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 plasma- 
cytomas with minimal or no monoclonal component were
reported in 14% of patients after autologous H SCT from 
the Spanish Registry and in a few cases after allogeneic 
transplantation.2 Localization of MM in CNS are even 
rarer; they usually appear as a terminal event of a progres-
sive systemic disease, although a few cases of CNS relapse 
without overt medullary plasmacytosis have been report-
ed.3,4 Recently, the Arkansas group reported on 18 MM 
patients with CNS involvement after H SCT, for an overall incidence of approximately 1%. The progno-
sis of these patients is very poor,5,6 despite the use of 
aggressive local and systemic treatment, including autolo-
gous stem cell transplantation. Extramedullary recurrences 
in sites other than the CNS were reported to respond suc-
cessfully to thalidomide treatment by Biagi;7 however, the 
group of Bladè described progression of soft-tissue mass-
es in 11 patients treated with thalidomide.8

In our case, the patient received radiotherapy to the 9th 
thoracic vertebra and then bortezomib, with disappear-
appearance of the cranial nerve palsies and the masses involving the ribs. Bortezomib is a proteasome inhibitor that has been reported to induce responses in about one-third of patients with refractory or relapsed MM.7 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.6

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; how-
ever, 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 fur-
ther pharmacokinetic and clinical studies.

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Key words: bortezomib, multiple myeloma, extramedullary relapse.

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Table 1. Univariable and multivariable analyses (Cox).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR (CI 95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariable analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (&gt; 65 yrs or older)</td>
<td>2.26 (1.32-3.86)</td>
<td>0.028</td>
</tr>
<tr>
<td>Albumin (&lt; 40 g/L)</td>
<td>2.51 (1.44-4.41)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;150×10^9/L)</td>
<td>2.74 (1.64-4.67)</td>
<td>0.00022</td>
</tr>
<tr>
<td>Leukopenia (&lt;4×10^9/L)</td>
<td>1.83 (1.05-3.19)</td>
<td>0.032</td>
</tr>
<tr>
<td>LDH (over normal)</td>
<td>2.13 (1.43-3.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>β2 microglobulin (over normal)</td>
<td>1.89 (1.02-3.5)</td>
<td>0.042</td>
</tr>
<tr>
<td><strong>Multivariable analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (&gt; 65 yrs or older)</td>
<td>2.24 (1.29-3.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>Albumin (&lt; 40 g/L)</td>
<td>2.49 (1.39-4.46)</td>
<td>0.0022</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;150×10^9/L)</td>
<td>1.69 (1.08-3.55)</td>
<td>0.026</td>
</tr>
<tr>
<td>Leukopenia (&lt;4×10^9/L)</td>
<td>1.93 (1.03-3.6)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

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).

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, leukaemia, 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), leukaemia (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 Dhodapkar’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 Walderström’s macroglobulinemia.

**Key words:** Waldenström’s macroglobulinemia, prognostic factors, fludarabine.

lymphadenopathy, splenomegaly, hepatomegaly, myelofibrosis, percentage of lymphoid cells in the bone marrow smears, blood cell counts (thrombocytopenia (<150×10^9/L), leukaemia (<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, and Dhodapkar. Multivariable Cox model was used to identify the set of prognostic variables.

**Hypotheses of proportional hazards were tested using Grambsch and Therneau method.** The variable selection method consisted in a stepwise procedure comparing different models combining several predictors on the basis of the modified Akaike criterion. The predicted prognostic information was measured by the separation (PSEP = \( p^{\text{max}} - p^{\text{min}} \)) where \( p^{\text{max}} \) is the predicted probability of dying by 100 months for a patient in the group with the worst prognosis, and \( p^{\text{min}} \) the corresponding value for those of the best prognosis group. 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
Letters to the Editor

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

<table>
<thead>
<tr>
<th>Total</th>
<th>CR</th>
<th>PR</th>
<th>NR</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis [years] median (min–max)</td>
<td>5.8</td>
<td>5.1</td>
<td>5.1</td>
<td>0.044</td>
</tr>
<tr>
<td>[months] median (min–max)</td>
<td>2.76 (0.98–5.90)</td>
<td>2.65 (0.98–5.90)</td>
<td>2.11 (0.98–5.90)</td>
<td>0.283</td>
</tr>
<tr>
<td>Median PLT before rituximab [×10^9]/L (n=10) median (min–max)</td>
<td>5.9</td>
<td>5.9</td>
<td>4.9</td>
<td>0.250</td>
</tr>
<tr>
<td>Duration of remission* [months] median (min–max)</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>0.885</td>
</tr>
<tr>
<td>Patients in continuous remission* [n]</td>
<td>8/13</td>
<td>9/13</td>
<td>5/16</td>
<td>0.266</td>
</tr>
<tr>
<td>Duration of continuous remission* [months] median (min–max)</td>
<td>13.5</td>
<td>12</td>
<td>15</td>
<td>0.647</td>
</tr>
<tr>
<td>Relapsed patients* [n]</td>
<td>5/13</td>
<td>4/13</td>
<td>1/6</td>
<td>0.266</td>
</tr>
<tr>
<td>Time to relapse* [months] median (min–max)</td>
<td>6</td>
<td>9</td>
<td>2</td>
<td>0.157</td>
</tr>
</tbody>
</table>

*Pearson’s χ² 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 <30×10^9/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 5×10^9/L (range: 2-27). In 18/22 patients the platelet count before rituximab was <10×10^9/L. Only one patient had a platelet count >20×10^9/L because of steroid treatment for a second intracranial hemorrhage. Bleeding symptoms were mild (grade 2) in 13/22 patients, 7/22 patients suffered from moderate bleeding (grade 3) requiring intervention and 2/22 patients had documented intracranial hemorrhage (grade 5) 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 >100×10^9/L; partial remission (PR), PLT >30×10^9/L; no

**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.

Up to 30% of children suffering from immune thrombocytopenic purpura (ITP) fail to achieve remission within six months. 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 successfully used in adults with chronic ITP and in a small number of pediatric patients. We report on the efficacy of a single dose of rituximab in childhood chronic ITP.

![Table 1](http://www.haematologica.org/article/2005/2/281.html)