ening and enhancement of meninges, the biopsy-proven MM recurrence in extramedullary sites, and the absence of viruses in CSF suggested that myeloma cells had involved the central nervous system (CNS).

Extramedullary manifestations such as multiple plasmacytomas with minimal or no monoclonal component were reported in 14% of patients after autologous HSCT from the Spanish Registry[1] and in a few cases after allogeneic transplantation.[2] Localizations of MM in CNS are even rarer; they usually appear as a terminal event of a progressive systemic disease, although a few cases of CNS relapse without overt medullary plasmacytosis have been reported.[3,4] Recently, the Arkansas group[5] reported on 18 MM patients who relapsed with CNS involvement after HSCT, for an overall incidence of approximately 1%. The prognosis of these patients is very poor,[5,6] despite the use of aggressive local and systemic treatment, including autologous stem cell transplantation. Extramedullary recurrences in sites other than the CNS were reported to respond successfully to thalidomide treatment by Biagi;[6] however, the group of Bladè[7] described progression of soft-tissue masses in 11 patients treated with thalidomide.

In our case, the patient received radiotherapy to the 9th thoracic vertebra and then bortezomib, with disappearance of the cranial nerve palsies and the masses involving the ribs. Bortezomib is a proteasome inhibitor[8] that has been reported to induce responses in about one-third of patients with refractory or relapsed MM.[9] Bortezomib has an extensive tissue penetration; however, data from studies conducted in non-human primates have indicated that bortezomib does not penetrate into the CNS or into various regions of the eye.[10]

This is the first report on the activity of this promising agent on extramedullary plasmacytomas. The resolution of all neurological symptoms and signs and the normalization of cerebral MR images could also be due to an immunological graft-versus-myeloma (GVM) effect; however, since the patient did not develop clinical GVHD, a GVM effect is unlikely and bortezomib's activity in the rare CNS localizations of MM should be confirmed by further pharmacokinetic and clinical studies.

Francesca Patriarca, Simonetta Prosdocimo,* Valentina Tomadini,* Annarosa Vasciaveo,° Benedetto Bruno,# Renato Fanin**

**Division of Hematology, Department of Clinical and Morphological Researches, University of Udine; °Institute of Radiology, Department of Clinical and Morphological Researches, University of Udine; #Division of Hematology, S. Giovanni Battista Hospital, University of Turin, Italy*

Key words: bortezomib, multiple myeloma, extramedullary relapse.

Correspondence: Francesca Patriarca, MD, Clinica Ematologica, Policlinico Universitario, p.zale S. Maria della Misericordia, 33100 Udine, Italy. Phone: international +39.0432.559662. Fax: international +39.0432.559661. E-mail: francesca.patriarca@med.uniud.it

References

1. Alegre A, Granda A, Martinez-Chamorro C, Diaz-Mediavilla J, Martinez R, Garcia-Larana J, et al. Different patterns of relapse after autologous peripheral blood stem cell transplantation in multiple myeloma: clinical results of 280 cases from the Spanish Registry. Haematologica 2002;87:609-14.
2. Biagi JJ, Mileshkin L, Grigg AP, Westerman DW, Prince HM. Efficacy of thalidomide therapy for extramedullary relapse of myeloma following allogeneic transplantation. Bone Marrow Transplant 2001;28:1145-50.
3. Veisten A, Brizard A, Randriamalata E, Babin P, Preud'homme JI, Guilhot F. Central nervous system relapses after autologous stem cell transplantation for myeloma. Report of two cases. Haematol Cell Ther 1997;39:327-30.
4. Patriarca F, Zaja F, Silvestri F, Sperotto A, Scalise A, Gigli G, et al. Meningeal and cerebral involvement in multiple myeloma patients. Ann Hematol 2001;80:758-62.
5. Fassas AB, Muwalla F, Berryman T, Benramdane R, Joseph L, Anaissie E, et al. Myeloma of the central nervous system: association with high-risk chromosomal abnormalities, plasmablastic morphology and extramedullary manifestations. Br J Haematol 2002;117:103-8.
6. Petersen SL, Wagner A, Gimsing P. Cerebral and meningeal multiple myeloma after autologous stem cell transplantation. A case report and review of the literature. Am J Hematol 1999; 62:228-33.
7. Rosinol L, Cibeira MT, Bladè J, Esteve J, Aymerich M, Rozman M, et al. Extramedullary multiple myeloma escapes the effect of thalidomide. Haematologica 2004;89:832-6.
8. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase II study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609-17.
9. Kane RC, Bross PF, Farrell AT, Pazdur R. Velcade: U.S. FDA approval for the treatment of multiple myeloma progressing on prior therapy. Oncologist 2003;8:508-13.
10. Adams J, Kauffman M. Development of the proteasome inhibitor Velcade (Bortezomib). Cancer Invest 2004;22:304-6.

Monoclonal Gammopathies

Advanced Waldenström's macroglobulinemia: usefulness of Morel's scoring system in establishing prognosis

New treatments for patients with Waldenström's macroglobulinemia (WM) have necessited the development of prognostic indices. Using a sample of 92 patients with refractory or relapsing WM treated in a randomized trial, we show that Morel's prognostic scoring system for patients at diagnosis is also effective in patients with advanced disease.

haematologica 2005; 90:279-281
(http://www.haematologica.org/journal/2005/2/279.html)

In Waldenström's macroglobulinemia (WM), alkylating agents, alone or combined with corticosteroids, used to be the first line treatment for patients with symptomatic disease.[1] However, preliminary results suggest that fludarabine is effective in 30 to 40% of previously treated patients.[2] Therefore, we conducted a randomized multicenter clinical trial comparing the efficacy of fludarabine to that of the cyclophosphamide-doxorubicin-prednisone combination in 92 patients with WM in first relapse or with primary refractory disease.[3] Two prognostic studies, concerning only newly diagnosed patients, have been recently proposed by Dhodapkar[4] and our group.[5] In order to test the external validity of these staging systems for patients with relapsing WM or primary refractory disease, we applied them to our cohort of 92 patients. The clinical characteristics of the 92 patients have been reported elsewhere. In brief, 46 patients were randomized in each arm and assigned to receive 6 courses of either CAP (cyclophosphamide, doxorubicin, prednisone) or fludarabine. Fifty patients were in first relapse and 42 patients had primary resistant disease. There was no difference in overall survival between the two arms.[3] With actualized data at the reference date of the 1st June 2004, the conclusions of the comparison were not modified. Survival was measured from randomization to death or last follow-up, using 01/06/2004 as the reference date. Survival curves were plotted using the Kaplan-Meier method[6] and compared by log-rank tests. The following predictors were tested: age ≤ 65 years, male gender, general status (WHO) of 2 or more, presence of peripheral

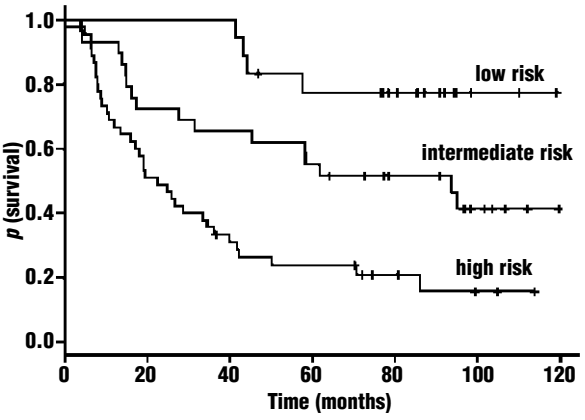

Figure 1A. Morel (log-rank test, $p< 0.0001$).

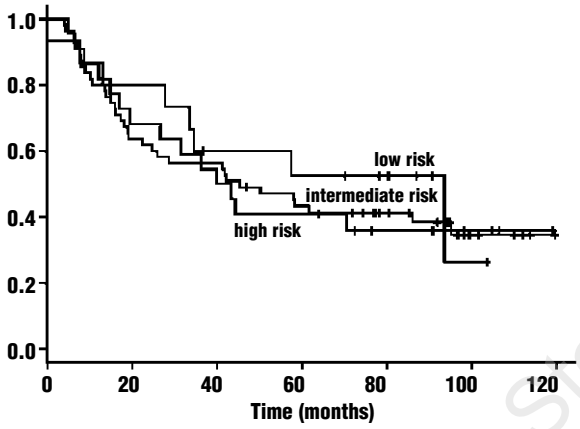

Figure 1B. Dhodakpar (log-rank test, $p= 0.85$).

lymphadenopathy, splenomegaly, hepatomegaly, myelofibrosis, percentage of lymphoid cells in the bone marrow smears, blood cell counts (thrombocytopenia (<150× 10^9/L), leukopenia (<4×10^9/L), anemia (<12 g/dL), total number of cytopenia (0 to 3), monoclonal IgM level (< vs ≥ 40 g/L), albumin level (< vs ≥ 40 g/L), β2 microglobulin level (< vs ≥3 mg/L), lactate dehydrogenase (normal vs elevated), presence of cryoglobulinemia, positivity of antiglobulin test, and scoring systems proposed by Morel,[5] and Dhodapkar.[4] Multivariable Cox model was used to identify the set of prognostic variables.[7] Hypotheses of proportional hazards were tested using Grambsch and Therneau method.[8] The variable selection method consisted in a stepwise procedure comparing different models combining several predictors on the basis of the modified Akaike criterion.[9] The predicted prognostic information was measured by the separation (PSEP = $p^{High} - p^{Low}$) where p^{High} is the predicted probability of dying by 100 months for a patient in the group with the worst prognosis, and p^{Low} the corresponding value for those of the best prognosis group.[10] Patients identified with Morel's scoring system as low-risk (19.5%), intermediate-risk (31.5%), and high-risk (48.9%) had significantly different survivals (p=0.00001, Figure 1A), while patients with low-risk (16%), intermediate-risk (60%), and high-risk (24%) according to Dhodapkar's score did not have no significantly different survivals (p=0.85, Figure 1B).

Table 1. Univariable and multivariable analyses (Cox).

Parameter	HR (CI 95%)	p
Univariate analysis		
Age (> 65 yrs or older)	2.26 (1.32-3.86)	0.028
Albumin (< 40 g/L)	2.51 (1.41-4.41)	0.0013
Thrombocytopenia (< 150×10^9/L)	2.74 (1.6-4.67)	0.00022
Leukopenia (< 4×109/L)	1.83 (1.05-3.19)	0.032
LDH (over normal)	2.13 (1-4.55)	0.05
β2 microglobulin (over normal)	1.89 (1.02-3.5)	0.042
Multivariate analysis		
Age (> 65 yrs or older)	2.24 (1.29-3.89)	0.004
Albumin (< 40 g/L)	2.49 (1.39-4.46)	0.0022
Thrombocytopenia (< 150×10^9/L)	1.69 (1.08-3.55)	0.026
Leukopenia (< 4×10^9/L)	1.93 (1.03-3.6)	0.04

Univariable prognostic analyses identified an adverse prognostic value for survival of age 65 years or older, serum albumin level lower than 40 g/L, thrombocytopenia, leukopenia, high LDH, increased level of β2 microglobulin (all p=0.05). Multivariable Cox regression identified thrombocytopenia (p=0.026), low serum albumin level (p=0.0022), leukopenia (p=0.04) and age (p=0.004) with joint prognostic significance. Predicted prognostic information demonstrated a PSEP=0.774-0.156=0.618 for Morel's classification and a PSEP=0.358 -0.263=0.095 for Dhodakpar's score, thus indicating a far better ability to discriminate between poor and good prognosis for Morel's classification.

Of note, the best model for the present data included only covariates appearing in Morel's score. This may be explained by our moderate sample size and/or discrepancies between the studies. First, the percentage of patients without anemia may be too small among those with refractory disease or relapse, so that these characteristics may lose their prognostic importance. Secondly, all patients in the present study received intensive therapy with fludarabine or a regimen including doxorubicin so that the prognostic value of some factors may be erased.

We conclude that Morel's score, proposed for overall survival of WM, is also effective for predicting the long-term efficacy of fludarabine or CAP in patients with advanced WM. However, additional studies might be useful to identify the optimal staging system for predicting long-term efficacy of therapy in advanced Waldenström's macroglobulinemia.

Vincent Lévy,° Pierre Morel,# Raphaël Porcher,°@ Sylvie Chevret,°^ Eric Wattel,@ Véronique Leblond§*

**Centre d'Investigations Cliniques, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris; °ERM 321 INSERM, Paris; #Service d'Hématologie Clinique, Hôpital Schaffner, Lens; @Département de Biostatistique et Informatique Médicale, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris; ^Service d'Hématologie, Hôpital Edouard Herriot, Lyon; §Service d'Hématologie, Hôpital de la Pitié Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France*

Key words: Waldenström's macroglobulinemia, prognostic factors, fludarabine.

Correspondence: Dr. Vincent Lévy, Centre d'Investigations Cliniques, Hôpital Saint Louis, 1 avenue Claude Vellefaux, 75010, Paris, France. Phone: international +33.1.42499494. Fax: international +33.1.42499397. E-mail: vincent.levy@sls.ap-hop-paris.fr

References

1. Dimopoulos MA, Panayiotidis P, Moulopoulos LA, Sfikakis P, Dalakas M. Waldenström's macroglobulinemia: clinical features, complications, and management. J Clin Oncol 2000; 18:214-26.
2. Foran JM, Rohatiner AZ, Coiffier B, Barbui T, Johnson SA, Hiddemann W, et al. Multicenter phase II study of fludarabine phosphate for patients with newly diagnosed lymphoplasmacytoid lymphoma, Waldenström's macroglobulinemia, and mantle-cell lymphoma. J Clin Oncol 1999;17:546-53.
3. Leblond V, Levy V, Maloisel F, Cazin B, Fermand JP, Remenieras JJ, et al. Results of a multicentric randomized study comparing the efficacy of fludarabine to that of cyclophosphamide, doxorubicine and prednisone in 92 patients with Waldenström's macroglobulinemia in first relapse or primary refractory disease. Blood 2001;98:2640-4.
4. Dhodapkar MV, Jacobson JL, Gertz MA, Rivkin SE, Roodman GD, Tuscano JM, et al. Prognostic factors and response to fludarabine therapy in patients with Waldenström's macroglobulinemia: results of United States intergroup trial (Southwest Oncology Group S9003). Blood 2001;98:41-8.
5. Morel P, Monconduit M, Jacomy D, Lenain P, Grosbois B, Bateli C, et al. Patients with the description of a new scoring system and its validation on 253 other patients. Blood 2000; 96:852-8.
6. Kaplan E, Meier P. Non-parametric estimation from incomplete observations. J Am Statist Assoc 1958;35:457-81
7. Cox D. Regression models and life tables. J R Statist Soc B 1972;34:187-201.
8. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residual. Biometrika 1994; 81: 515-26.
9. Hurvich CM, Tsai CL. Regression and time series model selection in small samples. Biometrika 1989;76:297-307.
10. Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med 2000;19:453-73.

Platelets

Effect of a single dose of rituximab in chronic immune thrombocytopenic purpura in childhood

Twenty-two children with immune thrombocytopenic purpura (ITP) with long-lasting thrombocytopenia, adversely affecting their quality of life, were treated with a reduced rituximab regimen in order to eliminate B cells producing anti-platelet antibody. A single dose of rituximab resulted in a response rate similar to that reported for cases in which 4 doses of rituximab were used.

haematologica 2005; 90:281-283
(http://www.haematologica.org/journal/2005/2/281.html)

Up to 30% of children suffering from immune thrombocytopenic purpura (ITP) fail to achieve remission within six months.[1] The quality of life in these children with chronic ITP is substantially reduced as they suffer from the permanent fear of bleeding, multiple physician visits or hospital admissions, side effects of treatment or recurrent bleeding events. In order to eliminate the B-cell clone producing the anti-platelet antibodies, the chimeric cytotoxic CD20-antibody rituximab was succesfully used in adults with chronic ITP[2-6] and in a small number of pediatric patients.[7,8] We report on the efficacy of a single dose of rituximab in childhood chronic ITP.

Table 1. Patients' characteristics itemized according to response to therapy, relapse rates, time to relapse and duration of continuous remission.

	Total n=22	*CR n=7*	*PR n=6*	*NR n=9*	*p**
Sex [n] (f-m)	14-8	6-1	4-2	4-5	0.231
Age at diagnosis [years] median (min-max)	5.8 (2.5-15.2)	11 (5-13.7)	4.3 (2.6-9.8)	5.0 (2.5-15.2)	0.044
ITP duration before rituximab [months] median (min-max)	44 (14-103)	53 (22-72)	47 (17-103)	38 (14-51)	0.283
Median PLT before rituximab [n×10⁹] median (min-max)	5 (2-27)	8 (2-27)	6 (2-11)	5 (2-9)	0.250
Duration of remission° [months] median (min-max)	12 (2-24)	12 (2-24)	10 (2-16)	–	0.885
Patients in continuous remission° [n]	8/13	3/7	5/6	–	0.266
Duration of continuous remission° [months] median (min-max)	13.5 (2-16)	12 (2-16)	15 (4-16)	–	0.647
Relapsed patients° [n]	5/13	4/7	1/6	–	0.266
Time to relapse° [months] median (min-max)	6 (2-24)	9 (4-24)	2	–	0.157

**Pearson's χ^2 test for categorical variables, Kruskal Wallis test for continuous variables. °NR excluded.*

The study protocol was approved by the local ethics committee and the patients were enrolled in the study after written consent from their guardians. Twenty-two children (8 boys, 14 girls) suffering from chronic ITP with documented platelet counts <30×10⁹/L for longer than 12 months were treated. The median age of the patients at diagnosis of ITP was 5.8 years (range 2.5-15.2), the median duration of documented thrombocytopenia was 44 months (range: 14-103) and the median platelet count before treatment was 5×10⁹/L (range: 2-27). In 18/22 patients the platelet count before rituximab was <10×10⁹/L. Only one patient had a platelet count >20×10⁹/L because of steroid treatment for a second intracranial hemorrhage. Bleeding symptoms were mild (grade 2)[9] in 13/22 patients, 7/22 patients suffered from moderate bleeding (grade 3)[9] requiring intervention and 2/22 patients had documented intracranial hemorrhage (grade 5)[9] in their ITP history. Prior to rituximab patients had been treated with intravenous immunoglobulins (IVIG) and/or steroids (21/22 IVIG, 19/22 steroids). A transient response was documented in 12/21 IVIG-treated patients, and 12/19. Anti-D treatment was given to 4/22 patients without response. Splenectomy prior to rituximab treatment was performed in 2/22 patients and partial embolization of the spleen in one patient; none of these 3 patients had a response. Bone marrow aspiration was performed in all patients before treatment to exclude thrombocytopenia due to megakaryocytopenia. All patients received a single intravenous dose of rituximab (375 mg/m²). The patients received no other treatment in addition to rituximab. Criteria for response to therapy were defined as follows: complete remission (CR), PLT > 100×10⁹/L; partial remission (PR) PLT >30×10⁹/L; no