**Introduction**

Hairy cell leukemia (HCL) is an indolent lymphoproliferative malignancy characterized by infiltration of the bone marrow, liver, spleen, and occasionally lymph nodes with neoplastic B cells with cytoplasmic hair-like projections. Diagnosis of HCL is historically based on the unique appearance of neoplastic lymphocytes (hairy cells), which are typically tartrate-resistant acid phosphatase (TRAP) stain-positive, and morphologic features of bone marrow and/or spleen. By the method of immunophenotyping, hairy cells express the pan B-cell antigens CD19, CD20 and CD22, as well as monoclonal surface immunoglobulin of IgG or multiple heavy chain isotypes. Characteristically, they also express CD11c, CD25 and CD103.

Splenectomy used to be the standard treatment option, leading to significant improvements in cytopenia, but only of limited duration. Recently, nucleoside analogs such as 2-chlorodeoxyadenosine (2-CDA or cladribine) and 2-deoxycoformycin (DCF or pentostatin) have been successfully used to treat patients with HCL. In Western countries, the overall response rate to cladribine ranged from 75% to 100% after a single course. However, to our knowledge, there are only 2 case reports about treatment results with cladribine.
in Taiwan. In this study, we describe the clinico-pathologic features of 5 HCL patients and the treatment outcome with combined splenectomy and cladribine.

**Methods**

**Patients**

Between December 1996 and June 2005, 33 patients who were diagnosed with malignant lymphoma and who underwent splenectomy were sampled. Five patients were identified with HCL based on clinical picture and pathologic features of bone marrow and spleen, including electronmicroscopic findings and immunophenotyping results (pan B-antigens and DBA44 in 2 patients). All patients were treated with splenectomy followed by cladribine. Cladribine was administered at a dosage of 0.1 mg/kg/day by continuous intravenous infusion for 7 days as described previously. Complete blood counts (CBCs) were reviewed monthly and tumor response was assessed according to the following criteria: complete response (CR) was defined as the disappearance of hairy cells from the peripheral blood and bone marrow, disappearance of lymph node enlargement and hepatomegaly, and normalization of the neutrophil count (≥ 1.5 × 10⁹/L), platelet count (≥ 100 × 10⁹/L) and hemoglobin level (≥ 12 g/dL). Partial response (PR) was defined as ≥ 50% decrease in hairy cells in the peripheral blood and bone marrow, ≥ 50% decrease in lymphadenopathy and hepatomegaly, and normalization of the neutrophil and platelet counts.

**Statistical analysis**

Because of the limited number of cases studied, only descriptive statistics are presented.

**Results**

**Clinical findings**

The clinical features of the 5 cases are summarized in Table 1. There were 3 men and 2 women, and the median age was 47 years (range, 27–77 years). All patients presented with splenomegaly, and the weight of the spleen ranged from 372 g to 5,000 g. None had peripheral lymphadenopathy except 1 who had retroperitoneal lymphadenopathy. Pancycopenia was noted in all 3 men. Leukocytosis, especially lymphocytosis, was noted in the 2 women.

**Pathologic findings**

As presented in Table 2, the typical neoplastic leukemic cells (hairy cells) in peripheral blood were identified in...
only cases 4 and 5 (the 2 women with lymphocytosis). Bone marrow examinations were done in all patients, but only 3 patients were diagnosed with HCL based solely on the bone marrow findings (Figure 1). In contrast, HCL was diagnosed in all spleen pathologic specimens. Immunophenotypic findings revealed that hairy cells possessed pan B-cell antigens (CD20 and/or CD22) in all cases, and DBA44 stain was positive in 2 cases (not available for the other 3 cases). A moderate degree of bone marrow fibrosis was noted in cases 1 and 3 but was not consistent with the degree of splenomegaly. No cytogenetic abnormality was identified; however, there were no metaphase cells in 1 case.

**Treatment**
As shown in Table 3, all patients underwent splenectomy either at the time of diagnosis or immediately after diagnosis (median time from diagnosis to splenectomy was 2 days; range, 0–49 days), with no major complications noted. Due to reasons related to national insurance coverage and the complex process of license approval of cladribine by the National Department of Health, cladribine was administered after splenectomy at a median time of 2 months from diagnosis (range, 0.5–5 months). There were no significant acute or chronic side effects except for 1 episode of grade 4 neutropenia. Figure 2 shows the changes in white blood cell and platelet counts of these patients. Four patients achieved CR at a median time of 2 months (range, 2–6 months), and 1 patient achieved PR at 4 months, but she returned to Vietnam and was thus lost to follow-up. Tracing her CBC data with correspondence, we found that it had normalized 1 year after treatment. After a median follow-up of 29 months (range, 4–96 months), all patients were alive without severe infection or secondary malignancy.

**Discussion**
HCL appears to be a very uncommon disease in Taiwan. Although there is no central registry for HCL in Taiwan, the incidence of HCL in Hong Kong Chinese was roughly estimated to be 0.35 cases per 1,000,000 persons per year. This is much lower than the 0.2 per 100,000 persons per year reported in Western series. Because of the rarity and unavailability of cladribine in Taiwan until 1997, the treatment outcome of HCL in Taiwan was seldom reported. The present study, despite being only of 5 cases, is the

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**Table 2.** Pathologic features of the 5 patients with hairy cell leukemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Peripheral hairy cells</th>
<th>TRAP stain*</th>
<th>DBA44 stain †</th>
<th>CD20 †</th>
<th>Bone marrow fibrosis</th>
<th>Cytogenetics* ‡</th>
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<td>1</td>
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<td>Negative</td>
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<td>Positive</td>
<td>No</td>
<td>46,XY</td>
</tr>
<tr>
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<td>Negative</td>
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<td>Positive</td>
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<tr>
<td>5</td>
<td>Yes</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>No</td>
<td>No metaphase cells</td>
</tr>
</tbody>
</table>

*Of peripheral blood hairy cells; †results of immunophenotyping from spleen specimens; ‡bone marrow specimens were used for cytogenetic analysis. TRAP = tartrate-resistant acid phosphatase; ND = not done.
first and largest series concerning the treatment outcome of this rare disease in Taiwan.

Generally, the clinicopathologic features of HCL in Taiwanese patients are similar to that in Western countries. Of note, we found that the pathologic features of the spleen were more characteristic and enabled the diagnosis of HCL. In the spleen, hairy cell infiltrates localize to the red pulp, and the white pulp is typically atrophic. The cells infiltrate the red pulp cords extensively and exhibit widely spaced nuclei and variable nuclear indentations. Probably because of the clear contrast and extensive involvement, diagnosis of HCL from spleen is much easier than from bone marrow, in which limited specimen and occasional hypocellularity may confound the diagnosis. In our study, the diagnosis of HCL could not be made by bone marrow findings only in 2 patients. Limited specimen with hypocellularity was the reason in 1 patient, and atypical features of hairy cells in bone marrow accounted for the other. This diagnostic viewpoint has never been paid much attention; however, it may have value in diagnosis since specific markers such as CD25 or CD103 are not routinely available in pathology laboratories. Furthermore, the morbidity and mortality of splenectomy was not high due to advances in surgical technique. There were no significant complications in any of our cases, and cytopenia, especially thrombocytopenia, recovered well in most of them before cladribine therapy. Although in the era of purine analogs, which are highly effective in HCL treatment, splenectomy is not routinely necessary, splenectomy is not only 1 part of the treatment but is conducive to the diagnosis in our study as described above and could be considered in some specific circumstances.

Two purine analogs are currently available to treat HCL. Pentostatin is the first one reported to be highly...
Splenectomy and cladribine for hairy cell leukemia

effective in HCL, with the CR rate ranging from 82% to 87%, and 5-year and 10-year overall survivals of about 90% and 80%, respectively. Cladribine also exerts a dramatic response in HCL with a single treatment course. Recently, a long-term follow-up report by Chadha et al showed that overall response was 98%, and 79% of patients who achieved CR had an overall survival of 87% after 12 years. Because of their effectiveness and safety, purine analogs have replaced other treatment modalities to become first-line therapy for HCL. Yang and Ho reported the first case of HCL treated with splenectomy and cladribine in 2001. Long-term remission was achieved by splenectomy and a single 7-day course of cladribine in a 48-year-old man without significant adverse effects. Chen et al presented another 2 cases, treated with cladribine but not combined with splenectomy, who experienced rapid (within 4–6 weeks) and durable remission. In our study, excellent treatment outcome by cladribine was also observed. Four of 5 (80%) patients achieved CR within 2–6 months without significant adverse effects. Case 4 initially presented with marked leukocytosis and appeared to have suboptimal response to cladribine. After obtaining CBC data from correspondence, late CR seemed to be achieved, although we could not get her bone marrow or other data. In spite of typical morphologic features and positive TRAP stain, HCL variant should be suspected in this case. The rate of secondary malignancy has been reported to be as high as 17% in Western series, but none was noted in our patients (who had a shorter follow-up duration).

In summary, the clinicopathologic features of Taiwanese patients with HCL in our study did not appear to differ from that of patients in Western series. Splenectomy is safe and effective in ameliorating cytopenia and has great contribution to diagnosis. Similar to the Western experience, cladribine produces an excellent treatment outcome with acceptable side effects and should be considered as first-line treatment for HCL patients in Taiwan.

Acknowledgments

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References