Reduction of Joint Damage in Severe Rheumatoid Arthritis by High-Dose Chemotherapy and Autologous Stem Cell Transplantation

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Objective. To examine the influence of high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) on joint damage in patients with rheumatoid arthritis.

Methods. Eight patients with active, refractory, progressively erosive RA were treated. The conditioning regimen consisted of intravenous administration of high doses of cyclophosphamide (totaling 200 mg/kg), with subsequent reinfusion of the positively selected graft. Radiographs of hands and feet were obtained before, and at 1 and 2 years after transplantation. All radiographs of hands and feet obtained up to 6 years before transplantation were also collected to compare radiographic progression before and after HDC + ASCT. Scoring of all radiographs was performed according to the Larsen scale by a trained investigator who was blinded with regard to the clinical data.

Results. Radiographic assessment by the Larsen scale showed a decreased progression of joint damage. Before transplantation, the mean Larsen score increased at a rate of 8.9 points per year. During the 2 years after transplantation, the mean rate of progression in the Larsen score decreased to 2.7 points per year (P = 0.023 by paired t-test).

Conclusion. The results of the present analysis demonstrate major beneficial effects of HDC + ASCT on the rate of joint destruction during the first 2 years of followup after treatment.

A number of clinical studies on the effects of high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) have demonstrated long-term improvements of disease activity in patients with rheumatoid arthritis (RA) that was previously refractory to disease-modifying antirheumatic drugs (DMARDs) (1–9). The rationale of this strategy is based on the concept of immunoablation by intensive immunosuppression, with subsequent regeneration of naive T lymphocytes derived from reinfused hematopoietic progenitor cells (10). Though its effects on disease activity in patients with RA that is refractory to conventional medication have been well documented, radiographic outcome has not been addressed. We conducted an open study to investigate the effects of HDC + ASCT on the progression of joint damage in a cohort of patients with treatment-refractory active, destructive RA.

PATIENTS AND METHODS

Patient selection. The study was a single-center side study of a multicenter, open-label phase I/II trial to examine the clinical and immunologic effects of HDC + ASCT in severe RA (8). The protocol was approved by the Ethics Committee of Leiden University Medical Center. All patients provided written informed consent. Patients had an established diagnosis of RA according to the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria (11), consisting of progressively erosive disease with involvement of the large joints. In all cases, the disease was refractory to treatment with DMARDs, including the maximum tolerable dosages of methotrexate and combination therapy. Exclusion criteria were organ failure of any kind, acute or chronic infection, and concurrent neoplastic disease.

Treatment schedule. Autologous hematopoietic stem cells were mobilized using a single infusion of 4 gm/m² cyclophosphamide (CYC), followed by filgrastim (granulocyte colony-stimulating factor), until the time of leukapheresis. Immunomagnetic selection of CD34+ cells from the leukapheresis product was performed to obtain a minimum of 2 × 10⁶ CD34+ cells/kg and a maximum of 2 × 10⁷ CD3+ cells/kg.
All DMARDs were discontinued before mobilization, and corticosteroids were tapered thereafter when possible. Nonsteroidal antiinflammatory drugs were continued at the lowest dosage needed to control pain and morning stiffness. The conditioning regimen consisted of CYC 50 mg/kg/day intravenously for 4 consecutive days (total 200 mg/kg). The interval between the last dose of CYC and the infusion of stem cells was at least 48 hours.

**Clinical evaluation.** Disease activity was assessed using the Disease Activity Score (DAS) (12) and the ACR response criteria (13).

**Radiographs.** Radiographs of the hands and feet were obtained at the start of the study and 1 and 2 years after HDC/ASCT. To compare the progression of joint damage before and after transplantation, radiographs of the hands and feet obtained up to 6 years before transplantation were also collected and scored. Radiographs were scored by one independent, experienced assessor who was blinded with regard to the clinical data. One set of radiographs (hands and feet) obtained at a single time point was scored simultaneously. Further scoring of the sets was done in chronological order. Each set could be compared with the previous one. Total scores of radiographs at consecutive time points could increase or be stable, but could not decrease. The radiographs were assessed according to the Larsen scale for small joints (14,15).

**Statistical analysis.** The radiographic progression before transplantation was compared with the radiographic progression after transplantation, by Student’s paired t-test. Wilcoxon’s rank sum test was used to analyze the clinical data. All available data were used. P values less than 0.05 were considered significant.

**RESULTS**

**Patient data.** Eight patients with active, progressively erosive, refractory RA entered the study (mean age 48 years, range 35–55 years; disease duration 12.8 years, range 7–20 years). All patients had received the maximum tolerable dosage of methotrexate. Four patients had also been treated unsuccessfully with anti-tumor necrosis factor (anti-TNF). All patients had a DAS >3.7 at baseline, defined as high disease activity, and progressive erosive disease (12,13).

**Clinical results.** The mean DAS was 5.41 at baseline (range 3.82–7.24) and decreased to 2.39 at 3 months after transplantation (range 0.89–4.36) (P = 0.012). The decrease in DAS remained statistically significant up to 24 months after transplantation; the mean DAS at 24 months after transplantation was 3.42 (range 1.16–4.98) (P = 0.012). The course of the DAS is shown in Figure 1. The mean C-reactive protein (CRP) concentrations in serum followed the same trend as the DAS, dropping from 56 mg/liter before transplantation (range 0–129) to 14 mg/liter at 3 months after transplantation (range 2–24) and to 40 mg/liter at 24 months after transplantation (range 0–88) (Figure 1). The decrease in CRP was statistically significant after 3 months (P = 0.050), but not at 24 months after transplantation (P = 0.249). The ACR 20%, 50%, and 70% response criteria were met by 5 of 8, 5 of 8, and 2 of 8 patients, respectively, at 12 months, and 4 of 8, 3 of 8, and 1 of 8 patients at 24 months.

DMARDs were reinstituted at varying intervals after transplantation in all patients (Figure 2) because of flares of disease activity. The mean time that patients did not receive DMARDs was 14.8 months (95% confidence interval 7.4–22.2). When signs of disease activity

![Figure 1](https://example.com/image1.png)

**Figure 1.** Disease Activity Score (DAS) and C-reactive protein (CRP) levels in 8 patients. Levels were determined at screening and before and up to 24 months after transplantation. Values are the mean and SEM.

![Figure 2](https://example.com/image2.png)

**Figure 2.** Time after high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) until reinstitution of disease-modifying antirheumatic drugs (DMARDs). The mean time that patients did not receive DMARDs was 14.8 months (95% confidence interval 7.4–22.2).
returned, methotrexate was reinstituted at dosages ranging from 5 to 17.5 mg/week. One patient was subsequently treated with leflunomide (20 mg/day) after a lack of response to methotrexate. In 1 of 4 patients treated with prednisone (10 mg/day) before transplantation, prednisone was discontinued during the 2-year followup, while the 3 other patients still needed prednisone at dosages of 7.5–10 mg/day.

Radiographic outcome. The progression of joint damage as expressed in points per year was measured by dividing the increase in joint damage (Larsen score for small joints) by the time in years between measurements (Figure 3). Before transplantation, a mean rate of progression of 8.9 points per year was found (range 2.1–26.2). In the first year after transplantation, the rate of progression decreased to 1.3 points per year (range 0–4.3; \( P = 0.032 \) compared with before transplantation), a mean reduction of 85% in the rate of joint damage.

The effect on the rate of joint reduction was maintained during the second year of followup, with a mean rate of progression of joint destruction of 2.7 points per year (range 0.4–6.9 points; \( P = 0.023 \) compared with before transplantation).

**DISCUSSION**

The present study is the first to demonstrate the effects of HDC + ASCT on joint damage in patients with severe RA. Eight patients with intractable RA treated with HDC + ASCT at a single institution were longitudinally monitored for disease activity and joint damage, using a standardized protocol. These patients participated in a multicenter phase I/II clinical trial to evaluate the safety and efficacy of HDC + ASCT, the short-term results of which were previously published (8). Adverse events were assessed according to World Health Organization toxicity criteria: nausea, vomiting, and alopecia were observed in all patients. Other treatment-related morbidities included thrombosis of the vena subclavia due to an intravenous catheter (1 of 8 patients), hydradenitis (1 of 8 patients), metrorrhagia (1 of 8 patients), herpes zoster (1 of 8 patients), pseudomembranous enterocolitis (1 of 8 patients), pneumothorax (1 of 8 patients), and febrile neutropenia necessitating temporary antibiotic treatment (5 of 8 patients).

The present study extends these data by showing effects on DAS and joint damage during the 2 years following the intervention. As assessed by the DAS, the beneficial effects persisted, although DMARDs ultimately had to be reinstituted in all patients at different intervals after HDC + ASCT to keep disease activity at low levels. Of note, treatment with these drugs had not been efficacious before transplantation. The robust effects of HDC + ASCT translated into a significant reduction in the rate of joint damage, which was most marked in the first year after the intervention, when most patients were not taking DMARDs. Our study thus demonstrates that short and intensive treatment with a single immunosuppressive agent retards the rate of joint reduction, even at extended followup.

Nevertheless, the beneficial effects waned, and the treatment was curative in none of the patients. This clinical observation is supported by findings in synovial tissue infiltrates from RA patients who have undergone transplantation, showing marked reductions in, but re-emergence of, T cells in the synovium. T cells have been shown to activate osteoclasts, and this could be a mechanism whereby HDC + ASCT exerts its effects on joint damage.

Our results regarding joint damage are consistent with those of previous studies using different treatment strategies and other methodologies to assess joint damage (16–18). The present study, however, involved patients with end-stage and progressively erosive disease that had not responded to DMARDs. Furthermore, in 4 of 8 patients, TNF blocking therapy had also not been efficacious. We used each patient as his or her own control by comparing the rate of joint destruction before and after the intervention. Though many trials have demonstrated the effectiveness of DMARDs in preventing or retarding radiographic damage in early RA, the present study is, to our knowledge, the first to show that the rate of joint damage in advanced RA that is refractory to DMARD treatment can be significantly retarded with HDC + ASCT, presumably by suppressing disease activity to a very low level.
REFERENCES