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The survival curve for the 27 patients who received melphalan alone for induction and maintenance therapy is shown in Fig. I. This curve includes the 14 patients known to have died of the disease, the 11 who were well, and the 2 who died of unrelated or unknown causes, as detailed above. The median survival was 286 mo.

DISCUSSION

A variety of therapeutic measures, including splenic or whole body irradiation, 32P, or chemotherapy have been used to modify favorably the progression of CGL. The clinical results have been gratifying in that painfully enlarged spleens shrink, dangerously high white cell counts fall, and symptoms abate. With busulfan therapy, for example, the white count predictably falls to the normal range and the spleen usually decreases in size to below the limits of palpation in two-thirds to three-quarters of the patients. For the melphalan-treated patients in this series, very similar initial responses were obtained. The white cell count decreased to normal for all the patients; for 21 of the 24 patients with enlargement of the spleen, the spleen size was reduced below the limits of palpation. During this period symptoms decreased and all but six patients felt completely well.

Despite careful control of the disease, the illness eventually becomes more difficult and eventually impossible to control with available treatments. The time from diagnosis to this exacerbation or transformation is variable; 34 and 24 mo were found for busulfan and dibromomannitol, respectively, in a recent series, with no statistically significant difference. Similarly, for the melphalan-treated group reported in this paper the median duration of disease control was 25.3 mo. Regardless of the therapy, death usually occurs within months of this disease progression.

Survival may be enhanced by therapy directed against the disease during its early stages. It is clear from one prospective, randomized study that patients treated with busulfan survive longer than those treated with splenic radiation. However, it is not clear that busulfan, among several other chemotherapeutic agents, is associated with the longest survival. There is considerable variation, ranging from 1 to 4 yr, in the median survival times reported for the busulfan-treated groups. The survival times obtained from two independent series of patients treated with hydroxyurea, and now for melphalan, also fall within this range.

The clinical trials with busulfan began in 1953: since then some of its associated unique side effects have emerged. The most hazardous problem, pulmonary fibrosis, may present itself as a preterminal and irreversible problem of refractory pulmonary insufficiency. The illness is not found in CGL patients treated with other modalities, seems related to the total dose of busulfan, and was not found in a group of patients treated for a short period of time. Its frequency is low; possibly less than 1 in 50 patients develops the clinical syndrome of pulmonary insufficiency. Cellular atypia, however, may be present in 30%-50% of autopsied cases. The other severe, and fortunately even less frequent, toxicity is the wasting syndrome. For both of these complications, the prudent course is to eliminate busulfan from the therapy. However,