The Significance of Splenomegaly in 101 Adults With Acute Lymphoblastic Leukemia (ALL) at Presentation and During Remission

By Alan Friedman, Peter Schauer, Roland Mertelsmann, Constance Cirrincione, Howard Thaler, Peggy Dufour, Stephen B. Ellis, Hal Teitelbaum, Sanford Kempin, Timothy S. Gee, Zalmen Arlin, and Bayard Clarkson

Splenomegaly is a common manifestation of ALL. An enlarged spleen at presentation appears to reflect an increased tumor burden and has been shown to be an adverse prognostic feature in children with ALL.1 The presence of splenomegaly in patients who have achieved a complete hematologic remission can be a difficult clinical problem, with the possibility of relapse being an important consideration in the differential diagnosis. A recent report has shown that splenomegaly in children in remission may not be due to leukemic infiltration and furthermore has suggested that the spleen is a source of a protective host response against the leukemia that may predispose children having splenectomy to relapse.2 In view of these studies in children demonstrating the prognostic significance of an enlarged spleen both at diagnosis and during remission, we have examined the incidence and prognostic significance of splenomegaly in 101 adults with ALL at diagnosis and during remission and the effects of splenectomy on survival.

MATERIALS AND METHODS

One-hundred-one previously untreated or minimally pretreated adults (<15 yr) with ALL were treated at Memorial Sloan-Kettering Cancer Center between 1968 and 1979 according to the L2 (29 patients), L10 (34 patients) or L10M (38 patients) protocols. All protocols contained induction regimens consisting of prednisone, vincristine, and an anthracycline. In addition, selected patients with large tumor burdens from all three protocols received cyclophosphamide as part of their induction therapy. Different multidrug regimens were employed for consolidation and maintenance. All patients received CNS prophylaxis with intrathecal methotrexate. Details of these protocols have been published.3,4 Fifty-nine patients were male and 42 female whose ages ranged from 15 to 78 yr with a mean of 29.1. There were no differences in age or sex distribution across protocols. The clinical charts of all patients were reviewed for the presence of splenomegaly at any time during the course of disease.

The Kaplan-Meier product limit method was used for survival time and remission duration curves. Survival was measured from the date of diagnosis to the date of death or last follow-up (May 1, 1980). Three patients who began treatment on one protocol but received maintenance therapy on different protocols were considered censored observations with respect to the initial protocol on which they were treated. Patients who died in complete remission (CR) were treated statistically as disease-related deaths. Remission duration was calculated from the date of complete remission to the date of relapse or last follow-up. For comparison of survival patterns and remission duration of two or more groups, the log rank procedure was applied. Categorical data were examined by the chi-square procedure. Continuous data were analyzed using the t test for independent subjects. Significance was evaluated using the logarithmic transformation of WBC and square root transformation of platelets. All p-values refer to two-sided tests.

RESULTS

The clinical features of all patients at presentation are summarized in Table 1. Splenomegaly, defined as a clinically palpable spleen, was present at initiation of chemotherapy in 48% of patients (48/101). In only 7 patients was the spleen massively enlarged (>5 cm below the costal margin). Hemoglobin, white blood cell, and platelet counts were not significantly different between patients with normal and palpable spleens. The complete remission (CR) rate did not
differ significantly between patients with or without splenomegaly, with 40 of 48 patients (83%) with splenomegaly and 44 of 53 patients (83%) without a palpable spleen achieving CR. Although the median survival time for patients with splenomegaly was 32.4 mo and 48.0 mo for patients with clinically normal spleens, the overall survival patterns for the two groups were not significantly different (p = 0.42; see Fig. 1). Similarly, there was no statistically significant difference in remission duration distributions between patients with normal spleens and those with palpable spleens (p = 0.43; see Fig. 2), although the median length of remission for patients with splenomegaly (29.5 mo) was somewhat shorter than that for patients with normal spleens (45.0 mo).

Of 38 patients who have relapsed, 4 (11%) manifested splenomegaly at the time of hematologic relapse. In one patient this was the first clinical sign of relapse, but in all cases relapse was promptly confirmed by examination of the bone marrow. Six additional patients had splenomegaly persist (4 patients) or reappear (2 patients) during complete hematologic remission. In these patients, careful evaluation of bone marrow aspirates and biopsies, CSF examination, and marker studies failed to produce evidence of relapse. One patient has been followed closely and 5 have had splenectomies. Table 2 lists the pertinent clinical characteristics, results of splenectomy, and subsequent course of these patients. There was no evidence of leukemia found on pathologic examination in any of the resected spleens. All 5 patients who had splenectomies have remained in complete hematologic remission for 20–63 mo after splenectomy. One of these patients had an isolated CNS relapse 18 mo after splenectomy but is currently in a second complete remission for 9 mo. Three patients have had therapy discontinued and have been in an unmaintained complete remission from 8 to 42 mo. One patient with persistent splenomegaly who did not have a splenectomy remains in a continuous first complete remission for 69 mo. She has been off all therapy for 26 mo.

DISCUSSION

Our experience with splenomegaly in adults is in contrast to that reported for children with ALL. In children with ALL, splenomegaly is a common finding occurring in as many of 69% of patients at diagnosis. Approximately 29% of children with ALL have massive splenic enlargement (>5 cm). An enlarged spleen, particularly if massive, is an adverse prognostic
feature in childhood ALL and is thought to be due to infiltration with leukemic cells and to reflect increased tumor burden. In contrast, in this study, splenomegaly was present in 48% of adults at diagnosis, and only 7% of patients had massive splenomegaly. The ability to achieve a CR was not influenced by the presence of splenomegaly, and no statistically significant difference in remission duration or survival was observed between patients with and without splenomegaly.

A recent report concerning persistent splenomegaly in children with ALL during complete remission suggests that the mechanism of splenomegaly and its prognostic significance may be different at presentation and during remission. Manoharan et al. have reported five cases of splenomegaly occurring in children in remission of ALL. Splenectomy performed in three of these patients failed to reveal any evidence of leukemia, although all three patients have subsequently relapsed and died. The remaining two patients who did not have their spleens removed continued in complete remission 2 and 6 yr after the splenomegaly was first noted. This, together with experimental data reported by others, was interpreted to indicate that the spleen was an important factor in an as yet undefined immunologic response to the leukemic cells and that its removal could be detrimental to the patient.

In this series, 10 of 84 (12%) patients who achieved CR had persistence, appearance, or reappearance of splenomegaly during maintenance therapy. In 4 patients concurrent relapse was easily diagnosed by bone marrow aspiration. In contrast, 6 patients had no evidence of recurrent leukemia after careful clinical evaluation. Splenectomies performed in 5 of these patients failed to reveal relapse or any other specific etiology for the splenomegaly. One of these patients (patient 4, Table 2) is particularly interesting and has been previously reported. This patient with T-cell ALL was discovered to have an antibody to autologous leukemia cells in his serum during remission. After splenectomy, this antibody became undetectable, suggesting that the spleen had been its source. This patient has remained in continuous complete remission for a total of 50 mo, including 41 mo since splenectomy, and has been off all therapy for 18 mo. The durability of his remission despite disappearance of this antibody to his own leukemia may indicate that this antibody was not protective, or alternatively, that the optimal antileukemic effect of the antibody may have been exerted during the 8 mo of remission with splenomegaly prior to splenectomy. All other patients with splenomegaly during remission have remained in complete hematologic remission, although one patient has had an isolated CNS relapse. Analysis of the sera of two additional patients (patients 2 and 5, Table 2) failed to demonstrate a similar antibody against autologous leukemia cells prior to or after splenectomy (data not shown).

In our experience with the L2, L10, and L10M protocols, the presence of splenomegaly in adults with ALL at presentation is of no major prognostic significance. Splenomegaly during remission is not itself an indication for splenectomy. Although the spleen may be a source of an immunologic response to the leukemia in adults, splenectomy has not been detrimental in our patient population and is not inadvisable if other indications exist.

REFERENCES

3. Gee T, Haggbin M, Dowling M, Cunningham A, Middleman


The significance of splenomegaly in 101 adults with acute lymphoblastic leukemia (ALL) at presentation and during remission

A Friedman, P Schauer, R Mertelsmann, C Cirrincione, H Thaler, P Dufour, SB Ellis, H Teitelbaum, S Kempin, TS Gee, Z Arlin and B Clarkson