associated with intracellular redox changes and elevated plasma tumor necrosis factor-α concentration. Br J Haematol 1997;99:625-31.
8. G, Finazzi S, Maiolo AT. Folate measurement in patients on regular hemodialysis treatment. Am J Kidney Dis 1999; 33:492-7.
9. Trotti R, Carratelli M, Barbieri M, Micieli G, Bosone D, Rondanelli M, et al. Oxidative stress and a thrombophilic condition in alcoholics without severe liver disease. Haematologica 2001;86:85-91.
10. Lantos J, Roth E, Czopf L, Nemes J, Gal I. Monitoring of plasma total antioxidant status in different diseases. Acta Chir Hung 1997;36:188-9.

Thalidomide before autologous stem cell transplantation in VAD-refractory multiple myeloma patients

We used thalidomide to treat 10 patients with advanced stage multiple myeloma who had failed to obtain at least a partial response after a VAD-based induction therapy. Seven out 10 cases achieved clinical and histologic responses and proceeded to collection of peripheral blood stem cells and transplantation and ASCT.

haematologica 2003; 88:597-599
(*http://www.haematologica.org/2003_05/597.htm*)

Sensitivity of multiple myeloma (MM) to induction chemotherapy has been recognized as a powerful prognostic factor of a favorable outcome after high-dose therapy.[1-3] Recent papers have underlined the importance of a rapid response to induction therapy in candidates for autologous stem cell transplantation (ASCT), since those who had a M-component which halved in <0.5 months[4] or after the first 2 cycles of VAD[5] were more likely to achieve a complete response after ASCT. Moreover, patients who had a refractory disease after conventional therapy could fail to mobilize a sufficient number of peripheral blood stem cells (PBSC), due to the persistence of a massive bone marrow plasma cell (BMPC) infiltration.

For these reasons, we considered patients with a less than 50% decline of the M-component and the persistence of a massive BMPC infiltration after conventional chemotherapy as poor candidates for ASCT and treated them with thalidomide with the aim of reducing the BMPC infiltration before stem cell collection and of leading them to ASCT with the minimum amount of disease.

The patients' clinical characteristics and induction therapy are described in Table 1. Thalidomide was started at 100 mg daily and escalated up to a maximum of 400 mg daily.

PBSC were collected after 7 g/m^2 cyclophosphamide plus granulocyte colony-stimulating factor. The conditioning regimen consisted of 12 mg/kg busulfan and 120 mg/m^{2}melphalan. Responses were evaluated with EBMT, IBMT and ABMTR criteria. After thalidomide administration, 7 patients demonstrated a partial response, whereas the other 3 cases presented refractory or progressive disease (Table 2). An initial reduction of M-component that exceeded 25% was evident by at least 8 weeks, but the maximum decrease of M-component of 60% (median value, with range 57-70%) was reached after a median of 16 weeks of thalidomide therapy (range 8-28). In all the 7 responsive patients, bone pain disappeared, $\beta_2$microglobulin serum concentrations dropped, hemoglobin levels increased and 2 transfusion-dependent patients no longer needed any more packed red cell support. Simultaneously, BMPC infiltration markedly decreased, with a median reduction of 84% (range 40-95%) from pre-treatment values and all the responsive patients

Table 1. Clinical characteristics of the patients.

Patient no. (age/sex)	*Ig isotype*	*Stage*	*Therapy prior to thalidomide*	*Median dose of thalidomide*	*Response*	*Outcome*
1 (60/M)	IgGλ	III A	VAD×4, MP×3	400 mg	partial 3 months after ASCT	Continuing response
2 (61/M)	IgAκ	III A	VAD×4, CTX×3	400 mg	partial 4 months after ASCT	Continuing response
3(61/M)	IgAλ	III A	VAD×4, MP×4	400 mg	partial 5 months after ASCT	Continuing response
4 (59/F)	IgGκ	III A	VAD×4	400 mg	partial 8 months after ASCT	Continuing response
5 (49/M)	IgGκ	III A	VAD×4	200 mg	partial 9 months after ASCT	Continuing response
6 (62/M)	IgGκ	II A	VADx4	400 mg	partial 8 months after ASCT	Continuing response
7 (46/M)	IgGκ	III A	VAD×4	300 mg	partial 3 months after ASCT	Continuing response
8 (44/M)	IgGκ	III B	VAD×4	400 mg	progression TMO	Sibling allogeneic
9 (50/F)	Bence Jones	IIIA	VAD×4	400 mg	progression	Waiting for MUD TMO
10 (59/F)	Bence Jones	IIIA	VAD×4	400 mg	no response	Waiting for sibling allogeneic TMO

M:male, F:female, VAD: vincristine, doxorubicin, dexamethasone, MP:melphalan, prednisone, CTX: cyclophosphamide, MUD: marrow unrelated donor, thal:thalidomide.

Table 2. Laboratory data before and during thalidomide treatment.

Case	M-component g/L or g/24h*			Marrow PC%			Hemoglobin g/dL			β2-microglobulin mg/dL		
	diagnosis	after CHT	after Thal	diagnosis	after CHT	after Thal	diagnosis	after CHT	after Thal	diagnosis	after CHT	after Thal
1	81	80	24	100	70	30	6.7	8.9	12.7	unknown	unknown	unknown
2	12	7	2	90	70	8	9.7	11.5	13.2	10.5	4.5	2.8
3	48	40	16	50	70	30	13.2	11.0	13.6	4.5	4.4	2.5
4	35	58	23	80	90	30	10.2	8.8	14.4	3.1	3.5	2.2
5	80	42	16	80	70	10	10.0	11.4	13.0	3.4	3.7	1.9
6	53	31	23	90	90	15	12.6	11.4	13.0	1.5	2.4	2.2
7	66	45	15	85	100	5	10.0	11.0	12.6	2.7	2.2	1.3
8	69	55	87	90	80	100	7.6	10.9	8.0	4.7	2.2	5.3
9	4*	7*	22*	70	90	90	9.0	8.4	7.1	3.5	3.6	8.2
10	7*	5*	6*	90	100	100	8.4	11.2	10.6	5.3	2.9	6.6

CHT: induction chemotherapy, Thal:thalidomide, PC: plasma cell.

reached a median plasmocytosis of 15% (range 5-30%) of total marrow cellularity.

The median daily dose of thalidomide was 400 mg for 8 patients, 300 mg for 1 patient and 200 mg for another patient. The planned dose of 400 mg could not be reached in 1 patient because of WHO grade II peripheral neuropathy and in another because of myalgia.

The 7 responsive patients yielded a median number of 4.1 $\times 10^6$/Kg CD34+ cells (range 2-13.5) with 1 or 2 aphereses. After myeloablative treatment, the median time to reach a neutrophil count of 0.5×10^9/L was 11 days (range 10-13) and to reach 50×10^9/L platelets was 15 days (range 12-17). Four patients had a short-lasting febrile episode with evidence of bacteremia in 1 case and 4 patients had WHO grade III mucositis. At a median of 5 months after ASCT all these patients showed a BMPC infiltration of 5% or lower, even if serum immunofixation was still positive in all but one case.

Thalidomide has recently emerged as an active drug in about one-third of MM patients, who had usually been heavily pretreated or had relapsed after 1 or 2 lines of high-dose therapy.[6-8] Moreover, two case reports[9-10] described a total of 7 patients refractory to conventional chemotherapy, 3 of whom heavily pretreated with 4 to 5 lines of chemotherapy, who underwent ASCT after a preparative treatment with thalidomide. In our study, in 7 out 10 patients who had failed to obtain at least a partial response after VAD-based induction therapy, thalidomide achieved a > 50% decrease of the M-component, an improvement of anemia and performance status and a marked reduction of BMPC infiltration which was even more pronounced than the M-component decrease (84% vs 60%). Response appeared within 8 weeks, as already observed in other studies,[7-8] but was maximum after a median of 16 weeks.

Even though it could be expected that the above mentioned reduction of BMPC infiltration would favor mobilization and collection of PBSC, the activity of thalidomide on the bone marrow environment, through inhibition of vascular endothelial growth factor and fibroblast growth factor 2, disturbance of adhesion molecule expression and modulation of the cytokine milieu,[10] could have a negative impact on the collection of PBSC. However, all the responsive patients in our series yielded a sufficient number of CD34+ cells, had a rapid and eventless hematologic recovery and, despite a still short follow-up, maintained their clinical and histologic responses.

We conclude that thalidomide can be a suitable preparative regimen to PBSC collection and ASCT for patients who demonstrate less than a partial response to conventional treatment.

Francesca Patriarca, Alessandra Sperotto, Simonetta Prosdocimo, Antonella Geromin, Francesco Zaja, Renato Fanin

Chair of Haematology, Bone Marrow Transplantation Unit, Department of Clinical and Morphological Research, University Hospital, Udine, Italy

Correspondence: Francesca Patriarca, MD, Division of Haematology University Hospital, p.le S. Maria della Misericordia 1, 33100 Udine, Italy. Phone: international +39.432.559662. Fax: international +39.432.559661. E-mail: francesca.patriarca@med.uniud.it

Key words: multiple myeloma, thalidomide, ASCT.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Juan Bladé, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. Blasé and the Editors. Manuscript received November 14, 2002; accepted March 24, 2003.

References

1. Bjorkstrand B, Goldstone AH, Ljungman P, Brandt L, Brunet S, Carlson K, et al. Prognostic factors in autologous stem cell transplantation in multiple myeloma: an EBMT Registry Study. European Group for Bone Marrow Transplantation. Leuk Lymphoma 1994;15:265-72.
2. Vesole DH, Tricot G, Jannagath S, Desikan KR, Siegel D, Bracy D, et al. Autotransplants in multiple myeloma: what have we learned. Blood, 1996;88:838-47.
3. Majolino I, Vignetti M, Meloni G, Vegna ML, Scimè R, Tringali S, et al. Autologous transplantation in multiple myeloma: a GITMO retrospective analysis on 290 patients. Haematologica 1999;84:844-52.
4. Alexanian R, Weber D, Giralt S, Dimopoulos M, Delasalle

K, Smith T, et al. Impact of complete remission with intensive therapy in patients with responsive multiple myeloma. Bone Marrow Transplant 2001;27:1037-43.
5. Patriarca M, Sperotto A, Fili' C, Zaja F, Prosdocimo S, Fanin R. Early chemosensitivity to VAD regimen predicts a favorable outcome after autologous stem cell transplantation in multiple myeloma. Haematologica 2002; 87:779-80.
6. Singhal S, Metha J, Desikan R, Ayers D, Robertson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;21: 1565-71.
7. Barlogie B, Desikan R, Eddlemon P, Spencer T, Zelis J, Munshi N, et al. Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. Blood 2001;98:492-4.
8. Ahamad I, Islam T, Chanan-Khan A, Hahn T, Wentling D, Becker JL, et al. Thalidomide as salvage therapy for VAD-refractory multiple myeloma prior to autologous PBSCT. Bone Marrow Transplant 2002;29:577-80.
9. Dmoszynska A, Hus M, Legic W, Walter-Croneck A, Wach M. Delayed stem cell transplantation in patients with relapsed or refractory multiple myeloma using thalidomide as preparative regimen Blood 1999;94:5345a[abstract].
10. Raje N, Anderson K. Thalidomide- a revival story. N Engl J Med 1999;18:1606-9.

Significant potentiation of anticoagulation by flu-vaccine during the season 2001-2002

Influenza-vaccination is increasingly used in patients under chronic anticoagulation. Whether it interferes with oral anticoagulants is under debate. We found, in a case-control study in ninety patients in the 2001-2002 season, that flu-vaccine induced a significant increase of INR, particularly in a subgroup of patients. INR should be carefully monitored in anticoagulated patients after flu vaccination.

haematologica 2003; 88:599-600
(*http://www.haematologica.org/2003_05/599.htm*)

Whether flu vaccination causes modifications of the prothrombin time in patients receiving oral anticoagulants is a clinically important controversy. In two small, prospective studies a prolongation of prothrombin time was demonstrated while in several other reports, mostly of small series, influenza vaccine was not found to interfere with anticoagulation.[1-4] However, the latest ACCP consensus conference on antithrombotic therapy discussing drug interactions with warfarin classified flu vaccine as an INR-potentiating drug.[5]

Anticoagulated patients are increasingly part of old age range groups and are often affected by ischemic heart disease, heart failure or diabetes, all conditions in which flu-vaccination is strongly indicated.[6] In the past vaccination season we evaluated, in a case-control study, the effect of flu-vaccination on prothrombin time in patients receiving chronic oral anticoagulant treatment. The INR of these patients had been stably within the therapeutic range over the previous 3 months. Ninety consecutive patients (58 males, 32 females, mean age 74, 69 with INR range 2-3, 21 with INR range 3-4.5, mean INR 2.79±0.83; 98% anticoagulated with warfarin, 2% with acenocoumarol) were enrolled in the study. One of the following flu vaccines was administered by a single intramuscular injection: Inflexal V (Berna), Isiflu V (Kedrion), Fluad (Chiron), or Agrippal (Chiron). In all patients INR values were recorded 3 times before (the last of which 5-7 days prior to) vaccination and once 7-10 days after vaccination. Forty-five patients not receiving vaccination and followed during the same period in our Center, well matched for gender, age, type of anticoagulant drug, INR target and stability within range over the past three months, were randomly taken as controls (Table 1). The INR was recorded in the controls at the same four time-points as in the cases. Influenza immunization produced an average increase in INR of 0.56: INR before vaccination (average of three determinations) was 2.79±0.83 in patients and 2.67±0.90 in controls (p=NS), while 7-10 days after flu-vaccination it was 3.35±1.04 in patients and 2.59±0.90 in controls (p<0.00005). Using a cut-off INR change of ≥0.5, two subpopulations were distinguished: in 49 out 90 patients vaccination produced a clear increase in INR (mean INR before 2.64±0.98; mean INR after 3.85±0.98, p<0.00001). In this subgroup 2 patients had bleeding episodes after the flu vaccination: epistaxis and muscular hematoma. In the remaining 51 patients no INR changes were observed (mean INR before 2.82±0.92; mean INR after 2.79±0.82, p=NS) (Figure 1). No patient in this subgroup or in the control group had any bleeding in the same period. There were no differences in age, sex, type of oral anticoagulant, or average anticoagulant dose between the two subgroups. We cannot exclude that administration of different flu vaccines may have accounted for the different response. Indeed, in a previous series, a significant potentiation of anticoagulation by flu-vaccination observed in

Table 1. Characteristics of cases (vaccinated patients) and controls (not vaccinated patients).

	Cases	*Controls*
Age (mean)	74	69
Sex (M/F)	58/32	30/15
Low range INR 2-3 (N)	69	37
High range INR 3-4.5 (N)	21	8
Warfarin/Acenocoumarol (W/A)	88/2	44/1
Major bleeding complications (N)	0	0
Minor bleeding complications (N)	2	0
Thrombotic complications (N)	0	0

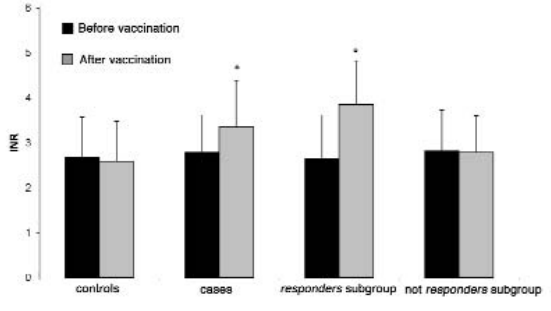

Figure 1. Effect of flu vaccination on INR in patients under long-term oral anticoagulation. INRs were recorded three times before (the last of which 5-7 days prior to) and one time (7-10 days) after vaccination in the cases and at the same time points in the controls. Data are expresses as means±SD. *p<0.00005; °p<0.00001.