Prolymphocytic leukemia (PLL) is a rare variant of chronic lymphocytic leukemia, characterized by a marked leukocytosis, splenomegaly and absence of lymphoadenopathy.

The clinical course is progressive in the majority of cases, due to the resistance of the disease to conventional chemotherapy. Retrospective studies show that the median survival is only 16 months and to date, alternative approaches have not proven to be more effective or are still under evaluation.

We treated 4 cases of PLL, resistant to standard chemotherapy, with pentostatin, a potent adenosine deaminase inhibitor. The inhibition of this enzyme induces the accumulation of dATP, with cytotoxic and growth inhibitory effects on T-cells.

Case reports

Four PLL patients (3 B-PLL and 1 T-PLL) were enrolled in this study. All patients had been unsuccessfully treated with 6-12 courses of conventional chemotherapy: mitoxantrone (10 mg/sqm day 1), vincristine (1.4 mg/sqm day 1), cyclophosphamide (800 mg/sqm day 1), bleomycin (8 mg/sqm days 1 and 8), methylprednisone (60 mg/sqm days 1-14) (CNOP-Bleo) were administered in 3 cases, while one patient was treated with CHOP.

Pentostatin was used as salvage treatment at a weekly dose of 4 mg/sqm for 6 weeks, and then every 15 days, at the same dosage, for 3-6 courses. Bone marrow involvement was evaluated with an aspiration before treatment and after 6, 9 and 12 courses.

Table 1 shows clinical and laboratory data of the patients before treatment with pentostatin and Table 2 shows the results of the treatment.

Case #1

A 65-year-old male presented with T-PLL in July, 1991. The complete blood count (CBC) revealed 260\times10^9/L WBC (95% lymphoid cells), Hb 9 (g/dL), and 60\times10^9/L platelets. The bone marrow was infiltrated by 90% of prolymphocytic cells and the karyotype showed hypodiploid changes with the number of chromosomes ranging between 41 and 43. Splenomegaly was relevant (diameter of the spleen 18 cm).

The patient was started on CNOP-Bleo treatment with a transitory reduction of WBC count. Chemotherapy was complicated by Pneumocystis carinii pneumonia. In May, 1992 he presented a progression of the disease so he was started on pentostatin treatment. After 3
Table 1. Laboratory and clinical features before pentostatin.

<table>
<thead>
<tr>
<th>case</th>
<th>sex/age</th>
<th>immunophenotype</th>
<th>cytogenetic abnormalities</th>
<th>disease duration before pentostatin (weeks)</th>
<th>performance status (WHO)</th>
<th>splenomegaly (echography measurement, cm)</th>
<th>bone marrow prolymphocytoid infiltration (%)</th>
<th>WBC x10^9/L (% of lymphoid cells)</th>
<th>plts x10^9/L</th>
<th>Hb g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/65</td>
<td>(CD2+, CD3+, CD4+, CD5+)</td>
<td>hypodiploidy</td>
<td>47</td>
<td>1</td>
<td>18</td>
<td>78</td>
<td>94 (80)</td>
<td>102</td>
<td>11.2</td>
</tr>
<tr>
<td>2</td>
<td>M/54</td>
<td>(CD19+, CD22+, CD25+, CD11+)</td>
<td>t(2;17)</td>
<td>6</td>
<td>1</td>
<td>25</td>
<td>90</td>
<td>82 (75)</td>
<td>78</td>
<td>6.4*</td>
</tr>
<tr>
<td>3</td>
<td>M/59</td>
<td>(CD19+, sIg+, CD20+, DR+, sIgk+)</td>
<td>i(8q), der(5), der(11), -Y</td>
<td>48</td>
<td>4</td>
<td>28</td>
<td>90</td>
<td>360 (92)</td>
<td>129</td>
<td>10.3</td>
</tr>
<tr>
<td>4</td>
<td>F/85</td>
<td>(CD19+, sIg+, CD22+, CD5+, CD20+)</td>
<td>not done</td>
<td>82</td>
<td>3</td>
<td>previous splenectomy</td>
<td>90</td>
<td>120 (96)</td>
<td>110</td>
<td>8.3*</td>
</tr>
</tbody>
</table>

*supportive care required.

Table 2. After 3 months on pentostatin treatment.

<table>
<thead>
<tr>
<th>case</th>
<th>response to treatment</th>
<th>bone marrow prolymphocytoid infiltration (%)</th>
<th>WBC x10^9/L (% of lymphoid cells)</th>
<th>plts x10^9/L</th>
<th>Hb g/dL</th>
<th>splenomegaly (cm)</th>
<th>remission duration</th>
<th>toxic effects</th>
<th>overall survival weeks</th>
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<tbody>
<tr>
<td>1</td>
<td>CR</td>
<td>&lt;5</td>
<td>6.6 (47)</td>
<td>150</td>
<td>13.5</td>
<td>14</td>
<td>14</td>
<td>none</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>PR</td>
<td>30</td>
<td>22 (50)</td>
<td>120</td>
<td>10</td>
<td>15</td>
<td>-62+</td>
<td>fever</td>
<td>87+</td>
</tr>
<tr>
<td>3</td>
<td>died in induction</td>
<td>not evaluable</td>
<td>113**</td>
<td>56**</td>
<td>/</td>
<td>/</td>
<td>/</td>
<td>none</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>PR</td>
<td>15</td>
<td>11 (43)</td>
<td>13</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td>114</td>
</tr>
</tbody>
</table>

*the patient died after 3 administrations of pentostatin for disease progression. **results obtained after the third administration of pentostatin.
months the peripheral CBC was normal, bone marrow prolymphocytes were under 5%, the karyotype was normal and the spleen diameter was 14 cm. Twelve total courses of pentostatin were administered. Consolidation treatment included splenectomy (the histological evaluation of the spleen showed no prolymphocytic infiltration) and then alpha-interferon treatment (3 MU every other day). After 14 weeks in CR he presented a morphologic and cytogenetic relapse, resistant to further pentostatin treatment. He died in May 1993.

Case #2
A 54-year-old male presented with B-PLL in October, 1992. Physical examination showed hepatosplenomegaly and laboratory tests showed wbc 96×10^9/L (lymphocytes 68%), Hb 8.3 g/dL, platelet 83×10^9/L. Bone marrow was infiltrated by 90% with prolymphocytic cells. The patient resulted resistant to conventional treatment (CNOP-Bleo), which was complicated by an herpes zoster infection. In November, 1992 he was started on pentostatin treatment. After 3 months the lymphocyte count decreased by 50% with no further need of RPBC and platelet transfusions. Prolymphocytic infiltration of bone marrow was 30%. After the 11th pentostatin course he presented high fever (Tc 40.5˚C), and the treatment was stopped. The patient underwent splenectomy (the histological study of the spleen demonstrated a diffuse prolymphocytic infiltration) followed by interferon therapy (3 MU every other day). The patient is presently alive in PR.

Case #3
A 59-year-old male with B-PLL, treated for 1 year with conventional chemotherapy (CHOP), came to our observation in October 1993. The patient presented severe splenomegaly, hepatomegaly and lymphoadenopathy. The wbc count was 360×10^9/L with 92% lymphoid cells. Treatment with pentostatin was started despite the low performance status (WHO 4).

We observed a slight and transient reduction of lymphocytosis but the patient died in progression of the disease after 18 days from the start of therapy.

Case #4
A 85-year-old female presented with B-PLL in July 1991. She was resistant to polychemotherapy (CNOP) and the treatment was complicated by an herpes zoster infection. The patient was splenectomized and α-interferon was administered (3 MU every other day), with partial response. The patient relapsed in February 1994 and was started on pentostatin treatment. After 6 courses the bone marrow prolymphocytic infiltration was lower than 15%. PR lasted 14 weeks. Fever complicated all pentostatin administrations (Tc max 39.5˚C). The patient refused further treatment after the 6th course and relapsed 3 months later. In August 1994 she died in disease progression.

Discussion
PLL is an agressive lymphoproliferative disorder characterized by poor response to conventional treatment. Other approaches, such as splenic irradiation, treatment with α-interferon or purine analogous have been attempted with poor results.1-6 Pentostatin is a fairly new drug, commonly used in the treatment of hairy cell leukemia.6-8 Its immunosuppressive effect is mediated by a reduction of T-lymphocytes, both helper and suppressor cells.2 Matutes et al. treated 31 T-PLL patients with pentostatin, obtaining 3 CR and 12 PR.1 In a recent EORTC study 20 PLL patients were treated with pentostatin: PR was achieved in 9 cases, being the B phenotype a favourable prognostic factor.9

We report 4 PLL cases treated with pentostatin as salvage therapy: CR was achieved in 1 case of T-PLL and PR in 2 cases of B-PLL. None of the patients presented renal, hepatic, cardiac or neurologic toxicity. Pentostatin administration was complicated in 2 cases by fever (WHO 3) and chills. Although immunosuppression has been reported as a common effect of pentostatin treatment we did not observe any opportunistic infections during or after the therapy.

CR could be achieved in 1 case only, nevertheless the treatment produced a delay in the progression of the disease, a reduction of supportive care requirements, and an overall increase of survival.
Our results suggest that pentostatin is a useful tool as second-line therapy of PLL, due to its low toxicity. Pentostatin used in monotherapy induced a low CR rate: we are evaluating combinations with other chemotherapeutic agents in order to increase the treatment efficiency and prolong the disease free survival of PLL patients.

References