Bone Marrow Transplantation (2003) 32, S53–S56

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Hematopoietic stem cell transplantation for severe rheumatoid arthritis

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Summary:

The substantial morbidity and mortality associated with rheumatoid arthritis (RA), while not widely appreciated, provide adequate justification for consideration of high-dose immunoablative therapy followed by hematopoietic stem cell transplantation. While some patients with RA follow a benign course, selected subsets of patients have been identified with 5-year survival rates of 40–70%. A number of factors that can be easily determined serve as useful prognostic indicators for poor outcome. These include the presence of many involved joints (total joint count), the degree of functional disability as measured by the health assessment questionnaire and the presence of rheumatoid factor. This article summarises the present status of hematopoietic stem cell transplantation for rheumatoid arthritis and proposes future directions for research.
Bone Marrow Transplantation (2003) **32,** S53–S56. doi:10.1038/sj.bmt.1703944
Keywords: rheumatoid arthritis; hematopoietic stem cell transplantation

Rheumatoid arthritis (RA), which affects up to 1% of the population, is rarely life threatening in the short term despite patients suffering considerable disability. However in the long term, up to 50% of patients are unable to work and life expectancy is reduced between 5–10 years.[1] Accordingly, hematopoietic stem cell transplantation (HSCT) has been suggested as a therapy for severe RA based on animal models and case reports of patients undergoing the procedure for other indications.[2] In 1999, the first 'biological' therapies emerged for general commercial use in the United States. These first ventures into the arena of highly selective immunotherapy have had a dramatic impact on the lives of patients with rheumatoid arthritis (RA) which may be properly characterised as a therapeutic revolution. For the majority of patients treated with anti-TNF therapy, substantial clinical improvement is accompanied by few if any immediate side effects. Recently, the first anti-IL-1 therapy has reached clinical use in the form of an IL-1 receptor antagonist (anakinra). Studies that combine the use of these biologicals are well underway. Meanwhile, the pharmaceutical pipelines contain newer biologicals that will soon be added to the rheumatologists' therapeutic formulary.

The revolution of biological therapy for RA has raised the bar for new treatments, but has not provided a complete therapeutic victory. Biologicals are expensive, have the nuisance factor of parenteral administration and require chronic use without which relapse is assured. Infectious complications of therapy are occasionally serious, including tuberculosis. Finally, there remains a significant subset of patients (20–40%)[3] who either only partly respond to biologicals or do not respond at all. Clearly, there remain patients in need of new therapeutic approaches. In addition, there will always remain an underlying longing by all patients for a 'cure' with its implied freedom from chronic medications. For these reasons, we believe that continued investigation of HSCT in RA is justified.

Mobililisation studies

Studies of stem cell mobilisation were considered necessary in RA as animal models and anecdotal clinical data suggested that colony-stimulating factors might cause a flare of disease. In addition, there was the possibility that RA and its treatment might prevent effective stem cell mobilisation. In 1997, the Leeds group reported a pilot study of G-CSF (filgrastim) at 5 μg/kg/day for stem cell mobilisation in five patients.[4] Efficacy, measured using peripheral blood CD34+ count, was considered adequate. Disease activity remained stable although the preadministration of intramuscular or intra-articular methylprednisolone (median 80 mg, range 40–120 mg) may have inhibited any proinflammatory effect of filgrastim.

In Australia, a phase I placebo-controlled study investigated the safety and efficacy of G-CSF in patients with severe active RA for the purpose of stem cell collection.[5] In a minority of patients, G-CSF administration was associated with an early or late transient flare of RA, which settled spontaneously or was responsive to an increase in prednisolone. Progenitor cell yields were

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satisfactory in all patients based on both $CD34^+$ counts and CFU-GM assays, and fulfilled recently published criteria in the EBMT/EULAR consensus guidelines for autoimmune disease (ie $CD34^+$ count $>2\times10^6$/kg and CFU-GM $>2\times10^4$/kg).[6] In all patients receiving G-CSF at 10 μg/kg/day, the target threshold of 2×10^6/kg $CD34^+$ cells was achieved with one leukapheresis. A further 33 patients underwent stem cell mobilisation with G-CSF alone in doses of 10–24 μg/kg per day for 5 days in a pilot randomised trial. Three patients (9.4%) experienced a self-limiting flare of disease with this regimen and an adequate stem cell yield was attained in all but one patient.[7]

In Paris, four patients received mobilisation with cyclophosphamide 4 g/m^2 followed by G-CSF 5 μg/kg/day.[8] As expected, $CD34^+$ cell yields were higher than with G-CSF alone and were sufficient for $CD34^+$ selection to be performed in three of the patients. The incorporation of cyclophosphamide also resulted in improvement in parameters of disease activity with one patient achieving ACR 70, two patients achieving ACR 50 and one patient ACR 20. Improvements were noted for both arthritis and extra-articular manifestations. However, after initial improvement relapse of arthritis occurred in all patients, reaching a peak at 4–6 months. Persistent disease activity was seen in three patients, although this never reached baseline levels even 2 years after the procedure. In one patient, the disease gradually remitted without additional treatment.

In Leeds, Bingham *et al*[9] were able to perform double selection on harvests in six patients mobilised with cyclophosphamide 2 g/m^2 and GCSF 263 μg daily. Durez *et al*[10] successfully mobilised and performed double selection using cyclophosphamide 1.5 g/m^2, etoposide 300 mg/m^2 and G-CSF 5 μg/kg/day. Reports of flare seem to be rare when cyclophosphamide is used in mobilisation and in some cases it seems to have resulted in sustained improvement of disease. However, the case of Joske *et al*,[11] which was mobilised with cyclophosphamide 4 g/m^2 and G-CSF flared on neutrophil recovery.

Pilot studies

Over 70 patients have now received autologous HSCT for severe RA in Australia, USA and Europe since 1996 providing important insights into the mechanism of the responses attained – see Table 1. In Australia, a dose escalation study involving eight patients established cyclophosphamide 200 mg/kg as a safe and effective conditioning regimen.[12] Four patients received 100 mg/kg cyclophosphamide prior to infusion of unmanipulated stem cell grafts resulting in only transient (3–4 month) ACR 20–50 responses. A further four patients, receiving 200 mg cyclophosphamide had more substantial (ACR 50–70) and sustained responses. Both groups tolerated the procedure well but recurrence occurred in the four patients receiving 200 mg cyclophosphamide from 6 to 24 months. It was subsequently noted that 3/4 rapidly responded to DMARDs suggesting an immunomodulation of disease despite recurrence.[13] A total of 31 further patients received this conditioning regimen in Australia in a pilot randomised trial between CD34 selected and unmanipulated HSCT.[7] In general, ACR 50–70 responses were attained in the majority of these therapy-resistant patients with no significant difference between the two arms. The major problem has been sustaining responses that have usually only lasted 6–12 months, but in 10% are still persisting at 2 years.

In contrast to the autologous setting, one would expect that a syngeneic HSCT could be curative and McColl *et al*[14] reported the first syngeneic PBSCT for autoimmune disease in the world. The importance of the syngeneic case lies in its demonstration that the T cell v_β repertoire was of donor origin possibly accounting for the sustained and impressive response the patient attained. This patient was in complete remission at last follow-up (J Szer, pers communication). This case appears to demonstrate the importance of full donor chimerism at the T-cell level – a situation that may be a necessity for allogeneic PBSCT to be totally successful.

The Dutch collaborative group have treated 14 patients with active, progressively erosive RA, who have failed at least four disease-modifying antirheumatic drugs. Patients were treated with cyclophosphamide 200 mg/kg before haemopoietic rescue with $CD34^+$-enriched harvests. Although no complete remissions were seen, significant improvements of disease activity were observed in all patients with 2–12 month follow-up. Five patients are off antirheumatic drugs. One patient experienced a flare several weeks after transplantation, which responded to low-dose prednisone and methotrexate.[15] Of interest, two of the responders were patients who had failed TNF antagonists.

In Belgium, a 22-year-old patient with refractory systemic and erosive RA was treated with busulphan

Table 1 Major published phase I/II trials using HSCT for severe RA

Conditioning	*Graft*	*Number of patients*	*Reference*
Cyclo 200 mg/kg	17CD34, 14 Unmanip	31	Moore *et al*[7]
Cyclo 200 mg/kg	CD34+, CD3−	6	Bingham *et al*[9]
Bu/Cy	CD34+, CD3−	2	Durez *et al*[10]
Cyclo 200 mg/kg	Unmanip	1	Joske *et al*[11]
Cyclo 100–200 mg/kg	Unmanip	8	Snowden *et al*[12]
Cyclo 200 mg/kg	CD34+	12	Verburg *et al*[15]
Cyclo 200/ATG 90	CD34+	4	Burt *et al*[16]
Cyclo 200/ATG 120	Unmanip	2	Pavletic *et al*[17]

CD34, CD34 selected graft; Unmanip, unmanipulated stem cell graft; CD3−; T, cell depleted.

16 mg/kg and cyclophosphamide 120 mg/kg followed by rescue with a highly purified autograft (98.4% $CD34^+$ cells and no detectable T cells). At 3 months, she was in complete remission off steroids. At 4 months, she was successfully treated for pneumocystis pneumonitis (communicated at the Basel Meeting, October 1998). She remains free of joint symptoms at 24 months. The remission has been maintained despite complete reconstitution of the T-cell repertoire to pretransplant levels.[10] The other patient treated with this protocol also achieved complete remission by 3 months, but died of multiresistant staphylococcus and carcinoma of the lung at 5 months (communicated at the Basel Meeting, October 1998). This protocol, with its use of a myeloablative preparative regimen and a high degree of T-cell depletion of the graft, appears to have produced the most impressive efficacy, although its use must be regarded with caution because of the significant toxicity.

In Leeds, six patients with RA resistant to four DMARDs have received treatment with cyclophosphamide 200 mg/kg and double selected autograft. No serious complications occurred either during autograft or up to 21 months of follow-up. All six patients have responded (2 with ACR 20, 3 with ACR 50 and 1 with ACR 70). One patient continues at ACR 50/20 at 6 months, but five patients relapsed at 1–9 months. However, these have made subsequent responses to cyclosporin A or cyclosporin A with methotrexate (two ACR 50, one complete remission, one no response, one insufficient follow-up). These data support the use of early salvage or maintenance treatment following a 'debulking' of disease by the high-dose treatment.[9]

In Chicago, four patients with RA have been treated with cyclophosphamide 200 mg/kg, ATG 90 mg/kg, methylprednisolone 3 g followed by a $CD34^+$ cell enriched (2.5–2.7 log T-cell depleted) autograft.[16] Two of the four patients in this trial demonstrated sustained ACR 70 responses, whereas the remaining two were less successful. Likewise two patients in Omaha had ACR 70 responses until 6 months when disease recurrence occurred.[17] Recently, Burt *et al* in Chicago performed the world's first allogeneic nonmyeloablative stem cell transplant for RA from a HLA-matched sibling.[18]

Future of HSCT for RA

There appears to be at least three directions available to enhance the results of HSCT in RA patients.[19] One approach would involve intensifying the conditioning regimen for autologous stem cell transplantation to be more myeloablative. The anticipated greater toxicity could be justified if more durable remissions were achieved.

Another approach would be to continue with the current well-tolerated regimen but add chronic post-transplant immune suppression. Such a course is planned by European investigators. The EBMT autoimmune diseases working party has the **A**utologous **S**tem cell **T**ransplantation **I**nternational **R**heumatoid **A**rthritis (ASTIRA) trial that will involve mobilisation with 4 g/m^2 cyclophosphamide and GCSF followed by randomisation between an unmanipulated HSCT with cyclophosphamide 200 mg/kg conditioning and maintenance DMARDs or maintenance DMARD therapy without HSCT. Patients who have failed TNF antagonists will be eligible for this trial. This latter approach is based on the proven safety record of high dose cyclophosphamide, but may be less attractive to patients who now have available to them increasing numbers of specific biological therapies to control their disease.

Allogeneic transplantation would represent yet another approach to the management of RA. Case reports of patients with RA who have undergone allogeneic transplantation for aplastic anaemia suggest complete and long-lasting remissions in the majority of patients.[20–23] The rationale for allogeneic HSCT is to change the host's genetic susceptibility to disease and also perhaps provide allogeneic graft *vs* autoimmunity (GVA) effect. This approach involves both the greatest risk of toxicity and the greatest potential for durable remission of disease.

At Northwestern University (Chicago, IL, USA), two new protocols have been opened. One is a more aggressive myeloablative approach to autologous transplantation using busulfex and cyclophosphamide. The other is allogeneic transplantation employing nonmyeloablative yet strongly immunoablative conditioning regimen combined with $CD34^+$ enrichment of donor stem cells. 'Cure' remains the Holy Grail of RA research and the deepest desire of our patients. Designing stem cell transplant protocols that minimise procedure-related morbidity and mortality may offer potentially curative therapy to patients with RA.

References

1 Pincus T, Callahan LF. What is the natural history of rheumatoid arthritis? *Rheum Dis Clin North Am* 1993; **19**(1): 123–151.
2 Snowden JA, Brooks PM, Biggs JC. Haemopoietic stem cell transplantation for autoimmune diseases. *Br J Haematol* 1997; **99**(1): 9–22.
3 Maini R, St Clair EW, Breedveld F et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999; **354**: 1932–1939.
4 McGonagle D, Rawstron A, Richards S *et al*. A phase 1 study to address the safety and efficacy of granulocyte colony-stimulating factor for the mobilization of hematopoietic progenitor cells in active rheumatoid arthritis. *Arthritis Rheum* 1997; **40**: 1838–1842.
5 Snowden JA, Biggs JC, Milliken ST *et al*. A randomised, blinded, placebo-controlled, dose escalation study of the tolerability and efficacy of filgrastim for haemopoietic stem cell mobilisation in patients with severe active rheumatoid arthritis. *Bone Marrow Transplant* 1998; **22**: 1035–1041.
6 Tyndall A, Gratwohl A. Blood and marrow stem cell transplants in auto-immune disease: a consensus report written on behalf of the European League against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 1997; **19**: 643–645.
7 Moore J, Brooks P, Milliken S et al. A pilot randomized trial comparing CD34-selected versus unmanipulated hemopoietic stem cell transplantation for severe, refractory rheumatoid arthritis. *Arthritis Rheum* 2002; **46**(9): 2301–2309.

8 Breban M, Dougados M, Picard F *et al*. Intensified-dose (4 gm/m^2) cyclophosphamide and granulocyte colony-stimulating factor administration for hematopoietic stem cell mobilization in refractory rheumatoid arthritis. *Arthritis Rheum* 1999; **42**: 2275–2280.
9 Bingham SJ, Snowden J, McGonagle D *et al*. Autologous stem cell transplantation for rheumatoid arthritis – interim report of 6 patients. *J Rheum* 2001; **64** (Suppl): 21–24.
10 Durez P, Toungouz M, Schandene L *et al*. Remission and immune reconstitution after T-cell-depleted stem-cell transplantation for rheumatoid arthritis [letter]. *Lancet* 1998; **352**: 881.
11 Joske DJ, Ma DT, Langlands DR, Owen ET. Autologous bone-marrow transplantation for rheumatoid arthritis [letter]. *Lancet* 1997; **350**: 337–338.
12 Snowden JA, Biggs JC, Milliken ST *et al*. A phase I/II dose escalation study of intensified cyclophosphamide and autologous blood stem cell rescue in severe, active rheumatoid arthritis. *Arthritis Rheum* 1999; **42**: 2286–2292.
13 Moore J, Milliken S, Ma D *et al*. Peripheral blood stem cell transplantation for rheumatoid arthritis – Australian experience. *J Rheum* 2001; **64** (Suppl): 8–12.
14 McColl G, Kohsaka H, Szer J, Wicks I. High-dose chemotherapy and syngeneic hemopoietic stem-cell transplantation for severe, seronegative rheumatoid arthritis. *Ann Inter Med* 1999; **131**: 507–509.
15 Verburg RJ, Kruize AA, van den Hoogen FH *et al*. High-dose chemotherapy and autologous hematopoietic stem cell transplantation in patients with rheumatoid arthritis: results of an open study to assess feasibility, safety, and efficacy. *Arthritis Rheum* 2001; **44**: 754–760.
16 Burt RK, Georganas C, Schroeder J *et al*. Autologous hematopoietic stem cell transplantation in refractory rheumatoid arthritis – sustained response in two of four patients. *Arthritis Rheum* 1999; **42**: 2281–2285.
17 Pavletic S, O'Dell J, Pirruccello S *et al*. Intensive immunoablation and autologous blood stem cell transplantation in patients with refractory rheumatoid arthritis: the University of Nebraska Experience. *J Rheumatol* 2001; **28** (Suppl 64): 13–20.
18 Burt R, Oyama Y, Barr W, Traynor A. Allogeneic nonmyeloablative stem cell transplantation (NST) for Refractory Rheumatoid Arthritis, EBMT 2003 Meeting, in press.
19 Burt RK, Barr W, Oyama YU *et al*. Future strategies in hematopoietic stem cell transplantation for rheumatoid arthritis. *J Rheumatol* 2001; **28** (Suppl 64): 42–48.
20 Baldwin JL, Storb R, Thomas Ed *et al*. Bone marrow transplantation in patients with gold-induced marrow aplasia. *Arthritis Rheum* 1977; **20**: 1043–1048.
21 Nelson JL, Torrez R, Louie FM *et al*. Pre-existing autoimmune disease in patients with long-term survival after allogeneic bone marrow transplantation. *J Rheumatol* 1997; **24** (Suppl 48): 23–29.
22 Snowden JA, Kearney P, Kearney A *et al*. Long-term outcome of autoimmune disease following allogeneic bone marrow transplantation. *Arthritis Rheum* 1998; **41**: 453–459.
23 McKendry RJR, Huebsch L, Leclair B. Progression of rheumatoid arthritis following bone marrow transplantation: a case report with a 13-year follow up. *Arthritis Rheum* 1996; **39**: 1246–1253.