Treatment of Relapse After Autologous Blood Stem Cell Transplantation for Severe Rheumatoid Arthritis

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ABSTRACT. There is little information about the clinical course of patients with rheumatoid arthritis (RA) who relapse after autologous blood stem cell transplantation (ASCT). We describe 6 patients with severe RA who received ASCT in 3 US centers. Duration of followup was between 24 and 42 months posttransplant. Five patients achieved major responses but relapsed 3–22 months posttransplant. Two patients with relapse improved remarkably after restarting disease modifying antirheumatic drugs (DMARD). Two patients developed a mild RA flare at 3 and 5 months posttransplant and improved spontaneously. All 4 patients who improved after an initial disease flare remained highly functional at 14–22 months posttransplant. All patients in this study were anti-tumor necrosis factor (TNF) drug naive; all received a TNF blocker as a second line posttransplant salvage therapy, but only 3 responded. Future ASCT strategies need to focus on improving the durability of the early posttransplant responses. (J Rheumatol 2001;28 Suppl 64:28–31)

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INTRODUCTION

Pilot studies of autologous blood stem cell transplant (ASCT) for patients with severe rheumatoid arthritis (RA) have been pursued by several groups[1-7]. In spite of strong evidence of safety in this patient group and an initial suggestion of therapeutic efficacy of ASCT, there is very little information about the clinical course beyond the first year posttransplant. Nearly all patients with refractory RA had 70–80% American College of Rheumatology (ACR) responses within 3 months after ASCT, but a rapid disease recurrence was common. Nevertheless, there is an emerging impression among investigators that some patients may experience a prolonged benefit from transplantation by responding to salvage therapy with DMARD. Because anti-tumor necrosis factor (TNF) agents became available only after the initiation of transplant studies for RA, their role in treating patients who relapse after ASCT remains unknown. We describe the clinical course after relapse in 6 patients with refractory RA who received ASCT in 3 US centers[1,2]. All patients were followed for more than 2 years after transplant.

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MATERIALS AND METHODS

Patients. We describe the extended followup information of 4 patients whose early posttransplant course has been reported[1]. Detailed transplant course of the other 2 patients has been described elsewhere, and here we emphasize the events pertinent to the treatment of relapse[8]. All 6 patients had seropositive RA and failed multiple DMARD regimens, but none had received anti-TNF drug treatment prior to transplantation (Table 1). All patients underwent collection of hematopoietic stem cells by chemomobilization using 2 g/m^2 cyclophosphamide and granulocyte colony-stimulating factor (Amgen, Thousand Oaks, CA, USA). High dose immunoablative regimen consisted of cyclophosphamide total dose 200 mg/kg administered over 4 days. Patients 1–4 received total 90 mg/kg of horse-derived anti-thymocyte globulin (ATG) pretransplant and T cell depleted stem cells by using CD34 positive selection (CellPro, Bothell, WA, USA). Patients 5 and 6 received unmanipulated stem cells, but T cell depletion was accomplished *in vivo* with 3 doses of 20 mg/kg antithymocyte globulin (total 6 doses) both before and after stem cell infusion[2]. Patient 4 also received 400 cGy of total body irradiation as part of the preparative regimen.

Assessment of disease status. In Patients 1–4 tender joint count was measured by assessing a total of 44 joints and the swollen joint count by assessing a total of 42 joints (hips were not assessed for swelling). Patients 5 and 6 had tender and swollen joint counts assessed by evaluating the total of 28 joints (proximal interphalangeal, metacarpophalangeal, wrists, elbows, knees, ankles, and metatarsophalangeal). Responses were evaluated using criteria proposed by the ACR[9]. The followup information was provided by offices of the primary rheumatologist or during the scheduled posttransplant evaluations. Relapse of RA was defined as the point when a disease modifying antirheumatic drug (DMARD) was started for treatment of RA symptoms posttransplant. Most patients were taking various doses of low dose oral prednisone (< 10 mg/day) and antiinflammatory agents.

RESULTS

Transplantation outcome. ASCT was tolerated in all individuals without major toxicities[1,2]. Patient characteristics and transplant related variables are summarized in Table 1.

Treatment of relapse (Table 2). Patient 1 achieved a rapid ACR 70 response at one month posttransplant and the number of tender and swollen joints showed a decrease from 41 and 27 to 7 and 4, respectively. All DMARD except hydroxychloroquine were discontinued. A mild worsening of RA at 3 months improved spontaneously and the low dose prednisone was discontinued at 8 months. At 22 months the number of tender and swollen joints increased and she started triple regimen with hydroxychloroquine, sulfasalazine, and methotrexate (MTX). At 3 years posttransplant RA was poorly controlled — she had 37 tender and 6 swollen joints, and started an anti-TNF drug, etanercept. At 42 months the number of tender and swollen joints improved to 15 and 4, respectively, and she continued on the TNF inhibitor and MTX.

Patient 2 had substantial improvement one month posttransplant but did not meet ACR 20 criteria because the tender

Table 1. Clinical characteristics and transplantation variables of 6 patients who received autologous blood stem cell transplantation for refractory RA.

Patient	Sex/Age	RA Duration, yrs	Transplant Year	Previous Failed DMARD*	CD34 Dose ($\times 10^6$/kg)	CD3 Dose ($\times 10^5$/kg)	Initial Response to Transplant
1	F 46	7	1997	HCQ, MTX, gold dapsone, CSA, minocycline, SSZ	2.16	8.62	ACR 70
2	F 42	7	1997	CSA, gold, HCQ, MTX, SSZ	6.52	5.99	< ACR 20
3	M 48	4	1998	AZA, gold, SSZ HCQ, MTX	1.78	ND	ACR 70
4	F 49	6	1998	MTX, HCQ, gold CTX, CHL	3.11	3.94	ACR 80
5	F 25	7	1998	Gold, MTX, HCQ SSZ, minocycline	8.5	900**	ACR 80
6	M 45	17	1998	Gold, MTX, HCQ, SSZ, minocycline	17.5	1720**	ACR 80

* In addition to monotherapy all patients failed various combinations of DMARD; all were typically taking concomitant oral or parenteral steroids, NSAID, or narcotic analgesics.
** Patients did not receive T cell depleted grafts; T cells were depleted *in vivo* with horse-derived antithymocyte globulin. HCQ: hydroxychloroquine; MTX: methotrexate, CSA: cyclosporine; SSZ: sulfasalazine; AZA: azathioprine; CHL: chlorambucil; CTX: cyclophosphamide.

Table 2. Treatment of relapses in 6 patients after autologous stem cell transplantation for severe RA.

Patient	First Salvage*	Response	Second Salvage	Response	Third Salvage	Response	Last Followup
1	22 mo MTX, SSZ HCQ	NR	36 mo Anti-TNF, MTX	ACR 30	—	—	42 mo ACR 30 continues, Anti-TNF, MTX
2	3 mo MTX, HCQ	NR	9 mo CSA, MTX, HCQ	NR	36 mo Anti-TNF, MTX, HCQ	ACR 40	42 mo ACR 40 continues, Anti-TNF, MTX
3	18 mo Leflunomide	NR**	30 mo Anti-TNF	ACR 50	—	—	32 mo ACR 50 continues, Anti-TNF
4	6 mo MTX	NR	12 mo IV CTX 1 g, MTX	NR	12–33 mo Leflunomide, anti-TNF	NR	33 mo Disabled, still on leflunomide
5	6 mo MTX, SSZ, HCQ	ACR 80	18 mo Synthroid, MTX, SSZ, HCQ	ACR 80***	25 mo Anti-TNF added	NR	36 mo Leflunomide at 29 mo added without benefit
6	6 mo MTX, SSZ, HCQ	ACR 60	14 mo Leflunomide, MTX, SSZ, HCQ	NR	16 mo Anti-TNF added	NR	24 mo Disabled, steroid pulses

* Months represent number of months posttransplant when treatment of recurrent symptoms was initiated. NR: Treatment benefit did not meet ACR 20% response criteria. ** Patient developed intolerance to leflunomide soon after starting therapy. *** Patient developed flare after onset of hypothyroidism; her RA improved with starting the thyroid hormone replacement.

joint count failed to improve. All DMARD except hydroxychloroquine were discontinued. At 3 months she started combination treatment with hydroxychloroquine 400 mg/day and MTX 20 mg/week. At 9 months she was again disabled and cyclosporine was started at 225 mg PO QD. At 30 months posttransplant she had 30 tender and 19 swollen joints and was enrolled in a randomized study of a TNF inhibitor versus placebo. At 36 months the numbers of tender and swollen joints were 23 and 9, respectively; she was taken off the study and started etanercept. At the last followup 42 months posttransplant she was still taking TNF inhibitor and MTX; the numbers of tender and swollen joints were 13 and 5, respectively.

Patient 3 had an ACR 70 response duration of 5 months. At 5 months he developed a mild flare of arthritis that improved rapidly with a temporary increase in systemic steroids. He continued off all drugs until 18 months posttransplant, when he started leflunomide for increasing tenderness of the left knee, shoulder, and hand joints. He developed some nonspecific symptoms that resolved rapidly after discontinuation of leflunomide. He continued with gradual worsening of RA, but refused all medications except increasingly frequent intramuscular steroid injections. Finally, at 30 months he started etanercept, which resulted in about 50% improvement of his symptoms at 32 months.

Patient 4 experienced an initial ACR 80 response, but then progressed relentlessly and at 6 months had 44 tender and 33 swollen joints. Oral MTX was initiated without improvement. Between 12 and 33 months she received salvage treatments with intravenous cyclophosphamide, leflunomide, and infliximab, all without improvement. Two and one-half years after transplant the tender and swollen joint counts were 34 and 30, respectively.

Patient 5 had an ACR 80 response at 3 months. At 6 months posttransplant she progressed and was started on the triple regimen with MTX 20 mg/wk, sulfasalazine 3000 mg/day, and hydroxychloroquine 400 mg/day. She regained ACR 80 and remained fully functional until 18 months posttransplant, when she developed hypothyroidism and again had active disease. She continued triple therapy and again achieved an ACR 80 response after starting thyroid hormone replacement. At 25 months etanercept was started for a new RA flare, but this resulted in no improvement. At 29 months leflunomide was added, with no benefit. At 36 months she had 13 tender and 14 swollen joints not meeting ACR 20 improvement from pretransplant baseline.

Patient 6 achieved an ACR 80 response at 3 months and went from complete disability back to fulltime work. At 6 months his response declined and he started the triple DMARD regimen, with a rapid improvement to ACR 60. At 14 months he developed progressive worsening of RA with 17 tender and 8 swollen joints. The addition of leflunomide and later etanercept did not help, and at 24 months he was again not working and dependent on frequent pulses of high dose prednisone.

DISCUSSION

The information presented here summarizes the current US experience with autologous blood stem cell transplantation for refractory RA. Duration of the followup was sufficiently long to make several observations regarding the effect of this therapy on RA and the characteristics of relapses. First, in this group of patients who have failed multiple DMARD regimens prior to transplant, 5 of 6 patients achieved a major response. Second, all 6 patients developed disease flare 3–6 months posttransplant, 2 improved remarkably after starting DMARD, one did not respond to addition of MTX. Two patients who experienced a mild flare at 3 and 5 months recovered spontaneously without the addition of DMARD. All 4 patients who improved after the first posttransplant RA flare experienced responses that lasted much longer than the initial posttransplant response. Anti-TNF drugs did show a suggestion of efficacy in 3 out of 6 patients who failed posttransplant salvage with DMARD.

The most encouraging aspect of this experience is that 4 of 6 patients who were suffering severe disability at the time of transplant were able to achieve and maintain a high level of function for 1–2 years posttransplant. It is important to emphasize that current worldwide experience with autologous transplantation for RA includes more than 70 patients, and no deaths have been described in patients who have been treated with 200 mg/kg cyclophosphamide based regimens[1-7]. Most of these patients experienced major responses early posttransplant and it is tempting to explore how such accomplishments could be transformed into a more durable benefit.

Two general strategies have been contemplated. One is to capitalize on the current efficacy and safety of the 200 mg/kg cyclophosphamide based protocols and implement routinely an early maintenance therapy before relapse occurs[10]. The best candidates for such intervention are the combinations of DMARD, anti-TNF drugs, or both. The question remains whether effective means exist to meaningfully prolong the duration of responses posttransplant. Better anti-RA drugs may be needed to make the "early maintenance" strategy successful. The alternative is to accept that at the current stage there are no sufficiently effective drugs that could successfully intervene in the disease pathology during the early posttransplant remission. This direction calls upon designing new pilot studies to improve the current transplant protocols. Some proposed approaches include: (1) engineering of the stem cell product, (2) selective lymphoablation, (3) more intensive myeloablation, and (4) allogeneic stem cell transplantation. This second strategy contains our confidence that today's science of hematopoietic stem cell transplantation is able to create effective and safe transplant protocols for patients with severe RA. As we move forward with the further investigation in this area collaborative efforts will be needed.

REFERENCES

1. Burt RK, Georganas C, Schroeder J, et al. Autologous hematopoietic stem cell transplantation in refractory rheumatoid

arthritis. Arthritis Rheum 1999;42:2281-5.
2. Pavletic S, O'Dell J, Ursick M, et al. Autologous blood stem cell transplantation can overcome and modulate therapeutic resistance in severe rheumatoid arthritis [abstract]. Blood 1999;94:404b.
3. Joske DJL. Autologous bone marrow transplantation for rheumatoid arthritis. Lancet 1997;350:337-8.
4. Durez P, Tongouz M, Schandene L, Lambermont M, Goldman M. Remission and immune reconstitution after T-cell depleted stem cell transplantation for rheumatoid arthritis [letter]. Lancet 1998;352:881.
5. Verburg R, van den Hoogen F, Schattenburg A, et al. High-dose cyclophosphamide followed by autologous stem cell transplantation for the treatment of intractable RA [abstract]. Arthritis Rheum 2000;43 Suppl:S290.
6. Snowden JA, Biggs JC, Milliken ST, Fuller A, 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.
7. Tyndall A, Fassas A, Passweg J, et al. Autologous haematopoietic stem cell transplants for autoimmune disease — feasibility and transplant-related mortality. Bone Marrow Transplant 1999; 24:729-34.
8. Pavletic SZ, O'Dell JR, Pirruccello SJ, et al. Intensive immunoablation and autologous blood stem cell transplantation in patients with refractory rheumatoid arthritis: The University of Nebraska experience. J Rheumatol 2001;28 Suppl 64:13-20.
9. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
10. Snowden JA. High dose therapy and autologous hematopoietic stem cell transplantation in rheumatoid arthritis — the feasibility of phase III trials. J Rheumatol 2001;28 Suppl 64:55-9.