Prolymphocytic leukemia (PL) has been distinguished from classical chronic lymphocytic leukemia (CLL) on the basis of its clinical presentation, cytologic morphologic presentation, and therapeutic unresponsiveness. This uncommon disease typically presents in an elderly male with the subacute onset of massive splenomegaly in the absence of significant lymphadenopathy. A marked lymphocytosis, frequently greater than $2 \times 10^5/mm^3$, is characteristic. The majority of these lymphocytes are large with a prominent single nucleolus (Fig. 1). Stained smears and electron micrographs demonstrate consistent differences between these cells and those of both classical CLL and lymphosarcoma cell leukemia. In most cases, these prolymphocytes have B-cell markers. Varying degrees of anemia and/or thrombocytopenia are present. The clinical course of patients with PL has been generally brief; infection and bleeding are the major complications.

This report describes the results of systematic treatment approaches to PL. The relative value of various types of chemotherapy, splenic irradiation, and splenectomy are discussed.

**Patients**

Five patients were determined to have PL on the basis of clinical presentation and cellular morphology. The clinical characteristics are described in Table 1. The mean age of the three men and two women was 66 years. All had massive splenomegaly in the absence of lymphadenopathy. All had blood and bone marrow smears demonstrating the typical morphology of PL. In four patients, the initial leukocyte count was greater than $1 \times 10^5/mm^3$. Anemia and thrombocytopenia were present in all but one patient. Surface markers studies were available on Patients 1, 2, and 4. All demonstrated surface immunoglobulin on fluorescence staining, indicating B-cell lineage of the prolymphocytes. The intensity of the fluorescence was graded in patients 2 and 4. In both of these cases, the staining was heavy, more characteristic of malignant lymphoma than CLL.

**Treatment**

Five types of treatment were given. Initial therapy in four patients was vincristine (1.2 mg/m$^2$ IV [intravenously] weekly) and prednisone (40 mg/m$^2$ orally daily) for two weeks. If this proved unsuccessful, treatment was changed to either chlorambucil (40 mg/m$^2$ orally day 1, with escalation as tolerated) and prednisone (40 mg/m$^2$ orally days 1–7) repeated every three weeks or splenic irradiation (50 rad daily, maximum of 2200 rad). Patients whose general medical condition permitted underwent splenectomy. Finally, various other types of chemotherapy were used in refractory patients: daily cyclophosphamide, 100 mg/m$^2$ orally (Patient 1); monthly cyclophosphamide, 1000 mg/m$^2$ IV, with prednisone, 40 mg/m$^2$ orally each day for 7
days (Patients 2, 3, and 4); and monthly Adriamycin (doxorubicin), 40 mg/m² IV with (Patient 2) and without (Patient 3) leukopheresis.

Response was defined as an improvement in splenomegaly, leukocytosis, anemia, or thrombocytopenia, as described in Table 2, lasting at least four weeks.

Results

The results are summarized in Table 2. No patient responded even briefly to vincristine and prednisone. Chlorambucil/prednisone produced responses in two patients: Patient 2 had a reduction in the leukocyte count and splenomegaly, as did Patient 4, who also had a rise in hemoglobin and platelet count. The duration of these responses was 12 and 14 months, respectively. Splenic irradiation produced responses in all four patients who received it. All had a significant improvement in splenomegaly, three had a diminution of the leukocyte count, and one had a rise in hemoglobin. However, only Patient 5 had a prolonged response (14 months); the remainder relapsed within three months. Splenectomy was performed on two patients. Patient 2 had an excellent result: Hemoglobin and platelet count returned to normal, and the total leukocyte count remained less than 20,000/mm³. Despite the persistence of prolymphocytes in the peripheral blood, the patient remained entirely asymptomatic off all therapy for 23

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- : no significant lymphadenopathy; +: spleen tip at least 8 cm below costal margin; ++: spleen tip at least 16 cm below costal margin.
months. Subsequently, relapse occurred with marked leukocytosis unresponsive to doxorubicin and leukopheresis. Patient 5 died of progressive disease five months after splenectomy. Patients 1 and 3 were unacceptable surgical risks for splenectomy, and Patient 4 refused the procedure. None of the patients responded to the other chemotherapy regimens. The median survival of all patients was 33 months.

**Discussion**

A number of modalities have been used to treat PL. This series demonstrates that the vincristine/prednisone combination is not effective. This is consistent with the experience in other B-cell neoplasms such as classical CLL and plasma cell dyscrasias. Alkylating agents and splenic irradiation have been noted by others to produce only brief responses at best.\(^1\)\(^-\)\(^3\) In contrast, this study did find that both chlorambucil/prednisone and splenic irradiation can ameliorate splenomegaly and improve the blood counts in some patients. Although the remissions are incomplete and of variable duration, these modalities may be of value.

Splenectomy has been performed for the treatment of PL. Galton et al.\(^1\) treated one patient with splenectomy. Although the leukocyte count did not change, the patient subjectively improved. Catovsky et al.\(^3\) described three cases treated with the combination of splenectomy and leukopheresis. All had a reduction in the leukocyte count and clinical improvement. However, Bearman et al.\(^2\) noted no significant response to splenectomy alone in several patients with PL. In the current series, the longest and most complete response occurred after splenectomy. Although prolymphocytes persisted in both the blood and bone marrow, there was no evidence of disease progression for nearly two years. Galton et al.\(^1\) have suggested that the spleen may be the major site of lymphocyte production in PL. If so, its removal might substantially reduce tumor burden, permitting an extended period of clinical and hematologic improvement.

Several groups have noted benefit from regimens containing doxorubicin. One complete\(^5\) and two partial remissions to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) have been reported. Neither of the two patients receiving single agent doxorubicin in this study responded. The complete CHOP regimen was not evaluated.

The survival of patients with PL has generally been considered brief. Galton et al.\(^1\) originally described a median survival of 17 weeks. In this study, in agreement with Bearman et al.,\(^2\) the median survival was more than twice as long. Whether this difference may reflect more effective treatment, better supportive care, or patient selection is unknown.

The optimal therapy for PL remains unknown. The present series indicates that chlorambucil/prednisone and splenic irradiation are of benefit in some patients. In refractory cases, splenectomy may provide a prolonged response without the need for additional chemotherapy. Further study of the role of splenectomy in PL is recommended.

**REFERENCES**