HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION SIGNIFICANTLY REDUCES THE RATE OF JOINT DAMAGE IN SEVERE RHEUMATOID ARTHRITIS.

Verburg RJ, Sont JK and van Laar JM.

Abstract.

Objective. To investigate the effect of high dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) on joint progression.

Background. High dose chemotherapy followed by autologous stem cell transplantation (ASCT) has been proposed as a new treatment option for patients with severe refractory rheumatoid arthritis (RA). A majority of patients, previously refractory to medication responds favorably. However the influence on joint damage has not yet been investigated.

Patients and Methods. 8 patients with erosive, refractory, progressively rheumatoid arthritis, were treated. The conditioning regimen consisted of intravenous administration of high doses of cyclophosphamide (totalling 200 mg/kg), with subsequent reinfusion of the positively selected graft. X-rays of hands and feet were taken before, at 1 and 2 years after transplantation. All X-rays of hands and feet upto 6 years before transplantation were also collected to compare radiological progression before and after HDC + SCT. Scoring of all photos was performed according to Larsen by a trained investigator blinded to the clinical data.

Results. Radiologic damage as assessed by the Larssen score showed a decreased progression of joint damage. Before transplantation the mean Larsen score increased with 8.9 points per year. During the two years after transplantation the mean Kellgren score decreased to 2.7 points per year (P=0.023; paired T-test)

Conclusions. The results of the present analysis demonstrate major beneficial effects of high dose chemotherapy and autologous stem cell transplantation on joint destruction during the first two years of follow-up.
Introduction.
A number of clinical studies on the effects of high dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) have demonstrated longterm improvements of disease activity in patients with rheumatoid arthritis (RA) previously refractory to disease modifying anti-rheumatic drugs (DMARD) [1-9]. The rationale of this strategy is based on the concept of immunoablation by intense immunosuppression with subsequent regeneration of naive T lymphocytes derived from reinfused hematopoietic progenitor cells [10]. Though its effects on disease activity have been well documented in RA patients refractory to conventional medication, the radiological 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 therapy-refractory, active, destructive rheumatoid arthritis. In addition, the magnitude and duration of these effects was assessed.
Patients and Methods.

Patient selection. The study was a single-center side study of a multi-center, open label phase I/II trial to study the clinical and immunological effects of HDC + ASCT in severe RA [8]. The protocol was approved by the Ethics Committee of LUMC. All patients provided written informed consent. Patients had an established diagnosis of RA according to ACR-criteria [11], progressively erosive disease with large joint involvement, refractory to DMARDs including maximal tolerable dose 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 cyclophosphamide (CyC) 4 g/m² followed by filgrastim (G-CSF) until leukapheresis. Immunomagnetic selection of CD34⁺ cells from the leukapheresis product was performed aimed at obtaining a minimum of 2 x 10⁶ CD34⁺ cells/kg and a maximum of 2 x 10⁴ CD3⁺ cells/kg. All disease-modifying antirheumatic drugs (DMARDs) were discontinued before mobilization and corticosteroids were tapered thereafter when possible. NSAIDs were continued in 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 infusion of the stem cells was at least 48 hours.

Clinical evaluation. Disease activity was assessed using the disease activity score and ACR-response criteria [12].

Radiographs. Radiographs of hands and feet were taken at the start of the study and at 1 and 2 years after HDC and ASCT. In order to compare the progression of joint damage before and after transplantation, radiographs of hands and feet up to 6 years before transplantation were also collected and scored. Radiographs were scored by one independent, experienced assessor (A Cats, Leiden, The Netherlands) who was blinded to the clinical data. One set of radiographs (hands and feet) taken at a single timepoint 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 timepoints could increase or be stable, but not decrease. The photos were scored according to the Larsen score of the small joints (LSJ score) [13].

Statistical analysis. The radiological progression before transplantation was compared with the radiological progression after transplantation by the paired t-test. Clinical data were analyzed with the Wilcoxon rank-sum test. All available data were used.
Results.

Patient data. Eight patients with active, progressively erosive, refractory RA entered the study (mean age 48 years, range 35-55, disease duration 12.8 years, range 7-20). All patients had received the maximal tolerable dose of methotrexate, 4 patients had also failed treatment with anti-TNF antibody. All patients had a disease activity score (DAS) > 3.7 at baseline, defined as high disease activity, and progressive erosive disease [12,13].

Clinical Results. The mean DAS at baseline was 5.41 (range 3.82-7.24) and decreased to 2.39 at three 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 mean 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/l before transplantation (range 0-129) to 14 mg/l at 3 months after transplantation (range 2-24) and to 40 mg/l 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 20%, 50%, 70% ACR response criteria were met by 5/8, 5/8, 2/8 patients respectively at 12 months, and 4/8, 3/8, 1/8 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 patients were off-DMARDs was 14.8 months (95% confidence interval=7.4-22.2 months). When signs of disease activity returned methotrexate was reinstituted at doses ranging from 5 tot 17.5 mg/week. One patient was subsequently treated with leflunomide 20 mg/day after failing to respond to methotrexate. In one of four patients treated with prednisone (10 mg/day) before transplantation, prednisone could be discontinued during the 2-years follow-up, while the three other patients still needed prednisone at doses from 7.5-10 mg/day.
Figure 1. Mean Disease Activity Score and CRP (mg/l), at screening, before and up to 24 months after transplantation (+/- SEM, n=8).
Figure 2. Time after HDC and ASCT until DMARDs were reinstituted. On the X-axis the time in months after HDC and ASCT, on the Y axis the percentage of patients that did not use DMARDs. The mean time patients were off DMARDs was 14.8 months (95% confidence interval=7.4-22.2).
Radiological 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 progression of 8.9 points per year was found (range 2.1-26.2). The first year after transplantation the rate progression decreased to 1.3 point per year (range 0-4.3, P = 0.032), reflecting a mean reduction in the rate of joint damage of 85 %. The effect on the rate of joint reduction was maintained during the second year of follow-up with a mean rate of joint destruction of 2.7 points per year (range 0.4-6.9, P = 0.023 compared to before transplantation)
Figure 3. Mean radiological progression (points per year) according to the Larsen score of the small joints. The years before (left column), the first year after transplantation (second column), the second year after transplantation (third column).
Discussion.
The present study is the first to report the effects of high dose chemotherapy and autologous stem cell transplantation (HDC + ASCT) on joint damage in patients with severe rheumatoid arthritis (RA). Eight patients with intractable RA treated with HDC + ASCT at a single center institution were longitudinally monitored for disease activity and joint damage, using a standardized protocol. These patients participated in a multi-center phase I/II clinical trial to evaluate safety and efficacy of HDC + ASCT, the short-term results of which were previously published [8]. Adverse events were assessed according to WHO toxicity criteria: Nausea, vomiting and alopecia was observed in all patients. Other treatment related morbidities included thrombosis of the vena subclavia due to an i.v. catheter (1/8), hydradenitis (1/8), metrorrhagia (1/8), herpes zoster (1/8), pseudomembranous enterocolitis (1/8), pneumothorax (1/8) and febrile neutropenia necessitating temporary antibiotic treatment (5/8). The present study extends these data by showing effects on DAS and joint damage during the 2 years following the intervention. As for the DAS, the beneficial effects persisted although DMARDs ultimately needed to be reinstituted in all patients at different intervals after HDC + ASCT to maintain low levels of disease activity. Of note, patients had been refractory to these drugs before transplantation. The robust effects of HDC + ASCT translated into a significant reduction in the rate of joint damage that was most marked in the first year after the intervention when most patients were off-DMARDs. Our study thus demonstrates that a short and intensive immunosuppressive treatment with a single agent retards the rate of joint reduction, even at extended follow-up. Nevertheless, the beneficial effects waned and the treatment was curative in none of the patients. This clinical observation is supported by findings on synovial tissue infiltrate in transplanted RA patients, showing marked reduction but reemergence of T cells in 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 on joint damage are in keeping with previous studies using different treatment strategies, and other methodologies to assess joint damage [14-16]. The present study however involved patients with end-stage disease and progressively erosive disease not responding to DMARDs. Furthermore 4 out of 8 patients failed to respond to TNF blocking therapy. Also, we used the patient as his 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 radiological damage in early RA, our study is to our knowledge the first report showing that the rate of joint damage in advanced RA refractory to DMARDs can be significantly retarded, presumably by suppressing disease activity to a very low level.
Reference List
