

Haemopoietic Stem Cell Transplantation in Autoimmune Diseases

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The concept of using haemopoietic stem cell transplantation (HSCT) as a potential treatment for severe autoimmune disease is not new. Its potential has been demonstrated by over two decades of laboratory studies in which various forms of animal autoimmune diseases have been cured, reversed, or prevented by allogeneic, syngeneic, and autologous bone marrow transplantation⁽¹⁻⁴⁾. Evidence in humans has been provided by those patients with autoimmune disease who have received HSCT for malignancy or aplastic anaemia^(3,4). Such cases suggest that allogeneic HSCT is potentially curative of autoimmune disease and that the favourable outcome may be related to a 'graft-versus-autoimmune' effect, as supported by a possible correlation between cure, relapse, and graft-versus-host disease (GVHD)⁽³⁻⁸⁾. However, the substantial morbidity and mortality associated with allogeneic HSCT in its present form precludes its application to most patients with autoimmune disease⁽⁹⁾.

Although data from 'coincidental' cases suggest that autologous HSCT offers a lesser chance of cure, substantial remissions are possible^(3,4), and the risks are arguably acceptable for an experimental therapy for severe life threatening or chronically disabling autoimmune disease resistant to conventional therapies. Recent improvements in the safety of autologous HSCT, including the use of peripheral blood stem cells (PBSC), have resulted in reductions in treatment related mortality, morbidity and costs and enabled us to investigate its specific use to treat severe autoimmune and inflammatory diseases⁽⁹⁾.

The First International Meeting in Stem Cell Therapy in Autoimmune Disease was held in Basel, Switzerland in 1996. Subsequently, consensus guidelines were published and the International Autoimmune Disease Stem Cell Project Database was established^(9,10). To date over 200 cases of rheumatic, neurological, and haematological autoimmune diseases have been registered, almost entirely of patients who have undergone autologous HSCT. The immediate objective of the database is to establish the best candidate diseases for this intensive approach, both in terms of tolerability and efficacy. By 2001, the EBMT/EULAR Autoimmune Disease Working Party (Chair, Professor Alan Tyndall, Basel) aims to have in progress a number of controlled trials in various autoimmune diseases.

A significant number of clinical reports have now appeared in the literature in which a variety of regimens have been used to treat a diverse selection of severe autoimmune and inflammatory diseases, including multiple sclerosis^(11,12), systemic lupus erythematosus⁽¹²⁻¹⁸⁾, scleroderma⁽¹⁹⁻²²⁾, relaps-

ing polychondritis⁽¹⁷⁾, and haematological diseases such as immune thrombocytopenia⁽²³⁾ and Evans' syndrome⁽²⁴⁾. It is not possible to describe the outcome of each case in detail here, and the reader is referred to the original articles and a recent review⁽²⁵⁾. The remainder of this article will focus on rheumatoid arthritis.

High dose therapy and autologous HSCT in rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown aetiology which affects 1% of the population, predominantly females, with an onset between the third and fourth decades of life. Its major distinctive feature is a chronic symmetrical and erosive synovitis of the peripheral joints. RA causes significant morbidity⁽²⁶⁾. Of those who have the disease for more than 12 months, a majority will continue to have exacerbations for the rest of their lives, and about half of affected individuals are unable to work 10 years after contracting the disease. RA shortens life; survival over 25 years of a cohort of 100 RA patients was 45% compared with 63% in age-matched non-RA controls⁽²⁷⁾. Some have likened the mortality of the most severe and aggressive form of RA ('malignant' RA) to triple vessel coronary artery disease or stage IV Hodgkin's disease. At St. Vincent's Hospital, Sydney we considered severe resistant RA to be good candidate disease for high-dose therapy and autologous HSCT; there are many patients with resistant disease, efficacy is easily and non-invasively assessed, and it is possible to select patients with good vital organ function who would be expected to tolerate high-dose therapy well. The background rationale in RA is based on studies of HSCT in animal arthritis⁽²⁸⁾ along with the observation of significant remissions of 'coincidental' RA who have undergone HSCT for malignancy or aplastic anaemia^(3,5,29,30).

The first phase of our strategy was to investigate the safety and efficacy of stem cell mobilisation in severe RA. We considered formal investigation of stem cell mobilisation to be necessary in view of potential RA flare with colony-stimulating factors and the possibility that mobilisation might be affected by RA and/or its treatment⁽³⁾. In a double blind placebo-controlled dose escalation study, flare occurred in 3/10 patients treated with G-CSF compared with 0/6 receiving placebo. Greater than 2×10^6 /kg CD34+ cells were collected in all patients and achieved with a single apheresis in patients receiving G-CSF $10 \mu\text{g}/\text{kg}/\text{day}$ ⁽³¹⁾. Comparison of PBSC harvests from RA patients with those from healthy donors showed less efficient mobilisation of CD34+

cells but normal *in vitro* progenitor cell function and a relative increase in monocytes, a cell important in the pathogenesis of RA⁽³²⁾. One other report has suggested that mobilisation flare might be prevented with pretreatment with steroids⁽³³⁾. At this time, it seems reasonable to recommend that the risks of mobilisation-induced flare and the pros and cons of pretreatment with intramuscular or intra-articular steroids should be discussed with the individual patient. With increasing numbers of RA patients undergoing HSCT, we have noted the occurrence of mobilisation failure in a minority (unpublished data). The use of greater doses of G-CSF or the addition of cyclophosphamide priming may be advantageous in such cases⁽³⁴⁾.

As the toxicity of high-dose cyclophosphamide had never been formally established in RA, the next stage in our strategy was a phase I/II dose escalation study of cyclophosphamide first at 100mg/kg then 200mg/kg followed by unmanipulated autologous PBSCT⁽³⁵⁾. The procedure was well tolerated in all patients with dose-dependent toxicity. The clinical responses in the cohort receiving cyclophosphamide at 100mg/kg (n=4) lasted only 2-3 months, but the responses following cyclophosphamide at 200mg/kg (n=4) were more impressive with significant clinical improvement sustained beyond 17-19 months in all patients. The two patients with the shortest duration of disease achieved the most profound responses. Temporary increases in disease activity were observed in some patients, but this responded well to the reintroduction of disease modifying agents. These results are encouraging, but the failure to abolish disease activity completely means that further modification should be pursued.

Other centres have published encouraging results in inflammatory arthritis using various protocols. In Perth, Australia, Joske and colleagues reported a 48-year-old wheelchair-bound man with severe refractory RA who received cyclophosphamide 200 mg/kg followed by an unmanipulated autograft⁽³⁶⁾. At two years post transplant he is in complete remission. Burt and colleagues in Chicago have reported two patients with RA treated with cyclophosphamide 200 mg/kg, anti-thymocyte globulin (ATG) 90 mg/kg, methylprednisolone 3g followed by a CD34+ cell enriched autograft⁽¹²⁾. The first patient has had a profound response sustained beyond 1 year, but a second patient has had only modest improvement. In Belgium, Durez and colleagues reported a 22 year old patient with refractory systemic and erosive RA who was treated with busulphan 16mg/kg and cyclophosphamide 120mg/kg followed by rescue with a highly purified autograft. She remains free of joint symptoms at eleven months, and the remission has been maintained despite complete reconstitution of the T cell repertoire to pre-transplant levels⁽³⁷⁾. In Omaha, a 25-year-old female with a 7-year history of RA received cyclophosphamide 200 mg/kg and ATG 60 mg prior to and 60 mg following infusion of unmanipulated autograft. At day +100 there were major reductions in disease activity⁽³⁸⁾. Wulffraat and colleagues in Utrecht, the Netherlands, have treated four

patients with refractory juvenile chronic arthritis with cyclophosphamide 200 mg/kg, ATG 20 mg/kg, and 4 Gy total body irradiation (TBI) followed by rescue with bone marrow depleted of T cells to a level of less than 10⁵/kg. At twelve months, three are in remission and one has mild oligoarticular disease without systemic activity⁽³⁹⁾. At the Royal Melbourne Hospital, a 38-year-old man with severe resistant adult onset Still's disease achieved longstanding remission after cyclophosphamide, ATG and a syngeneic PBSC transplant⁽⁴⁰⁾.

There are several potential avenues for clinical trials aimed at refining this approach. Firstly, additional intensification might be possible with the combined use of cyclophosphamide with other forms of chemotherapy or cell specific antibodies. Secondly, the question of whether 'autoreactive' T-cells or other immune effectors might have been reinfused with the autologous harvest could be answered in clinical trials of graft manipulation and a multi-centre trial is now in progress in Australia. Patients receive cyclophosphamide 200 mg/kg and are randomized to haemopoietic rescue with either unmanipulated rescue or CD34+ cell selected rescue. A third approach to extending responses is to combine high-dose therapy with ongoing maintenance or disease-holding treatment. Systematic clinical studies could test various forms of maintenance therapy such as DMARDs or other immunomodulators. Finally, patient selection may be important. Although numbers are small, our data have shown variation in responses to treatment between patients in both cohorts. Analysis of greater numbers may identify subgroups of patients more responsive to therapy than others (e.g. short duration of RA, presence of absence of rheumatoid factor, HLA-DRB1 type).

Conclusion

From the limited data available, high dose therapy and autologous HSCT seems to be producing promising results in RA and other autoimmune diseases, although like malignancy, there seems to be a heterogeneity of response. Analysis of greater numbers will optimise patient selection and identify the best regimens for each disease, both in terms of tolerability and efficacy. The mechanism of action is not clear but may merely represent altered immune reconstitution following autologous HSCT. A higher grade 'hope,' supported by some animal data and the observation of tolerance following allogeneic HSCT, is that of a 're-educated' and tolerised immune system. Clearly, this approach is far more attractive if clinical improvement can be achieved without non-specific immune suppression. There have been recent advances in allogeneic HSCT⁽⁴⁰⁾, and, eventually, it may be acceptable to consider its use in severe autoimmune diseases, although this is likely to be restricted to the minority of patients with compatible siblings. As most severe autoimmune diseases cause severe compromise in function and quality of life but are not immediately life threatening, investigators should tread carefully and safety considerations should be paramount.

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