoma or multiple myeloma, possibly reflecting the severe disability of patients entering such trials. Their results need to be validated in a comparative study. At this point a phase III randomized study including immunoablative therapy is being developed.

Autologous HSCT in the treatment of SLE

To date, 32 cases of autologous HSCT following immunoablative conditioning in refractory SLE have been reported to the registries worldwide [13]. The majority of patients registered with the EBMT/EULAR registry received high dose cyclophosphamide and anti-thymocyte globulin as the conditioning regimen. The first patient, a

RA = rheumatoid arthritis

46 year old woman, underwent immunoablative treatment in Genoa, Italy in 1996. Two years later she was reported to be in good remission on maintenance therapy with lower doses of corticosteroids, and minimal proteinuria [14]. Since then, 22 cases have been reported in the literature. Nine patients with severe refractory SLE were included in a clinical trial in Chicago; the conditioning regimen consisted of high dose cyclophosphamide, antithymocyte globulin and methylprednisolone. Two patients died following mobilization of HSCT: one from active disease and the other due to disseminated mucormycosis. All seven grafted patients improved significantly following the procedure and entered remission with no clinical or serologic disease activity, with a follow-up ranging between 12 and 40 months [15].

Other published reports involving smaller numbers of patients are encouraging in terms of the number of remissions in refractory SLE. However, two more deaths were also reported. One patient developed thrombotic thrombocytic purpura following autologous HSCT, and she subsequently died of plasmapheresis complications [16]. In the second case, graft failure occurred after autologous HSCT. Despite salvage with allogeneic HSCT from her HLA-identical sibling the patient died in aplasia. Investigators were able to document that substances in the patient's serum might have been responsible for graft failure in this case [17].

Autologous HSCT in systemic sclerosis

Given the limited conventional therapeutic options, especially for the rapidly progressive diffuse type of this devastating disease, SSc is the second most frequent indication for immunoablative treatment in the EBMT/EULAR registry. Several positive reports involving small groups of patients were published in the past 5 years, including the famous case of a 13 year old girl who had severe progressive lung involvement and underwent autologous HSCT following conditioning with high dose cyclophosphamide and the CAMPATH-G monoclonal antibody. After the procedure she entered remission and was off corticosteroids for 2 years, gaining height rapidly [18]. Recently, experience with autologous HSCT in SSc was summarized based on data from a phase I/II multicenter clinical trial [19]. The trial included 41 patients, the majority of them with predominantly diffuse skin forms of the disease. Different conditioning regimens were used for immunoablation. However, most included high dose cyclophosphamide. A significant improvement in skin score occurred in 69% of evaluable patients; deterioration was noted in 7%. Lung function did not change significantly and pulmonary hypertension did not progress in evaluable patients. Progression after the procedure was observed in 19%, 11 patients (27%) died at census, and 7 deaths were procedure-related.

Mortality associated with autologous HSCT in SSc is above the limit expected with the same procedure in non-Hodgkin's lymphoma or multiple myeloma. However, the reported mortality reflects severe organ involvement and damage by underlying disease before transplantation in patients referred in their late stage of the disease. Based on this experience, inclusion and exclusion criteria were established for a first randomized phase III clinical trial (ASTIS) in systemic sclerosis including immunoablative therapy. This trial has just been launched.

Autologous HSCT in rheumatoid arthritis and juvenile chronic arthritis

Four years ago Joske [20] published the case of a 47 year old man with severe RA and confined to a wheelchair. After conditioning with high dose cyclophosphamide and *in vitro* lymphodepleted HSCT, the clinical and serologic activity of the disease was minimalized. Six months after the procedure the patient was able to walk 2 km and remained in remission 2 years later [20]. The Chicago group also reported marked improvement of RA not responding to conventional treatment in two patients. An interesting but small randomized study performed by Snowden et al. [21] confirmed that the dose of cyclophosphamide is important: four patients receiving a dose of 100 mg/kg did worse after autologous HSCT than patients who were given 200 mg/kg. However, there are also negative reports in RA and HSCT: three patients treated in Tasmania experienced only transient remission of RA [22]. RA is one of the most common autoimmune diseases and the majority of patients respond to conventional types of treatment. Therefore, there is a lack of data regarding how HSCT affects the course of this disease. Additional results from phase I/II studies are needed before a randomized clinical trial for intractable forms of RA can be set up.

The most common indication for immunoablative treatment in childhood is the refractory form of juvenile chronic (idiopathic) arthritis. The largest series has been reported from Utrecht [23]. Twelve children with severe systemic or polyarticular juvenile idiopathic arthritis underwent immunoablative treatment. Rheumatologic follow-up at 3 monthly intervals up to 36 months showed a marked decrease in arthritis severity as expressed by the core-set criteria for juvenile chronic arthritis activity. However, these children remain at risk both for severe viral infections due to prolonged lymphopenia and for developing fatal macrophage activating syndrome.

There are several case reports on autologous HSCT in other autoimmune diseases, most involving refractory immune-mediated hematologic cytopenias: Evans syndrome or AITP. Experience with these diseases is rather disappointing owing to the lack of or short-lasting response.

Questions and future directions of HSCT in autoimmune disease

Among the most discussed issues is the need for *in vitro* lymphodepletion to avoid reinfusion of autoreactive cells with the autologous graft. Following on Euler's provocative report on early relapse of autoimmune disease after unmanipulated HSCT, many investigators started to perform *in vitro* purging by various methods. There are still no firm data on the effect of this very expensive procedure on the disease, however most investigators agree on some kind of lymphodepletion, either *in vitro* or *in vivo*, the latter usually involving antithymocyte globulin. Immunoablative high doses of cyclophosphamide without stem-cell support on the one hand, and allogeneic transplantation from HLA identical siblings on the other, are also frequent topics [24,25]. Both approaches have possible advantages over autologous HSCT since they avoid the reinfusion of autoreactive cells. However, the effect of high dose cyclophosphamide should be confirmed in another series, and the

possible risk of flare of autoimmune disease with the prolonged administration of leukocyte growth factors should also be taken into account. Allogeneic transplantation, especially the recently introduced "minitransplants," is another attractive approach for its "graft-versus-autoimmunity effect." The lack of HLA-matched donors and the still unacceptable high peri-transplant morbidity and mortality handicap this method.

In conclusion, we can state that immunoablative therapy with HSCT support in otherwise intractable autoimmune disease is still an experimental approach that should be undertaken within prospective clinical trials. The available data are encouraging and sufficiently mature to embark on randomized phase III clinical trials involving autologous HSCT versus conventional treatment in systemic sclerosis and multiple sclerosis in order to finally assess the efficacy of immunoablative therapy. More data on the role of HSCT in other autoimmune diseases must be drawn from phase I/II studies. Other approaches such as allogeneic transplantation or high dose cyclophosphamide alone should also be assessed in larger series.

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