



High-dose chemotherapy

High-dose chemotherapy followed by stem cell transplantation in patients with resistant Waldenstrom's macroglobulinemia

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Summary:

Preliminary evidence suggests that high-dose chemotherapy followed by autologous or allogeneic stem cell transplantation may be effective in some patients with resistant Waldenstrom's macroglobulinemia. During the last 10 years, seven patients with Waldenstrom's macroglobulinemia have received transplants at the MD Anderson Cancer Center, four with autologous and three with allogeneic stem cells. Four patients achieved partial remission, and three patients have remained alive for at least 2 years. Our data confirm the feasibility of high-dose therapy in patients with macroglobulinemia and support the need for prospective studies of this modality in patients with chemosensitive disease. *Bone Marrow Transplantation* (2001) 27, 1027–1029.

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low grade lymphoma and chronic lymphocytic leukemia,^{3,4} but has been used rarely in WM. Furthermore, allogeneic transplantation may exploit a graft-versus-tumor effect. Here, we report the experience with high-dose chemotherapy in seven patients with WM treated at a single institution over a 10 year period.

Patients and methods

Since 1986, seven patients with WM received high-dose chemotherapy supported by autologous or allogeneic bone marrow or blood progenitor cell transplantation. All patients were male, the median age was 48 years (range 28 to 55 years) and all were resistant to conventional therapy. One patient had primary refractory disease and the others were transplanted during resistant relapse (Table 1). All patients were required to have normal liver and kidney function tests, a left ventricular ejection fraction $\geq 50\%$ and adequate lung function. Patients were treated with various conditioning regimens, according to treatment protocols developed for patients with low grade lymphoma or multiple myeloma, and approved by the Institutional Review Board. All patients signed written informed consent. Partial response was defined as at least 50% reduction of monoclonal protein and of tumor infiltrate at all involved sites. Complete response was defined as disappearance of the monoclonal protein, even by immunofixation, and resolution of all tumor sites.

Treatment characteristics

Treatment characteristics are summarized in Table 1. In brief, four patients underwent autologous stem cell transplant and three patients underwent allogeneic bone marrow or stem cell transplant. Three patients received a total body radiation-based conditioning regimen, three patients were treated with high-dose thiotepa, busulfan, cyclophosphamide, and one patient received a non-myeloablative preparative regimen consisting of fludarabine and cyclophosphamide. Five patients received bone marrow and two patients blood stem cells. Unmanipulated autologous bone marrow or stem cells were used. GVHD prophylaxis consisted of

Waldenstrom's macroglobulinemia (WM) is a low grade lymphoplasmacytoid disorder characterized by the production of monoclonal IgM immunoglobulin. The median age is approximately 65 years and systemic treatment is required when patients present with or develop anemia, hyperviscosity, hepatosplenomegaly or bulky lymphadenopathy. Treatment with alkylating agents induces a partial response in approximately 50% of patients, while the response rate to nucleoside analogues has been approximately 80%.¹ Nevertheless, complete responses are rare. The median survival of patients with WM has been 5 years, with 20% of patients living for more than 10 years.¹

Strategies aimed at improving complete response rates may improve long-term outcome. High-dose chemotherapy with autologous or allogeneic stem cell transplantation, has been effective in many patients with multiple myeloma,²

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Table 1 Seven WM patients with resistant disease undergoing high-dose chemotherapy with stem cell transplant during the last 10 years in our institution

Source of stem cells	Patient	Age	Prior treatment	Time to HDT (months)	Disease status prior to BMT	Preparative regimen	Response	EFS	OS
Autologous	1	55	2CDA-CTX, hyperCVAD	9	Refractory relapse	TBC	Death from CVA day 30	0	1
	2	43	CTX, 2CDA-dexa, hyperCVAD	11	Primary resistant	TBC	Partial response	26+	26+
	3	30	CHOP, FAMP-CTX, Danazol, IVIG	12	Refractory relapse	CTX + TBI	Partial response	108+	108+
	4	58	CVAD, IFN- γ , FAMP-Mitoxantrone	120	Refractory relapse	VP16-CTX + TBI	Partial response	31	37
Allogeneic	5	51	CVAD, 2CDA	15	Refractory relapse	TBC	Death from GVHD day 39	0	1
	6	30	L+P, VAD	30	Refractory relapse	TLI+CTX-VP16+TBI	Partial response	6	6
	7	60	COP, DAP+FAMP, ESHAP, 2CDA	108	Refractory relapse	FAMP + CTX	No response	20	24+

2CDA = 2-chlorodeoxyadenosine; CTX = cyclophosphamide; hyperCVAD = hyperfractionated cyclophosphamide, vincristine, adriamycin and dexamethasone; CHOP = cyclophosphamide, adriamycin, vincristin and prednisone; COP = cyclophosphamide, vincristin and prednisone; FAMP = fludarabine; L+P = chlorambucil + prednisone; IVIG = intravenous immunoglobulin; DAP = dexamethasone, ara-C, platinol; ESHAP = etoposide, steroids, ara-c, cisplatin; TBC = thiotepa, busulfan, cyclophosphamide; TBI = total body irradiation; TLI = total lymphoid irradiation; CVA = cerebrovascular artery thrombosis; EFS = event-free survival; OS = overall survival in months; HDT = high-dose therapy.

cyclosporine or tacrolimus-based therapy for all patients, with one patient also receiving T cell-depleted bone marrow.

patients remain alive for 24–108 months post transplant. Two of them are still in remission and one of them has required chemotherapy for recurrence.

Results

Engraftment and toxicity

Of the four patients receiving autograft, one died on day 30 from a cerebral artery thrombosis. The other three patients achieved neutrophil recovery on days 12, 17 and 13, respectively and platelet transfusion independence on day 9, 20 and 17 post transplant; none experienced serious toxicities. All allogeneic progenitor cell recipients achieved neutrophil recovery between days 13 and 25. Two patients achieved platelet transfusion independence on days 15 and 41, none developed severe regimen-related toxicity, but two patients died within 6 months from complications of acute or chronic GVHD. The patient who received a non-ablative preparative regimen, did not show signs of donor cell engraftment.

Response and survival

All three of the autografted patients who lived more than 30 days achieved partial remission (Table 1). One patient developed secondary AML and died 37 months after transplant; the other two patients are still alive without evidence of progression 20+ and 96+ months post transplant. Of two allografted patients evaluable for response, one had partial remission, in association with GVHD. Three of seven

Discussion

Four other series of patients with WM who received high-dose chemotherapy with autologous or allogeneic stem cell support have been reported in the literature and are summarized in Table 2.^{5–8} All studies confirm that high-dose chemotherapy with autologous stem cell support is feasible and effective in some patients. With current intensive regimens and supportive care, this procedure has been associated with a low incidence of life-threatening complications. Significant disease responses have been observed even in patients with advanced refractory disease, treated many months or years after the initial diagnosis. Using the existing experience with autologous stem cell transplant for myeloma and low grade lymphomas, as a guide for future studies,^{2,3,9} a rational approach would be to use high-dose melphalan, as a simple but highly active^{2,5,7,9} preparative regimen, followed by autologous stem cell support, for newly diagnosed patients with resistant disease, or for patients with short first remissions.

The data with allogeneic transplants were discouraging. Notwithstanding, a graft-versus-malignancy effect was shown, as has been well described for low grade lymphomas.^{3,10–12} Novel treatment strategies using reduced intensity preparative regimens are reasonable investigational treatment options which need to be further

Table 2 Review of published series with WM patients treated with high-dose chemotherapy followed by autologous or allogeneic stem cell transplant

Author/ Ref.	No. of patients	Disease status prior to transplant	Type of transplant	Preparative regimen	Response
Desikan <i>et al</i> ⁵	6	Multiple	Auto SCT	MEL 200	2 PR 2
		Relapse untreated	3	MEL 140+TBI	1 PR 1
		Sensitive	Auto SCT	MEL 200	2 PR 2
		Relapse	2		
Dreger <i>et al</i> ⁶	7	Progression	1 Auto SCT	MEL 200	1 CR1
		1st remission	3 Auto SCT	CY TBI	3 PR 2
					CR 1
		1st refractory	4 Auto SCT	CY TBI	4 PR 4
Mustafa <i>et al</i> ⁷	5	Sensitive disease	5 Auto SCT	High dose MEL	5 CR 4 SD 1
Martino <i>et al</i> ⁸	2	Sensitive	Allo BM	CY TBI	1 CR 1
		Relapse	1		
		Refractory	All BM	Chlorambucil, CY, TBI	PR 1
		Relapse	1		1

explored, in carefully designed clinical trials, for patients with relapsing or refractory WM and HLA-identical donors.

In conclusion, WM remains an incurable disease. Stem cell transplantation may be beneficial for some patients since this procedure may induce durable responses in patients resistant to conventional chemotherapy. Treatment of patients with chemosensitive disease may increase the complete response rate and deserves exploration in prospective trials.

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