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

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Citation

Verburg, R. J. (2005, October 26). *High dose chemotherapy and autologous hematopoietic stem cell transplantation for rheumatoid arthritis*. Retrieved from <https://hdl.handle.net/1887/3491>

Version: Corrected Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

CHAPTER 9

SUMMARY AND DISCUSSION

Summary.

Chapter 1.

Introduction and aim of studies.

This thesis describes clinical and immunological aspects of immunoablative therapy and autologous stem cell transplantation (HDC + SCT) in patients with refractory rheumatoid arthritis (RA). Rheumatoid arthritis is a chronic systemic disease of unknown etiology, characterized by multiple immune abnormalities. Chapter 1 addresses the backgrounds and rationale of this treatment modality in experimental and human rheumatic autoimmune diseases. Its rationale is based on the premise that the immune abnormalities underlying human autoimmune disease can be corrected by HDC and that SCT ensures recapitulation of a naïve, self-tolerant, immune system. HDC + SCT was shown to be effective in animal models with autoimmune diseases and patients with an hematological malignancy and concomitant rheumatic disease. Based on these observations a study protocol for patients with refractory rheumatoid arthritis was developed.

Chapter 2.

Decision analysis.

Chapter 2 describes the result of a decision analysis that was undertaken to investigate whether any beneficial effects of HDC + SCT outweigh its attending risks and treatment-related mortality (TRM) in a chronic but nonlethal disease like RA. A Markov model was employed because it allows for summation of consecutive health states. In this model we compared HDC+SCT versus continued pharmacological treatment in patients with active disease who have previously failed standard treatments (methotrexate, combination therapy, TNF-blockade) taking into account the possibility that events and outcomes vary or recur in time. With a TRM < 3.3%, HDC+SCT appeared to be the preferred treatment. The efficacy required to compensate for a TRM of 10% (e.g. after HLA-identical allogeneic SCT) was found to represent a potentially realistic scenario: a 50-70% improvement 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.

Chapter 3.

High Dose Chemotherapy and Hematopoietic Stem Cell Transplantation: A Study of Treatment Preference in RA Patients and Rheumatologists.

Chapter 3 describes the results of a survey on treatment preference in RA patients and rheumatologists. Specifically, it was examined whether the risks of HDC + ASCT are acceptable to RA patients and rheumatologists and whether risk taking by patients was associated with disease characteristics, socio-economic parameters and/or personality traits. This was based on a realistic scenario by means of a patient preference method in

which the trade-off between short-term risks and possible long-term gain of HSCT was investigated. It was shown that patients willing to accept risk of death had significantly higher VAS disease activity, VAS pain and HAQ. The patients who were willing to accept a risk of TRM related to HSCT the median required duration of benefit given a TRM of 2 % was 5 years (range 1-15). Physicians also required a median duration of benefit of 5 years.

Chapter 4.

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.

Chapter 4 describes the clinical and immunological effects of HDC + SCT in fourteen patients with intractable RA. From a technical viewpoint the treatment steps appeared feasible in all patients. The consecutive procedures of the treatment were well tolerated by most patients. Hematological recovery was uneventful in all patients, showing an inverse relationship with the age of the patient. Longlasting lymphopenia was observed, which could mainly be attributed to slow recovery of naive CD4⁺ T lymphocytes. With respect to efficacy, mobilization resulted in transient amelioration of disease activity in 5/14 patients (defined as ACR20 before conditioning), which was reinforced by the intensification of conditioning and transplantation procedures. In 8/12 of the patients clinical meaningful improvements (defined as good response according to EULAR response criteria) were recorded in more than 50% of follow-up visits. 4/12 patients failed to improve. The individual clinical response at 3 months was found to be predictive for the subsequent disease course. These disease courses displayed a dichotomous pattern, enabling categorization in 'responders' and 'nonresponders'. Nonresponders did not differ from responders with respect to disease or patient related variables, such as age, disease activity and duration, previous therapy, presence of rheumatoid factor.

Chapter 5.

High dose chemotherapy and autologous stem cell transplantation significantly reduces the rate of joint damage in severe rheumatoid arthritis.

Chapter 5 reports 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. Profound effects on DAS and joint damage were documented 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. The robust effects of HDC + ASCT on disease activity translated into a significant reduction in the rate of joint damage by 85% that was most marked in the first year after the intervention when most patients were off-

DMARDs. This 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.

Chapter 6.

The Outcome of Intensive Immunosuppression and Autologous Stem Cell Transplantation in Patients with Severe Rheumatoid Arthritis is Associated with Changes in the Composition of Synovial T Cell Infiltration.

Chapter 6 was undertaken to advance our understanding of the immunological effects of high dose chemotherapy and autologous stem cell transplantation (HDC+ASCT) in rheumatoid arthritis (RA). The induction of (partial) remission was associated with strong baseline expression and subsequent reduction of CD3, CD4, and the differentiation markers CD27 and the CD45-isoforms (RA, RB, RO) in synovium, while expression of these markers had returned to baseline levels at the 1-year biopsy, at a time disease had relapsed to varying extents in most patients. Of interest was the high proportion of CD45RB+ CD3+ T cells at 3 months post-transplant. This subset has recently been reported to be increased in peripheral blood of RA patients versus healthy controls, reflecting accelerated differentiation of naive CD45RA T cells under the influence of inflammation. These data provide strong evidence for an active role of T cells in perpetuation of disease activity.

Chapter 7.

IL-7 deficiency in rheumatoid arthritis: Consequences for therapy induced lymphopenia.

Chapter 7 shows that RA patients are relatively IL-7 deficient and that this deficiency is likely to be an important contributing factor to poor T-cell reconstitution in RA following high dose chemotherapy. Furthermore, in RA patients with stable, well controlled disease, IL-7 levels were positively correlated with the TREC content of CD4 T-cell demonstrating a direct effect of IL-7 on thymic activity.

Chapter 8.

Long term follow-up of quality of life in patients with severe rheumatoid arthritis after high dose chemotherapy and autologous stem cell transplantation.

The aim of chapter 8 was to analyse whether HDC + HSCT can increase the quality of life and the perception of general health of previously therapy-resistant, progressive RA patients. The quality of life during 5 years following HDC + HSCT in eight patients with refractory RA was investigated. This study demonstrates significant improvement of the quality of life, notably in the first 2 years post-transplantation. It was also showed that the utility scores of transplanted patients improved and that the gained QALYs for RA patients treated with HDC + HSCT outweighs a TRM lower than 2.8 %.

Disussion.

Phase I/II trials for autologous SCT in the treatment of RA.

In parallel with our study, other phase I/II studies were initiated to assess feasibility, toxicity and efficacy in small groups of patients. The results are shown in Table I.

The results from these heterogeneous studies are difficult to compare, but the treatment steps appeared feasible and safe in all patients. No unexpected major toxicity or treatment related mortality occurred, although in several patients infectious complications necessitated extra hospital admissions for parenteral antibiotic treatment were observed. One patient died as a consequence of sepsis. Recurrence of disease activity occurred in most patients usually within 2 years. Therefore this procedure is unlikely to be curative, however the use of disease modifying antirheumatic drugs (DMARDs) after recurrence of disease resulted in substantial improvement of disease activity in a majority of patients. Interestingly, patients had been refractory to these drugs (even in higher doses) before transplantation, suggesting that some degree of sensitivity to conventional drugs had been regained.

Long term remissions as well as relapses and progressive disease have been reported both in RA and other autoimmune diseases with the various regimens used but no definite conclusions with regard to T-cell depletion of the graft and/or conditioning regimen can be drawn. Brodsky et al. [7] reported that a conditioning regimen of cyclophosphamide 200 mg/kg without stem cell rescue resulted in duration of aplasia that lasted longer than seen after autologous transplantation. Apparently enough stem cells survive this conditioning regimen to regenerate the immune system. Moore et al. conducted a randomized trial to compare T cell depleted versus unmanipulated SCT after high dose chemotherapy (cyclophosphamide 200 mg/kg). 17 patients with T cell depleted autologous SCT and 14 patients with unmanipulated autologous SCT were treated. There were no significant differences with respect to length or quality of remissions between the two groups [11]. An analysis of the EBMT/EULAR database on 73 RA patients treated with high dose chemotherapy and autologous SCT found a significant response (at least ACR 50% response) in 67% of patients. Some disease activity was seen during follow-up, but the severity of flares was reported to be less in many and about half showed a response to antireumatic medication that they had failed previously [12]. McColl et al described a patient with refractory, active RA who was treated with cyclophosphamide 50 mg/kg antithymocyte globulin 90 mg/kg and SCT from his identical twin brother [13]. Four years posttransplantation the patient was still free of disease symptoms (Wicks, personal communication) without antireumatic medication. Syngeneic lymphocytes from the healthy donor or new populations of T cells derived from donor stem cells could have dispelled host T cells.

Reference	n	Stem cell source	T-cell depletion of graft	Conditioning	Initial improvement	Long term results	Remarks
Joske [1]	1	PBSC	No	CY 200 mg/kg	yes	Free of symptoms at 6 mo FU	100 % longterm favorable response
Durez [2]	1	PBSC	Yes	BU and CY	yes	Free of symptoms at 10 mo FU	100 % longterm favorable response
Burt [3;4]	4	PBSC	Yes	CY 200 mg/kg and ATG 270 mg/kg, one patient also TBI	Yes	2 patients are doing very well at 9 and 20 mo FU (ACR > 50%) 1 patient relapsed 1-3 mo FU 1 patient relapsed 3-6 mo FU	50 % longterm favorable response
Snowden [5]	4	PBSC	No	CY 100 mg/kg	Yes	transient response lasting 2-3 months	
	4	PBSC	No	CY 200 mg/kg	Yes	1 patient in complete remission at 1 yr (good response at 19 mo FU), 1 patient good response (FU = 18 mo), 2 patients experienced relapse at 4-5 mo and 3 mo	50 % longterm favorable response
Lowenthal [6]	3	2 PBSC 1 BM	Yes No	CY 200 mg/kg	Yes	Benefit lasted less than 4 weeks in all patients 1 patient complete remission at 21 mo FU, 1 patient complete remission 3 mo FU	No patient longterm favorable response
Brodsky [7]	2	-	-	CY 200 mg/kg	Yes	At 3 months 6 patients had a favorable response (ACR > 50%), 6 did not.	100 % favorable response
Verburg [8]	1 2	PBSC	Yes	CY 200 mg/kg	Yes	Relapse in all patients ranging from 1.5 - 9 mo, 3 within 3.5 mo FU, 3 more than 3.5 mo FU.	50 % longterm favorable response
Bingham [9]	6	PBSC	Yes	CY 200 mg/kg	Yes	Relapse at 6 mo for both patients.	5/6 patients good response to DMARDs
Pavletic [10]	2	PBSC	No	CY 200 mg/kg and ATG 60 mg/kg	Yes		favorable response to DMARDs

Table 1. Autologous stem cell transplantation in patients with therapy refractory RA. PBSC = Peripheral blood stem cell collection, BM = Bone Marrow, CY = cyclophosphamide, BU = busulfan, ATG = antithymocyte globulin, TBI = total body irradiation, FU = followup, mo = months, yr = year, DMARD = disease modifying antirheumatic drug.

These data do not allow definitive conclusions on whether the immunological effects of the treatment are only quantitative ('debulking' of inflammatory load) or qualitative as well (e.g. tolerization of pathogenic T lymphocytes). Based on the results of Brodsky [1] (conditioning regimen with high dose cyclophosphamide without SCT) one can speculate on the role of the autologous graft. Stem cells are capable of surviving high dose treatment with cyclophosphamide and disease remissions can apparently be caused by the cyclophosphamide-induced immunoablation itself without the possible immunomodulation of the SCT. The question remains whether autologous SCT is capable of immunomodulation by regeneration of naive tolerant lymphocytes or merely serves as a rescue to shorten the aplastic period.

From a T-cell centered perspective it might be inferred from the present studies that not all pathogenic T lymphocytes were eradicated or that some had been reinfused with the graft. This would imply that remissions can only be achieved by further intensification, e.g. by in vivo T cell depletion. Clearly, this could add to the toxicity. From the patient's and treating physician's perspective, responses were clinically meaningful in a majority of patients with resultant enhanced quality of life. It remains to be shown that any superior efficacy of a more rigorous approach will compensate for increased toxicity in terms of quality-adjusted-life-expectancy [14].

The aforementioned studies indicate *autologous* SCT is not curative for refractory RA. The observed reappearance of the autoimmune disease after autologous SCT can be attributed to many factors, including: 1. Survival of autoaggressive lymphocyte (either T- or B cells), synoviocytes or macrophages despite high dose chemotherapy. 2. Reinfusion of autoaggressive lymphocytes together with the stem cells. 3. Renewed activation of autoaggressive lymphocytes as a result of exposure to novel autoantigens 4. Reappearance of the autoimmune disease because defective stem cells were reinfused or 5. A combination of the above.

Future prospects.

Most protocols used did not increase immunosuppression to the point of immunoablation. More intensive immunoablative conditioning regimen followed by autologous SCT might induce more prolonged remissions. The concept that remissions may be maximized by removing pathogenic cells from the stem cell product has not been shown in humans, so the role of T cells in the graft remains, thusfar, unclear.

Allogeneic transplantation has not yet been tested as a primary treatment for patients with RA due to risks of transplant related mortality and graft versus host disease. Allogeneic SCT may be more effective than autologous SCT if intrinsic stem cell abnormalities exist in RA and if host hematopoiesis and abnormal immune cell populations

can be eradicated via a graft vs autoimmunity effect. Furthermore allogeneic SCT in RA would offer an opportunity to investigate whether self-tolerance can be restored. Recent advances in allografting have improved safety, thereby allowing application in non-malignant conditions such as RA.

The described cases are limited in number and differ in ways of stem cell collection, T and B cell depletion of the graft and conditioning regimen. The disease severity and the response in patients with RA also differs greatly. Therefore 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 parameters. Adequate assessment of risk/benefit requires properly designed and conducted prospective randomized controlled trials with a long follow-up. The issue is whether intense immune suppression aimed at immunoablation is superior to continuous moderate immune suppression with respect to toxicity and efficacy. Furthermore it should be investigated whether these effects can be maintained during a longer follow-up.

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