High dose chemotherapy and autologous hematopoietic stem cell transplantation for rheumatoid arthritis

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CHAPTER 8

LONG-TERM FOLLOW-UP OF HEALTH STATUS IN PATIENTS WITH SEVERE RHEUMATOID ARTHRITIS AFTER HIGH DOSE CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION.

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Abstract.
Objective. High dose chemotherapy (HDC) followed by autologous hematopoietic stem cell transplantation (HSCT) is an experimental treatment for patients with severe, refractory rheumatoid arthritis (RA). The present study was undertaken to assess the long-term follow-up of health status in RA patients treated with HDC + HSCT.
Methods. Health status and utililty scores were assessed in eight patients pre- and posttreatment with HDC + HSCT. Patients were followed up to five years post-transplantation. Health status was assessed by the Health Assessment Questionaire (HAQ), the SF-36 survey and Arthritis Impact Measurements Scales (AIMS). Utility scores were calculated using the SF-36 and EQ-5D questionaires, from which quality adjusted life years (QALYs) were derived.
Results. Most measures of health status improved in the first two years post-transplantation, notably HAQ, and functional status and health change dimensions of the SF-36 survey and AIMS. Utility scores as assessed by EQ-5D and SF-36 also significantly increased after transplantation lasting for 2 years. This was also reflected in the QALYs gained when compared to baseline. A sensitivity analysis, given a life expectancy of 20 years, revealed that HDC + HSCT yields more QALYs than conventional therapy when treatment-related mortality is lower than 2.8%.
Conclusion. HDC + HSCT temporarily increases the functionality and health status of severe, refractory RA patients. Taking into account that the reported treatment-related mortality of HDC + HSCT is 1.3%, this treatment can be considered as a relevant treatment option for severe RA patients.

Introduction.

Rheumatoid arthritis (RA) is a chronic disease that results in a reduced life expectancy, significant morbidity and impaired quality of life [1-3]. High dose chemotherapy followed by autologous hematopoietic stem cell transplantation (HDC + HSCT) is a new treatment strategy for patients with severe RA [4,5]. Several pilot studies have showed remarkable clinical improvement of previously refractory RA patients for up to 2 years, as measured by Disease Activity Scores (DAS) and CRP [5,6]. Although no cures were observed, sensitivity to DMARD therapy was restored after transplantation [4,5].

Previously, we reported on a clinical decision analysis, using a Markov model, for the favorability of HDC + HSCT over conventional therapy in relation to the effectiveness and risks of this treatment [7]. However, it remains unclear whether health status in refractory RA patients is actually enhanced by a treatment involving HDC + HSCT, which is important for the clinical decision process for severe RA patients.

The purpose of this study was to assess the health status of refractory, progressive RA patients after treatment with HDC + HSCT over a long-term follow-up period. In addition, we calculated patients' appreciation of health in utilities up to 5 years post-transplantation, through which we analyzed whether this treatment resulted in a gain of quality adjusted life years (QALY). To address these issues we performed validated health assessments in a group of RA patients treated with HDC + HSCT.

Methods.

Patient selection. Seven female patients and one male patient (mean age 43 years, range 35-51; mean disease duration 13 years, range 7-20) were treated at Leiden University Medical Center (LUMC) with HDC +HSCT as part of a multi-center phase I/II trial [6]. Patients had an established diagnosis of RA according to ACR-criteria, had progressively erosive disease with large joint involvement, and were refractory to DMARDs including maximal tolerable dose of methotrexate and combination therapy. Four patients had also failed TNF-blockade. All patients were rheumatoid factor positive and had high DAS_{44}-scores at baseline (mean score 5.4, range 3.82-7.24) as defined by EULAR criteria [8]. The protocol was approved by the Ethics Committee of LUMC and all patients provided written informed consent.

Study Design. Patients were followed at 3-monthly intervals for 2 years post-transplantation and once more at 5 years post-transplantation. Clinical outcome was assessed at all evaluations with the exception of the long-term evaluation at 5 years. Validated health assessments were performed at all evaluations.

Clinical outcome. Clinical responses were categorized according to the EULAR response criteria [8]. Furthermore, we measured functionality using the Standard Disability Index of the Health Assessment Questionnaire (HAQ).

Health status assessments. Health status of RA patients was measured before and after treatment with HDC + HSCT. A RA specific instrument, the Arthritis Impact Measurement Scales (AIMS), and a generic instrument, SF-36, were used.

The AIMS is a reliable and valid instrument designed to measure health status in a multidimensional fashion using specific scales, summary components and overall impact measures. The AIMS approach has been validated for use in the Netherlands (Dutch-AIMS) [9]. In this study an important summary component, the Arthritis Impact VAS, is used because it is a good indicator of the impact of RA on patients' general health [10]. The SF-36 health survey is a short-form health survey assessing patients' health status across eight dimensions, which results in 4 main categories: functional status, well-being, general health and health change [11].

Utility and Quality Adjusted Life Years (QALY). Utility is the valuation of health of the patient on a scale from 0 (death) to 1 (optimal health). Utilities were measured using the EQ-5D questionnaire [12] and the SF-36-derived utility index, SF-6D [11]. In both instruments patients describe their health status using a classification system. Utilities for these descriptions are obtained from large representative study populations in the United Kingdom, based upon a time trade-off procedure for the EQ-5D and a standard gamble procedure for the SF-6D [13]. The EQ-5D has been shown to be valid and reliable in detecting the self-reported clinical changes of health in RA patients. From the SF-36-derived utility scores, QALYs were calculated as the area under the curve (AUC).

Statistical analysis. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS for Windows 11.0). Significance was interpreted as p-values lower than 0.05. To assess whether there was a significant difference in health status scores up to 9 months after transplantation compared to baseline, analyses of variance were performed using the one-way ANOVA. Student's t-tests were used to explore at which timepoints after treatment the changes in QoL-scores from baseline were significant. Using a threshold analysis, the percentage of treatment-related mortality (TRM) was determined below which HDC + HSCT rendered more QALYs as compared to conventional treatment. In this analysis, it was assumed that patients with HDC + HSCT had higher utilties, according to the observed utility curve, but had also a higher TRM. For conventional therapy, it was assumed that utilities remained stable at baseline values.

Results.

Clinical results.

Eight patients with severe, refractory RA were treated with HDC + HSCT. The clinical outcome was categorized by the EULAR-criteria. One year after transplantation two patients showed good improvement, five patients moderate improvement and one patient had no improvement. At the end of the two years follow-up, two patients still fulfilled the criteria of good improvement, four that of moderate improvement and two patients that of no improvement.

Functionality, as measured by the HAQ, showed significant improvement, dropping from 1.59 (0.27) (mean [standard deviation]) before transplantation to 0.97 (0.18) ($p = 0.02$) and 1.07 (0.15) ($p = 0.05$) at 3 and 6 months post-transplantation respectively (Figure 1A). Analyses of variance also showed a significant decrease in the HAQ-scores ($p = 0.048$). Although after 6 months HAQ scores steadily increased up to 1.25 (0.18) at 5 years, they did not reach pretreatment values. Even though these values were not statistically significant, a change in HAQ score of 0.22 units or more is considered clinically significant, as was the case throughout the 5 years of follow-up [14] .

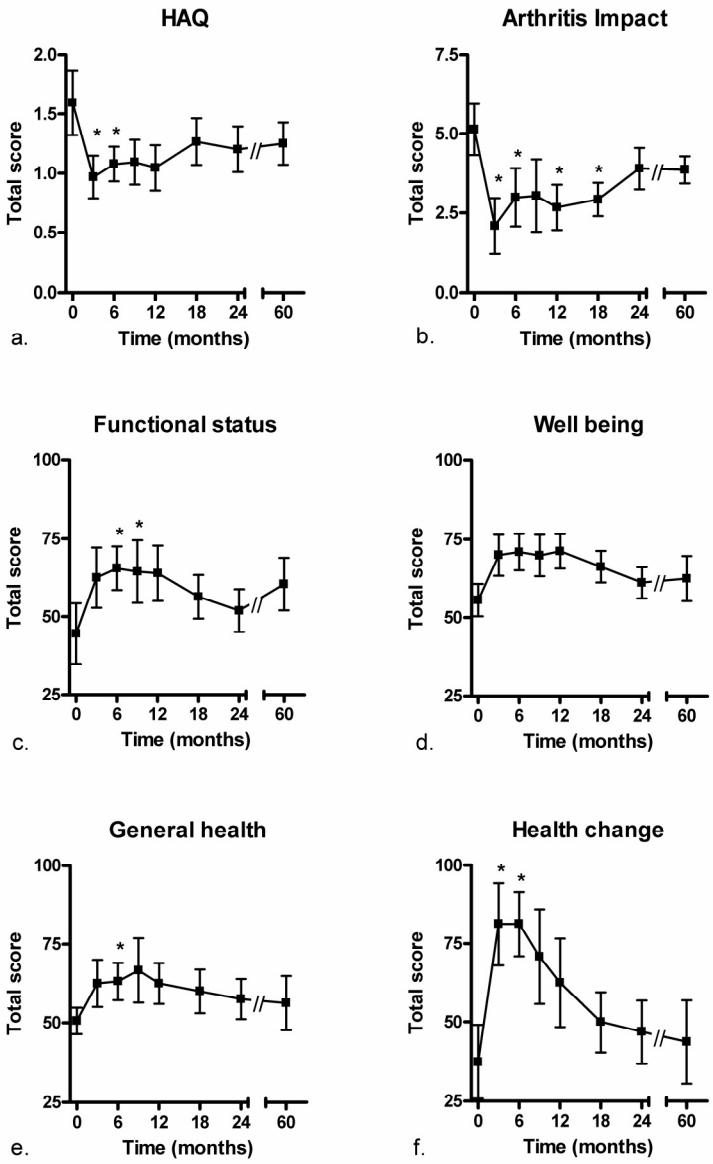

Figure 1. Health status of transplanted patients (n = 8). a. Health Assessment Questionnaire†; b. Scores on the horizontal graphical scale of the Arthritis Impact Measurement Scales (AIMS) †; c-f. Main dimensions of the SF-36 questionnaire‡. * $p < 0.05$

† lower scores indicate better health.

‡ higher scores indicate better health.

Health-related Quality of Life.

The Arthritis Impact VAS of the AIMS showed a significant decrease during the 12 months following transplantation, decreasing from 5.14 (0.81) [mean (SD)] to 2.09 (0.88) ($p = 0.008$) (Figure 1B). Analyses of variance also showed a significant decrease in AIMS scores post-transplantation ($p = 0.015$).

Three out of four main dimensions of the generic measure SF-36, except for the dimension of well-being, showed significant improvements in health status scores compared to baseline scores during the first 9 months after transplantation. Analyses of variance showed significant improvement in the dimension of health change ($p = 0.015$). Patients' reported scores on functional status significantly increased from 44.6 (9.73) before transplantion to 65.5 (7.03) at 6 months ($p = 0.04$) and 73.0 (7.20) at 9 months ($p = 0.04$). These scores on functional status gradually decreased during follow-up, but remained above pretreatment values throughout the 5 years follow-up (Figure 1C). General health scores significantly improved from 50.6 (4.17) before transplantation to 63.1 (5.90) at 6 months ($p = 0.05$) and 73.0 (9.82) at 9 months ($p = 0.05$) (Figure 1E). Health change scores significantly improved from 37.5 (11.6) before transplantation to 81.3 (13.2) at 3 months ($p = 0.02$) and 81.3 (10.3) at 6 months ($p = 0.01$) (Figure 1F).

Utility and Quality Adjusted Life Years.

Utility scores measured by the EQ-5D increased significantly from 0.51 (0.08) at baseline to 0.67 (0.04) at 9 months ($p = 0.03$) and 0.65 (0.03) at 12 months ($p = 0.02$) (Figure 2A). Utility scores as calculated from the SF-36 questionnaires also increased significantly from 0.59 (0.11) at baseline to 0.71 (0.04) at 6 months and 0.72 (0.12) at 9 months post-transplantation ($p = 0.04$) (Figure 2B). The total QALYs as calculated by the area under the curve in the first 2 years post-transplantation was 1.4 and after 5 years 3.3 . When compared to baseline utility scores, this increase of QALYs equals a lifetime improvement of 3.3 quality-adjusted months.

Using a threshold analysis, we calculated whether the gained QALYs, as compared to the baseline utility score, could compensate for the treatment-related mortality (TRM) of HDC + HSCT. Assuming a life expectancy of 20 years for a 50 year-old patient with severe, refractory RA, we found that HDC + HSCT equals conventional therapy in terms of QALYs when TRM is 2.8 % (Figure 3). In case of a life expectancy of 30 years the threshold TRM would be 2.15%, below which HDC + HSCT is favorable to conventional therapy.

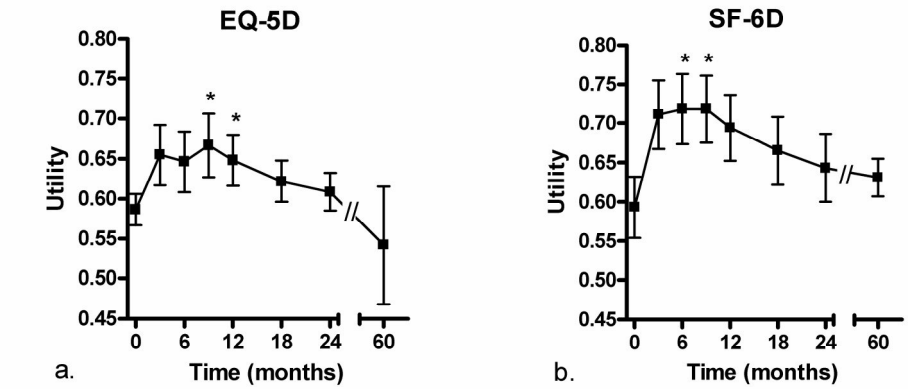

Figure 2.

a. Utility scores, as measured by EQ-5D, of transplanted patients (n = 8).

b. Utility scores, as measured by the SF-6D, of transplanted patients (n = 8).

* $p < 0.05$.

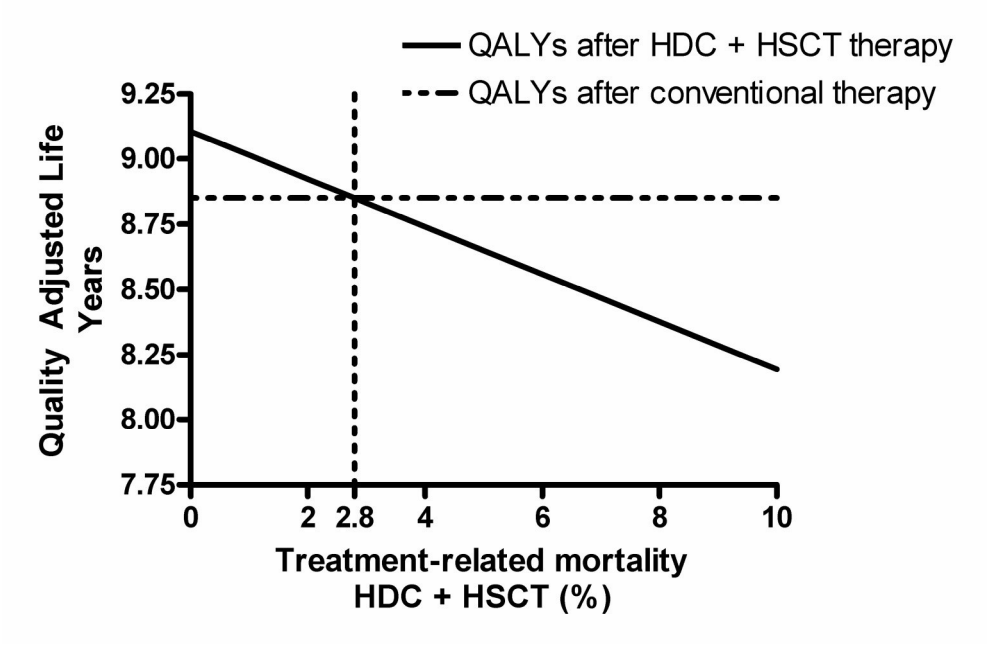

Figure 3. Threshold analysis for treatment-related mortality (TRM) of HDC + HSCT. A TRM < 2.8% favors HDC + HSCT as a preferable treatment when compared to continued conventional therapy in a putative 50 year-old RA patient with a 20 years life expectancy.

Discussion.

The aim of this study was to analyze the health status of previously therapy-resistent RA patients during 5 years following HDC + HSCT. Our study demonstrates significant improvement of health status, notably in the first 2 years post-tranplantation. We also showed that utilities of transplanted patients increased and that the QALYs gained for RA patients treated with HDC + HSCT outweigh a TRM lower than 2.8 %.

To our knowledge this is the first study on the long-term follow-up of health status of patients with severe, refractory RA. The health status of these patients improved after HDC + HSCT mainly in the first two years post-transplantation. HAQ scores improved more than 0.22 units, considered clinically significant, during the complete follow-up period. Utilities increased as measured by 2 different generic measures, SF-36 and EQ-5D. These utilities were comparable when taking into account that utilities based on the Standard Gamble (EQ5-D) structurally result in lower utilities when compared to those based on the Time-Trade-Off (SF-36). In addition, using the AIMS, we also showed significant improvement in the impact of artritis on the health status of transplanted patients up to 18 months after transplantation. The remarkable improvement of health status after HDC + HSCT was mainly achieved during the first year post-transplantation. Because conventional DMARD therapy was reinsituted after 9 months in 50% of the patients, it is likely that improvements in health status of RA patients can directly be related to HDC + HSCT in the first 9 months after treatment.

Furthermore, from a clinical perspective, it is interesting that the initial gain in utilities at 3 months after HDC + HSCT is significantly correlated with the patients' disability as defined by the HAQ scores ($r = -0.79$, $p = 0.02$; data not shown). This might indicate that functionality was the main factor influencing health status in patients treated with HDC + HSCT.

We calculated a lifetime improvement of 3.3 quality-adjusted months for refractory RA patients when treated with HDC + HSCT. This improvement is similar to that of thrombolytic therapy in patients with a suspected acute anterior myocardial infarction or adjuvant chemotherapy for women with node-positive breast cancer [15]. Wong et al. [3] showed a life-time improvement of 4 quality-adjusted months in RA patients treated with a TNF-blocking agent combined with methotrexate compared to methotrexate alone, based on data from the ATTRACT and ARAMIS [2]. However, these patients had less severe disease activity than our transplant patients and the safety and tolerability of continued TNF blocking therapy still has to be confirmed [3].

A recent report from the European Group for Blood and Marrow Transplantation and Autologous Blood and Marrow Transplant Registry showed that TRM after HDC + HSCT occured in 1 of 76 RA patients (1.3%) [5]. Therefore, our study shows that in a hypothetical 50-year-old RA patient with a life-expectancy ranging from 20 to 30 years, HDC + HSCT results in superior health status when compared to conventional therapy.

Of note, it should be taken into account that higher TRMs are acceptable when the average life expectancy is shorter.
The cost-effectiveness of HDC + HSCT was not investigated in this study. Gabriel et al. modeled the lifetime cost of RA compared to HDC + HSCT. They concluded that a potential curative intervention, employed within the first 2 years of diagnosis, that costs less than $ 60,000 US is likely to be cost-saving. Because this treatment was not curative, it is unlikely that HDC + HSCT is cost-saving at this moment.

From these data it can be concluded that HDC + HSCT improves health status of patients with refractory RA. Nevertheless, the treatment is not curative, as reflected in the return of heath status to near baseline values 2 years post-transplantation. Therefore, new experimental therapies should aim at prolonging the initial benefit of high dose immunosuppression without significantly increasing TRM.

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