Intensive Immunosuppression and Autologous Stem Cell Transplantation for Patients with Severe Rheumatoid Arthritis: The Leiden Experience

JACOB M. van LAAR, ROBERT J. VERBURG, WILLEM E. FIBBE, and FERDINAND C. BREEDVELD

ABSTRACT. Ten patients with active, destructive rheumatoid arthritis refractory to antirheumatic therapy enrolled in a study to evaluate the effects of intensive immunosuppression followed by autologous stem cell transplantation. Intensive immunosuppression was achieved with high dose cyclophosphamide as part of the mobilization (4 g/m^2) and conditioning (200 mg/kg) regimen. The autologous stem cell products were enriched for CD34+ cells to minimize the chance of reinfusing autoreactive lymphocytes. Eight patients completed all consecutive treatment steps, one patient withdrew after mobilization because of improvement, one patient was taken off study because of pulmonary embolism. The treatment appeared feasible and safe, and marked sustained clinical improvement was observed in 6 patients, 2 of whom were previously unresponsive to tumor necrosis factor blocking therapy. In 5 patients disease modifying antirheumatic drugs were successfully withdrawn after transplantation. The treatment induced significant lymphopenia, with low levels of naive CD4+ T cells in particular, without clinical sequelae. Titers of rheumatoid factor dropped but did not normalize. (J Rheumatol 2001;28 Suppl 64:25–7)

Key Indexing Terms:
INTENSIVE IMMUNOSUPPRESSION HEMATOPOIETIC STEM CELL TRANSPLANTATION
AUTOLOGOUS RHEUMATOID ARTHRITIS

INTRODUCTION

Intensive immunosuppression employing high dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) is emerging as a novel treatment strategy for selected patients with severe autoimmune diseases, such as rheumatoid arthritis (RA). Patients with a therapy-refractory, progressively erosive disease who are at risk of functional disability and early mortality are considered eligible for treatment with HDC + ASCT. Benefits of longterm improvement of disease activity and quality of life must be balanced, however, against hospitalization and adverse events including treatment related mortality.

DECISION ANALYSIS

Before embarking on a clinical study, we attempted to address the risk/benefit issue by decision analysis using a Markov model[1]. This model allows comparison of HDC + ASCT versus continued pharmacological treatment in patients with active disease who have previously failed standard treatments [methotrexate (MTX), combination therapy, tumor necrosis factor (TNF) blockade] taking into account the possibility that events and outcomes vary or recur in time. Transition probabilities between health states, and quality of life estimates for each particular health state, were obtained from published trials or estimated by an expert panel of 4 senior rheumatologists. This enabled computation of the cumulative number of quality adjusted life years for both strategies, ranging from a theoretical minimum of 0 (immediate death) to n × 1 after n years of perfect health. With a treatment related mortality (TRM) < 3.3%, HDC + ASCT appeared to be the preferred treatment. A sensitivity analysis was performed to determine the minimal desired effectiveness of HDC + ASCT when TRM was set at 10% (e.g., after HLA-identical allogeneic SCT). The efficacy required to compensate for this TRM was found to represent a potentially realistic scenario: a 50–70% response by American College of Rheumatology (ACR) criteria would need to be attained after transplantation in 60% of patients and maintained for 6 months, with a durable good clinical response being required in 20% of patients.

A PHASE I/II STUDY ON HDC + ASCT IN PATIENTS WITH INTRACTABLE RA

The results of the decision analysis guided us in the design of a treatment regimen that would combine efficacy with a low risk of TRM and morbidity. It was reasoned that this goal could be met by employing intensive immunosuppression rather than myeloablation, and *ex vivo* enrichment of autologous peripheral blood stem cells rather than *in vivo* lympho-

From the Departments of Rheumatology and Hematology, Leiden University Medical Center, Leiden, The Netherlands.

Supported by the Dutch Arthritis Association and Amgen Nederland.

J.M. van Laar, MD, Assistant Professor of Rheumatology; R.J. Verburg, MD, Fellow, Department of Rheumatology; W.E. Fibbe, Professor of Hematology, Department of Hematology; F.C. Breedveld, Professor of Rheumatology, Department of Rheumatology.

Address reprint requests to Dr. J.M. van Laar, Department of Rheumatology, C4-R, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. E-mail: j.m.van_laar@lumc.nl

cyte depletion. This treatment regimen had been successfully employed in a Dutch pilot study in patients with progressive systemic sclerosis[2]. Details of the treatment regimen are shown in Table 1. To suppress disease activity and to increase the yield of hematopoietic progenitor cells high dose cyclophosphamide was included in the mobilization procedure. Disease modifying antirheumatic drugs (DMARD) were discontinued prior to mobilization. The inclusion and exclusion criteria were in accordance with the international guidelines proposed by the European Group for Blood and Marrow Transplantation/EULAR[3]. Consequently, patients with active, progressively erosive RA who had failed 4 DMARD including combination therapy with maximal tolerable doses of methotrexate were considered eligible. The other eligibility criteria are listed in Table 2. Failure to TNF blocking agents was not a prerequisite, as these agents were not registered at the time of initiation of the study. However, 4 patients had failed TNF blocking agents in clinical trials.

Ten patients entered the study at our institute, as part of a multicenter study in the Netherlands[4]. Most of these patients had been extensively pretreated and had longstanding disease (Table 3). Another 12 eligible patients declined for varying reasons, with the potential risk of TRM ranking highest (estimated to be lower than 5%). One of these patients died during followup due to sepsis, underscoring the importance of a control group in transplant studies. Two of the 10 patients who did enter the study were not transplanted. One patient chose not to proceed to conditioning because she chose a wait-and-see strategy after mobilization, which alone induced a marked improvement of disease activity; another patient was withdrawn from the study when pulmonary embolism was diagnosed before conditioning (thought to be unrelated to the mobilization regimen). Mobilization, leukapheresis, conditioning, and ASCT were successfully completed in 8 patients. With one to 2 leukaphereses, sufficient stem cells were harvested in all patients to enable subsequent positive selection of CD34+ (Clinimacs Device, Miltenyi Biotec, Munich, Germany). The percentage of CD34+ and CD3+ cells thus obtained in the grafts (> 95% and < 0.1%, respectively) met the predesignated target levels. No unexpected toxicity was observed, although several infectious complications required treatment. Engraftment occurred rapidly, and duration of neutropenia (defined as $< 0.5 \times 10^9$ neutrophils/l) was 13 days (range 9–17) and median duration of platelet count $< 20 \times 10^9$/l was 3 days (range 0–5).

Clinical responses varied from persistent disease activity in 2 patients to clinically meaningful improvement of disease activity (≥ 50% reduction of disease activity score at ≥ 50% of visits) in 6 patients, 2 of whom had failed TNF blocking therapy (Figure 1). One patient has been in near complete remission for 18 months without antirheumatic drugs. In 3 patients DMARD (2 × MTX, 1 × leflunomide) were reinstituted after 3 months because of an unsatisfactory response to treatment. This resulted in subsequent improvement of disease activity in one patient. Immunophenotyping of peripheral blood

Table 1. Treatment regimen employed in phase I/II study in patients with intractable RA. DMARD were discontinued prior to mobilization, while steroids were tapered after conditioning depending on disease activity. NSAID were continued in the lowest dosage needed to control pain and morning stiffness.

1. Mobilization of autologous peripheral blood stem cells with a single IV infusion of cyclophosphamide (4 g/m^2), followed by G-CSF (filgrastim 10 µg/kg SC)
2. Leukapheresis followed by positive selection of CD34+ stem cells (Clinimacs) to diminish the risk of reinfusing potentially autoreactive lymphocytes. Leukapheresis was performed to obtain at least 5×10^6 CD34+ cells/kg body weight
3. Conditioning consisted of administration of cyclophosphamide (200 mg/kg IV) with methylprednisolone 2 mg/kg for consecutive days to increase tolerability of the conditioning
4. Reinfusion of the autologous graft 48 h after last cyclophosphamide infusion

G-CSF: granulocyte-colony stimulating factor; IV: intravenous; SC: subcutaneous.

Table 2. Eligibility criteria for patients with RA.

Inclusion criteria
- Progressive erosive disease
- Failure to respond to at least 4 second line drugs, including maximal tolerable dose of MTX, and combination therapy of at least 2 second line drugs
- Active disease as defined by:
  ≥ 6 swollen joints and
  ≥ 6 tender joints and
  ≥ 1 h early morning stiffnes or ESR > 28 mm/h
- Steinbrocker functional score class II-III
- Disease duration ≥ 3 years
- Age 18–60 years

Exclusive criteria
- Pulmonary impairment, defined as total lung capacity or vital lung capacity or DLCO < 70% of predicted values
- Cardiac impairment, defined as clinical evidence of heart failure with a left ventricular ejection fraction < 50% assessed by cardiac echography
- Liver disease, defined as ASAT or ALAT or bilirubin > 2 × upper limit of normal
- Renal impairment, defined as creatinine clearance < 70 ml/min
- Acute or chronic infection
- Concurrent neoplastic disease or evidence of myelodysplasia
- Recent joint arthroplasty (< 6 months)

Table 3. Patient characteristics.

Number	8 (7 female, 1 male)
Age, yrs, mean (range)	46 (32–55)
Rheumatoid factor positive	7/8
Disease duration, yrs (range)	13 (7–20)
Disease activity score at entry, mean (range)	5.3 (3.82–7.24)
Failed antirheumatic treatments	
MTX (8), sulfasalazine (7), hydroxychloroquine (8), cyclosporine (5), gold (7), TNF blocking agents (4), azathioprine (5), D-penicillamine (5). Four patients were corticosteroid dependent.	

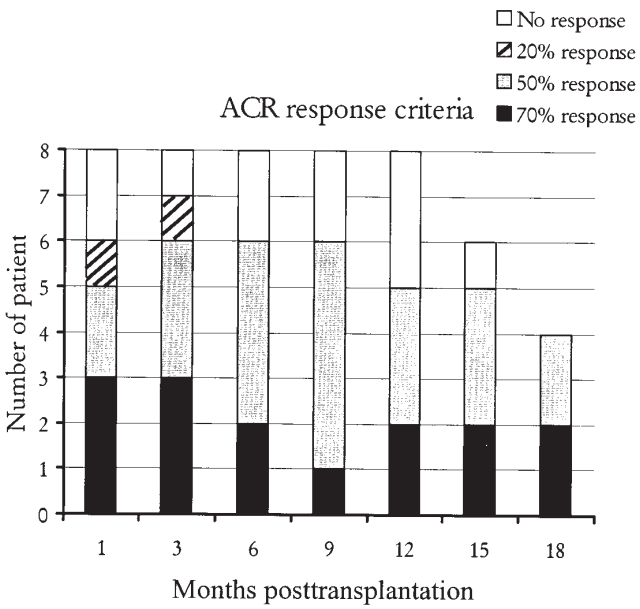

Figure 1. Clinical responses in 8 patients with RA treated with high dose cyclophosphamide followed by autologous CD34+ stem cell transplantation.

mononuclear cells revealed markedly depressed levels of circulating CD4+ CD45RA T cells in particular during the first 6 months of followup, but no clear correlation with clinical effects was apparent. A 40–45% drop in mean titer of IgM rheumatoid factor was observed after transplantation compared to baseline, which was statistically significant ($p < 0.05$, Wilcoxon signed ranks test) at one, 6, and 9 months.

SUMMARY

The results of the present study confirm the efficacy of HDC + ASCT in patients with intractable RA[5-8]. Although it was anticipated that patients with the more extensive joint destruction would benefit less than other patients, this assumption could not be corroborated in our pilot study. Interestingly, 2 of 4 patients who failed TNF blocking therapy responded to HDC + ASCT. Future studies should focus on identification of factors that predict a good clinical response, on improvement of effectiveness, and comparison with conventional pharmacological treatment[9,10]. Finally, the understanding that HDC + ASCT is not a routine treatment implies that patient preference plays a decisive role in the implementation of this new treatment modality. A significant number of our patients were not willing to take the risks associated with the treatment. The adaptation to functional disability of patients with longstanding intractable disease may be a contributing factor. To evaluate patients' opinions of the treatment procedures, we interviewed our patients after transplantation. The minimal duration of a good clinical response reported by the patients was 12–36 months in order to meet their expectations and compensate for the morbidity during the transplant period.

It should be emphasized that progress in the development of this novel treatment modality can only be achieved by multicenter studies employing uniform eligibility criteria, treatment regimens, and study variables.

REFERENCES

1. Verburg RJ, Sont JK, Vliet Vlieland TPM, et al. High dose chemotherapy followed by autologous peripheral blood stem cell transplantation or conventional pharmacological treatment for refractory rheumatoid arthritis? A Markov decision analysis. J Rheumatol 2001;28:719-27.
2. Van den Hoogen F, van Laar J, Schattenberg A, et al. High dose cyclophosphamide followed by autologous peripheral blood stem cell transplantation for the treatment of systemic sclerosis [abstract]. Arthritis Rheum 1999;42 Suppl:S169.
3. Tyndall A, Gratwohl A. Blood and marrow stem cell transplants in autoimmune disease. A consensus report written on behalf of the European League Against Rheumatism (EULAR) and the European Group for Blood and Marrow Transplantation (EBMT). Br J Rheumatol 1997;36:390-2.
4. Verburg RJ, Kruize AA, van den Hoogen FHJ, et al. High dose chemotherapy and autologous hematopoietic stem cell transplantation in patients with rheumatoid arthritis. Arthritis Rheum 2001,44:754-60.
5. 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;42:2275-80.
6. 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;42:2281-5.
7. Snowden JA, Biggs JC, Milliken S, Fuller AK, Brooks PM. A phase I/II dose escalation study of intensified cyclophosphamide and autologous blood stem cell rescue in severe, active rheumatoid arthritis. Arthritis Rheum 1999;42:2286-92.
8. Brodsky RA, Petri M, Smith BD, et al. Immunoablative high-dose cyclophosphamide without stem-cell rescue for refractory, severe autoimmune disease. Ann Intern Med 1998;129:1031-35.
9. Niethammer D, Kummerle-Deschner J, Dannecker GE. Side-effects of long-term immunosuppression versus morbidity in autologous stem cell rescue: striking the balance. Rheumatology 1999;38:747-50.
10. Van Laar JM. Immunological reconstitution following immune ablation and stem cell therapy. Arthritis Res 2000;4:270-5.