Early Recurrence or Persistence of Autoimmune Diseases After Unmanipulated Autologous Stem Cell Transplantation

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Autologous stem cell transplantation with or without in vitro lymphocyte depletion has been suggested as a new treatment option for severe autoimmune diseases. We describe five patients with autoimmune diseases (CREST syndrome, myasthenia gravis and Hashimoto's thyroiditis, systemic lupus erythematosus, atopic dermatitis, and rheumatoid arthritis) who underwent autologous bone marrow (n = 1) or peripheral blood progenitor cell (n = 4) transplantation with unmanipulated grafts as treatment for the autoimmune disease in one case or as treatment for a malignant disorder with a concomitant autoimmune disorder in four cases. In all patients serological and clinical signs of the autoimmune disease recurred early or persisted. These observations should be regarded as a cautionary note concerning the efficacy of high-dose therapy followed by transplantation of unmanipulated autologous stem cells for treatment of severe autoimmune diseases.

HIGH-DOSE chemotherapy followed by autologous stem cell transplantation (auto-SCT) has been proposed as a new approach to treat severe autoimmune diseases,[1-6] and corresponding guidelines have been published.[7]

To date, auto-SCT in autoimmune diseases has been a largely hypothetical option supported by theoretical considerations and a few animal studies, as reviewed elsewhere.[2-4,6,8] It is assumed that a vigorous immunoablative preparative regimen can delete the patient's immune system, including autoaggressive lymphocyte clones. Hematopoiesis and lymphopoiesis are reconstituted by subsequent auto-SCT. Therapeutic benefit may result from the intensified immunosuppressive regimen alone. Additionally, it seems possible that a newly developing immune system might acquire tolerance towards previous autoantigens even when derived from autologous SCT.[2-4]

It is not clear whether auto-SCT for autoimmune diseases should be performed by using bone marrow or peripheral blood progenitor cells,[9] which type of immunoablation should be used, or whether depletion of immunologically competent lymphocytes in the graft should be attempted.[7]

Observations of the course of disease after auto-SCT in autoimmune disease patients or in patients with malignant diseases and concomitant autoimmune diseases can help to answer these questions.

We describe five patients suffering from autoimmune diseases alone or from malignancies with concomittant autoimmune diseases, who underwent high-dose chemotherapy and subsequent auto-SCT with unmanipulated grafts. The autoimmune disease recurred or persisted in all cases.

Patients

This report summarizes the experience of four bone marrow transplantation (BMT) units (Genoa, Hamburg, Heidelberg, and Kiel) with patients who received high-dose therapy and subsequent auto-SCT either solely for an autoimmune disease or for a malignancy but simultaneously suffered from a concomittant autoimmune disease with serologic autoimmune markers. Being aware of the difficulties in defining "true" autoimmune diseases, we did not define inclusion criteria for the term "autoimmune disease."

Four patients with one or two clear autoimmune diseases (CREST syndrome, myasthenia gravis, Hashimoto's thyroiditis, systemic lupus erythematosus, and rheumatoid arthritis) and one patient with atopic dermatitis were identified (Table 1).

One patient (no. 1) underwent autologous BMT. Four patients (no. 2 through 5) underwent autologous peripheral blood progenitor cell transplantation (PBPCT). The preparative regimen consisted in high-dose chemotherapy alone in four patients (no. 1 through 3, and 5), and in combined radiotherapy and high-dose chemotherapy in one patient (no. 4) (Table 1). In all cases, the graft was cryopreserved, and in all cases the graft was not manipulated.

Case Reports

Case 1. The 41-year-old female nurse had suffered from an incomplete CREST syndrome with Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasis (without calcinosis), and with high-titer anticentromer antibodies up to 1:1,280 and severe arthralgias since 1990. Disease activity remained severe despite treatment with methylprednisolone (8 to 16 mg/d), cyclosporine A (5 mg/kg BW), and two courses of intravenous cyclophosphamide (each 1,600 mg). She agreed to be treated by auto-SCT. Following 3 × 50 mg/kg cyclophosphamide an autologous unmanipulated BMT was performed in January 1994 (Table 1). The anticentromer antibody titer declined (Table 2), and she experienced complete clinical remission for 2 months. In March 1994 the anticentromer antibody titer reincreased to pretransplantation levels and 4 weeks later she was in full clinical relapse.

Case 2. The 52-year-old female patient has suffered from Hashimoto's thyroiditis since 1973 and from severe

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Submitted February 29, 1996; accepted June 19, 1996.

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0006-4971/96/8809-0021$3.00/0

Table 1. Clinical Data

No./Initials Patient		Diseases		Auto-SCT				
No.	Sex/ Age	Autoimmune Disease	Malignancy	SCT Date	Place of Treatment	Myeloablative Treatment*	SCT Type	No. of Cells Per KG BW Within the Graft†
1/G.D.	F/41	CREST syndrome	—	1/94	Genoa	cyclophosphamide 9.8 g (*3 × 50 mg/kg*)	auto-BMT	480 × 10^6 Ly $CD3^+$: nd $CD34^+$: nd
2/M.S.	F/52	thymoma associated MG and Hashimoto's thyroiditis	ovarian cancer	12/92 3/93‡	Heidelberg, Würzburg	VIP (× 2)‡: ifosfamide 25.5 g (*3 × 133 mg/kg*) etoposide 2.55 g (*3 × 13 mg/kg*) cisplatin 255 mg (*3 × 1, 3 mg/kg*)	auto-PBPCT (× 2)‡	Ly: nd 422.6 × 10^6 $CD3^+$ 9.3 × 10^6 $CD34^+$ Ly: nd 150.9 × 10^6 $CD3^+$ 11.4 × 10^6 $CD34^+$
3/A.D.	F/28	systemic lupus erythematosus	high grade NHL	6/94	Kiel	BEAM: carmustine 588 mg (*2 × 3, 4 mg/kg*) etoposide 2.35 g (*8 × 3, 4 mg/kg*) cytarabine 3.14 g (*8 × 4, 8 mg/kg*) melphalan 2.19 g (*8 × 3, 3 mg/kg*)	auto-PBPCT	333.1 × 10^6 Ly 188.1 × 10^6 $CD3^+$ 10.7 × 10^6 $CD34^+$
4/H.G.	M/58	atopic dermatitis	centrocytic NHL	4/95	Hamburg	TBI 6 × 2 Gy etoposide 2.1 g (*1 × 30 mg/kg*) cyclophosphamide 8.4 g (*2 × 60 mg/kg*)	auto-PBPCT	89.0 × 10^6 Ly 30.0 × 10^6 $CD3^+$ 16.7 × 10^6 $CD34^+$
5/B.S.	F/51	rheumatoid arthritis	high grade NHL	6/95	Hamburg	busulfan 1.1 g (*4 × 4 mg/kg*) etoposide 2.0 g (*1 × 30 mg/kg*) cyclophosphamide 8.0 g (*2 × 60 mg/kg*)	auto-PBPCT	66.7 × 10^6 Ly 26.5 × 10^6 $CD3^+$ 2 × 10^6 $CD34^+$

Abbreviations: MG, myasthenia gravis; BW, body weight; TBI, total body irradiation.
* Total dose and (*italic*) dosage per kilogram of BW and day.
† No. of lymphocytes (Ly); no. of T cells ($CD3^+$) and no. of stem cells ($CD34^+$) within the respective autograft per kilogram of BW.
‡ Two PBPCT's were performed.

thymoma-associated myasthenia gravis since 1983. Myasthenic symptoms were diplopia, ptosis, proximal limb weakness progressing to myasthenic crisis requiring assisted ventilation, resulting in an Disability Status Scale of Oosterhuis (DSSO) score of 4. Anti-acetylcholine-receptor (AChR) antibodies were elevated as were antibodies to thyroid peroxidase (Table 2). Thymectomy and subsequent treatment with 100 to 150 mg/d azathioprine led to complete clinical remission of the myasthenia gravis with low titers of AChR-antibodies in 1986 (DSSO: 0). Without relapse of the myasthenia gravis (DSSO:0; AChR-antibodies: negative), azathioprine was continued until diagnosis of an ovarian cancer (FIGO IIIc R2) in September 1992. Treatment of the ovarian cancer consisted in carboplatin/treosulfane, etoposide/ifosfamide/cisplatin (VIP), and two cycles (December 1992 and March 1993) of high-dose chemotherapy with ifosfamide, etoposide, and cisplatin (Table 1), followed each time by unmanipulated auto-PBPCT, leading to complete remission. From May 1993 until September 1993, prophylactic intraperitoneal treatment with interleukin-2 and interferon was performed. The complete remission of the ovarian cancer remained stable until June 1994, then a relapse occured and renewed chemotherapy led to a second remission. Six months after the second auto-SCT (October 1993) clinical and serological signs of myasthenia gravis

Table 2. Laboratory Parameters

Pat. No.	Titers	Normal Range	> −3 yrs	−2 mo	−1 wk	+1 wk	+2 mo	> +3 mo	> +1 yr
1	anti-CM	negative	nd	1:1,280	nd	nd	1:160	nd	1:1,280
2*	anti-AChR	<0.4 nmol/L	4.5	<0.4	nd	nd	<0.4	156	59
	anti-TPO	<1:100	1:400	1:1,600	nd	nd	nd	1:400	nd
3	platelets	150-400/nL	172	145	127	15	nd	39	13
	ANA (IgG)	<1:40	1:10,240	1:320	1:1,280	1:320	nd	1:5,120	1:1,280
	anti-SS-A	<25 U/mL	nd	157	<25	<25	nd	147	138
	C4	200-550 mg/L	300	nd	260	230	nd	230	110
4	IgE	10-150 IU/mL	nd	nd	250	175	nd	364	nd
5	RF	<60 IU/mL	nd	nd	233	191	199	404	nd

Abbreviations: anti-AChR, anti-acetylcholine receptor antibodies; anti-TPO, anti-thyroid peroxidase antibodies; anti-CM, anti-centromer antibodies; ANA (IgG), anti-nuclear antibodies (isotype IgG); anti-SS-A, anti-Sjögren syndrome antibodies, subtype "A," 64 kD; C4, complement factor C4; RF, IgM rheumatoid factor; nd, not done.
* Course after the 2nd PBPCT.

reappeared (DSSO from 0 to 3). AChR antibody levels exceeded pre-SCT levels and antibodies to thyroid peroxidase were elevated (Table 2).

Case 3. The 28-year-old female patient had a 14-year history of systemic lupus erythematosus (SLE), including arthralgia, discoid rash, malar rash, photosensitivity, oral ulcers, moderate pancytopenian, elevated titers of antinuclear antibodies, and elevated titers of anti-double stranded-DNA antibodies.[10] The symptoms responded sufficiently to corticosteroids and hydroxychloroquine. In June 1992, a B-cell centroblastic high-grade non-Hodgkin's lymphoma (NHL), stage III BS with bulky disease, was treated with 5 cycles of cyclophosphamide/vincristine/procarbazine/bleomycin/doxorubicin/prednisolone (COP-BLAM), resulting in complete remission in October 1992. A NHL relapse, stage III BS, was diagnosed in December 1993. The NHL progressed despite two cycles of Dexa-BEAM and one cycle of dexamethasone/high-dose cytarabine/cisplatin (DHAP). Despite these aggressive chemotherapeutic regimens clinical (arthritis and malar rash) and serological (Table 2) SLE symptoms persisted. In June 1994, high-dose chemotherapy according to the BEAM protocol[11] (Table 1) followed by unmanipulated auto-PBPCT was applied and resulted in complete remission of the NHL and in complete clinical remission of the SLE, but serological SLE symptoms persisted: antinuclear antibodies partly exceeded pre-SCT levels (Table 2). Cytopenia persisted throughout. A bone marrow biopsy on day +180 revealed normal cellularity. One day +352 after SCT, hypocomplementemia was detected for the first time, and the patient developed clinical signs of relapsing SLE, including oral ulcers and increasing pancytopenia with severe thrombocytopenia and elevated antiplatelets antibodies. The thrombocytopenia led to a lethal intracerebral hemorrhage on day +378. The NHL was still in complete remission.

Case 4. This 58-year-old male patient had suffered from atopic dermatitis affecting up to 15% of the body surface area since early childhood. Treatment of the excoriating eczema and pruritus was based on adequate cutaneous hydration and more severe flares were treated with topical glucocorticoids. In April 1994, a centrocytic NHL, stage III AE, was diagnosed. Six cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) cycles induced partial remission. Complete remission was achieved following two additional doxorubicin/prednisolone/high-dose cytarabine/cisplatin (ASHAP) cycles. The atopic dermatitis remained active. In April 1995 he underwent total body irradiation and high-dose chemotherapy with etoposide and cyclophosphamide (Table 1), followed by unmanipulated auto-PBPCT. The NHL remained in complete remission. Symptoms of atopic dermatitis disappeared completely after auto-PBPCT. However, only 1 week after transplantation they reappeared and were more pronounced between day +100 and +180 than in pre-SCT years.

Case 5. The 51-year-old female patient had suffered from rheumatoid-factor-positive rheumatoid arthritis since 1979. Despite treatment with corticosteroids, gold salts, methotrexate, and cyclophosphamide the rheumatoid arthritis led to progressive joint destruction (Steinbrocker functional grade IV), necessitating joint replacement surgery of knee, hip, and wrist. In June 1994, a high-grade B-cell NHL (anaplastic large cell NHL), stage II B, was diagnosed. Treatment consisted in 5 CHOP, 1 IMVP-16, and 2 ASHAP cycles and led to partial remission (stage II). The rheumatoid arthritis remained active despite these multiple chemotherapeutic treatments. In June 1995, she underwent high-dose chemotherapy with busulphan, etoposide, and cyclophosphamide (Table 1) and subsequent autologous unmanipulated PBPCT. The lymphoma is currently in complete remission. Arthralgia and arthritis slightly improved for a period of only 5 weeks after auto-SCT and on day +120 a severe rheumatoid arthritis flare required treatment with up to 75 mg prednisone per day. Rheumatoid factor exceeded pre-PBPCT levels on day +120 (Table 2).

DISCUSSION

In the five patients described here, intensive cytotoxic therapy with subsequent autologous transplantation of unmanipulated SCT failed to induce more than transient remission of various autoimmune diseases. Clinical and/or serological signs of autoimmune diseases were detectable shortly after auto-SCT, and in some patients the autoimmune disease was even exacerbated.

Reappearance of the autoimmune disease was observed in all five patients. However, the data do not answer the question whether the reappearance is attributable to: (1) survival of autoaggressive lymphocyte clones, (2) reinfusion of these clones, (3) relapse of autoimmune diseases through recipient-inherent auto-antigen challenge, or (4) reappearance of autoimmune diseases because defective stem cells were retransplanted.

Autoaggressive lymphocyte clones might have survived the respective preparative regimen. To date, it is not clear, if any (or which) myeloablative regimen achieves complete immunoablation, ie, destruction of all antigen-determined lymphocytes including resting memory cells.[12,13] In our patients, standard preparative regimens were applied in the majority of cases, including repeated myeloablation in patient 2 and a combination of total body irradiation plus high-dose chemotherapy in patient 4. Possibly, other more effective immunosuppressive agents, eg, antithymocyte globulin in addition to high-dose cyclophosphamide[14] might increase the immunoablative potential of a preparative regimen without causing prohibitive toxicity.

Retransplantation of autoaggressive lymphocyte clones with the autologous graft is another possibility, which could explain the autoimmune disease recurrence. Allogeneic SCT transfers the donor immune system (including an eventual donor autoimmune disease) to the recipient, or can cure an autoimmune disease of the recipient. This has repeatedly been observed in animal experiments[15] and in the clinic.[3,16,17] Likewise, pathogenic lymphocyte clones or their precursors might be transplanted with the autologous graft and might have caused the rapid recurrence of autoimmune diseases described here. The retransplantation hypothesis is supported by the observation of autoimmune disease recurrence in patient 2, whose prior thymectomy should have rendered it difficult or impossible to regenerate a new immune system.

As another explanation, it cannot be excluded that persisting auto-antigen challenge from the recipient might induce recurrence of the autoimmune disease. However, the transfer of donor autoimmune diseases to the recipient through allogeneic SCT strongly supports the thesis that the autoimmune disease information is graft-inherent and is independent from an additional recipient-inherent stimulus.

Finally, recurrence caused by expansion of defective stem cells might be another explanation for autoimmune disease recurrence after auto-SCT. In several established animal models of autoimmune diseases the autoimmune disease is derived from defective stem cells.[18-20] However, there is some evidence that human stem cells may carry only the susceptibility to autoimmune diseases, but not the full program necessary to develop a clinical autoimmune disease,[21] and that manifestation of an overt autoimmune disease requires additional external triggers.[22] If human autoimmune diseases were stem cell-inherent, diseases like SLE should occur in the first months or years of life,[23] they should occur completely concordant in monozygotic twins,[24] and treatment-free remission following intensified conventional treatment protocols should not occur.[25,26] In these situations the immune system obviously regenerates from the respective stem cells without development of an overt autoimmune disease.

If lymphocytes or subsets thereof contained in unmanipulated autografts account for the autoimmune disease recurrence, thorough lymphocyte depletion of the graft might be a promising approach to circumvent this problem. Autologous transplantation of lymphocyte-depleted human stem cells, then, should reimplement the susceptibility for the respective autoimmune disease, but the disease would, possibly, not remanifest itself before renewed contact with the exogenous trigger. Techniques for separating hematopoietic stem cells from immunocompetent lymphocytes like purging by means of antilymphocyte antibodies or positive selection of $CD34^+$ stem cells are available.[27-29] It remains to be settled whether the magnitude of lymphocyte depletion currently achieved by these techniques can prevent regrowth of pathogenic lymphocyte clones.

The importance of lymphocyte depletion is supported by clinical and serological remission in a case of myasthenia gravis and malignant lymphoma following treatment with high-dose chemotherapy and autologous PBPCT of positively selected $CD34^+$ cells.[30] The patient had no myasthenia symptoms until renewed chemotherapy for relapsing lymphoma terminated the follow-up 1 year later. The hypothesis is further supported by a more recent report describing improvement of symptoms in 2 patients, who underwent autologous BMT for severe multiple sclerosis. The graft was not manipulated, but the patients received antithymocyte globulin after stem cell reinfusion, thus representing possibly an effective way of in vivo purging of the graft.[31] On the other hand, one case report describes remission of a concomitant SLE in a patient with malignant lymphoma following autologous and unmanipulated BMT.[32]

Another recent report possibly adds evidence supporting the necessity of lymphocyte depletion from the autologous graft for avoidance of autoimmune disease relapses. Cure of 7 of 10 patients with aplastic anemia has been described following high-dose cyclophosphamide (45 mg/kg/d for 4 days; total dose 180 mg/kg) without stem cell reinfusion.[26] Accepting that aplastic anemia is at least partially an autoimmune disease, it seems possible that this protocol was immunoablative, destroying completely the autoaggressive lymphocyte clones, and that a de novo regenerating immune system did not remember the antigenic properties of the previous targets.

The grafts were cryopreserved. Cryopreservation was reported to decrease number and function of some lymphocyte subsets,[33] and, thus, should not be responsible for recurrence of an autoimmune disease.

One might discuss, whether conditioning regimens alone might induce autoimmune symptoms through nonimmune cytotoxic organ injury. We regard this as highly unlikely: high-dose chemotherapy or irradiation alone in patients with malignancies usually does not cause exacerbation of preexisting autoimmune diseases, and allogeneic SCT, preceded by identical or similar conditioning regimens, does not lead to exacerbation—but repeatedly to cure—of autoimmune diseases, as has been reviewed elsewhere.[4]

In summary, the rapid recurrence or persistence of autoimmune diseases in all five cases reported here should be regarded as a cautionary note against recommending standard myeloablative therapy followed by transplantation of unmanipulated autologous hematopoietic stem cell grafts for autoimmune diseases. If auto-SCT is considered to treat severe autoimmune diseases, effective techniques for depleting the graft of lymphocytes along with more intensive immunoablative preparatory regimens should be investigated.

REFERENCES

1. Brooks PM, Atkinson K, Hamilton PJ: Stem cell transplantation for autoimmune diseases. J Rheumatol 22:1809, 1995

2. Burt RK, Burns W, Hess A: Bone marrow transplantation for multiple sclerosis. Bone Marrow Transplant 16:1, 1995

3. Marmont AM, van Bekkum DW: Stem cell transplantation for severe autoimmune diseases: New proposals but still unanswered questions. Bone Marrow Transplant 16:497, 1995

4. Marmont AM: Immune ablation followed by stem cell rescue: A new radical approach to the treatment of severe autoimmune diseases. Forum Trends Exp Clin Med 5:24, 1995

5. Tyndall A, Gratwohl A: Haemopoietic stem and progenitor cells in the treatment of severe autoimmune diseases. Ann Rheum Dis 55:149, 1996

6. Euler HH, Fastenrath S, Dreger P, Schmitz N, Marmont AM: Bone marrow transplantation. A new treatment option in severe SLE? Aktuelle Rheumatol 21:114, 1996

7. Marmont A, Tyndall A, Gratwohl A, Vischer T: Haemopoietic precursor-cell transplants for autoimmune diseases. Lancet 345:978, 1995

8. van Bekkum DW: BMT in experimental autoimmune diseases. Bone Marrow Transplant 11:183, 1993

9. Schmitz N, Linch DC, Dreger P, Goldstone AH, Boogaertz MA, Ferrant A, Demuynck HMS, Link H, Zander A, Barge A, Borkett K: Filgrastim-mobilized peripheral blood progenitor cell transplantation in comparison with autologous bone marrow transplantation: Results of a randomized phase III trial in lymphoma patients. Lancet 347:353, 1996

10. Fastenrath S, Dreger P, Schmitz N, Euler HH: Autologous unpurged bone marrow transplantation in a patient with lymphoma

and SLE: Short term recurrence of antinuclear antibodies. Arthritis Rheum 38:S303, 1995 (abstr, suppl)

11. Dreger P, Marquardt P, Haferlach T, Jacobs S, Muelverstedt T, Eckstein V, Suttorp M, Loeffler H, Muller-Ruchholtz W, Schmitz N: Effective mobilisation of peripheral blood progenitor cells with 'Dexa-BEAM' and G-CSF: Timing of harvesting and composition of the leukapheresis product. Br J Cancer 68:950, 1993

12. Ikuta K, Uchida N, Friedman J, Weissman IL: Lymphocyte development from stem cells. Annu Rev Immunol 10:759, 1992

13. Rolink AG, Reininger L, Oka Y, Kalberer CP, Winkler TH, Melchers F: Repopulation of SCID mice with long-term in vitro proliferating pre-B-cell lines from normal and autoimmune disease-prone mice. Res Immunol 145:353, 1994

14. Horstmann M, Stockschlader M, Kruger W, Hoffknecht M, Betker R, Kabisch H, Zander A: Cyclophosphamide/antithymocyte globulin conditioning of patients with severe aplastic anemia for marrow transplantation from HLA-matched siblings: Preliminary results. Ann Hematol 71:77, 1995

15. Blank M, Krause I, Lanir N, Vardi P, Gilburd B, Tincani A, Tomer Y, Shoenfeld Y: Transfer of experimental antiphospholipid syndrome by bone marrow cell transplantation. The importance of the T cell. Arthritis Rheum 38:115, 1995

16. Lampeter EF, Homberg M, Quabeck K, Schaefer UW, Wernet P, Bertrams J, Grosse-Wilde H, Gries FA, Kolb H: Transfer of insulin-dependent diabetes between HLA-identical siblings by bone marrow transplantation. Lancet 341:1243, 1993

17. Lowenthal RM, Cohen ML, Atkinson K, Biggs JC: Apparent cure of rheumatoid arthritis by bone marrow transplantation. J Rheumatol 20:137, 1993

18. Ikehara S, Inaba M, Yasumizu R, Nagata N, Toki J, Hisha H, Sugiura K, Oyaizu N, Kawamura M, Than S: Autoimmune diseases as stem cell disorders. Tohoku J Exp Med 173:141, 1994

19. Karussis DM, Vourka-Karussis U, Lehmann D, Abramsky O, Ben-Nun A, Slavin S: Immunomodulation of autoimmunity in MRL/lpr mice with syngeneic bone marrow transplantation. Clin Exp Immunol 100:111, 1995

20. Levite M, Zinger H, Zisman E, Reisner Y, Mozes E: Beneficial effects of bone marrow transplantation on the serological manifestations and kidney pathology of experimental systemic lupus erythematosus. Cell Immunol 162:138, 1995

21. Theofilopoulos AN: The basis of autoimmunity: Part II. Genetic predisposition. Immunol Today 16:150, 1995

22. Atkinson JP: Some thoughts on autoimmunity. Arthritis Rheum 38:301, 1995

23. Boumpas DT, Austin HA III, Fessler BJ, Balow JE, Klippel JH, Lockshin MD: Systemic lupus erythematosus: Emerging concepts. Part 1: Renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease. Ann Intern Med 122:940, 1995

24. Jarvinen P, Aho K: Twin studies in rheumatic diseases. Semin Arthritis Rheum 24:19, 1994

25. Euler HH, Schroeder JO, Harten P, Zeuner RA, Gutschmidt HJ: Treatment-free remission in severe systemic lupus erythematosus following synchronization of plasmapheresis with subsequent pulse cyclophosphamide. Arthritis Rheum 37:1784, 1994

26. Brodsky RA, Sensenbrenner LL, Jones RJ: Complete remission in severe aplastic anemia after high-dose cyclophosphamide without bone marrow transplantation. Blood 87:491, 1996

27. Shpall EJ, Jones RB, Bearman SI, Franklin WA, Archer PG, Curiel T, Bitter M, Claman HN, Stemmer SM, Purdy M, Myers SE, Hami L, Taffs S, Heimfeld S, Hallagan J, Berenson RJ: Transplantation of enriched CD34-positive autologous marrow into breast cancer patients following high-dose chemotherapy: Influence of CD34-positive peripheral-blood progenitors and growth factors on engraftment. J Clin Oncol 12:28, 1994

28. Dreger P, Viehmann K, Steinmann J, Eckstein V, Mueller-Ruchholtz W, Loeffler H, Schmitz N: G-CSF-mobilized peripheral blood progenitor cells for allogeneic transplantation: Comparison of T cell depletion strategies using different CD34+ selection systems of CAMPATH-1. Exp Hematol 23:147, 1995

29. Gribben JG, Nadler LM: Antibody-mediated purging, in Forman SJ, Blume KG, Thomas ED (eds): Bone Marrow Transplantation, Boston, MA, Blackwell Scientific, 1995, p 149

30. Salzman D, Tami J, Jackson C, Castro J, Boldt D, Freytes C, Berenson R, LeMaistre CF: Clinical remission of myasthenia gravis in a patient after high dose therapy and autologous transplantation with CD34+ stem cells. Blood 84:206a, 1994 (abstr, suppl 1)

31. Fassas A, Anagnostopoulos A, Kazis A, Sakellari I, Kapinas K, Kaloyannides P: Peripheral blood progenitor cell transplantation for treatment of multiple sclerosis. Preliminary report. Bone Marrow Transplant 17:69, 1996 (abstr, suppl 1)

32. Snowden JA, Habbah EE, O'Donnell J, Patton WN, Hart DNJ: Resolution of longstanding systemic lupus erythematosus after autologous bone marrow transplantation for non-Hodgkins lymphoma. A case report. Bone Marrow Transplant 17:70, 1996 (abstr, suppl 1)

33. Stiff PJ: Cryopreservation of hematopoietic stem cells, in Forman SJ, Blume KG, Thomas ED (eds): Bone Marrow Transplantation, Boston, MA, Blackwell Scientific, 1994, p 299