Treatment of Chronic Granulocytic Leukemia With Melphalan

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Thirty-three patients with newly diagnosed chronic granulocytic leukemia (CGL) were treated with melphalan between 1968 and 1976. Within 3 mo of beginning therapy subjective and objective disease parameters improved. Disease control was easily maintained with this agent until hematologic exacerbation occurred. The median duration of disease control was 25.3 mo, and the median duration of survival was 28.6 mo. Serious side effects were not produced. Thus melphalan appears to be another agent that may be used to control the manifestations of CGL prior to hematologic exacerbation.

MELPHALAN is often used for treating a variety of malignancies,[1-5] including multiple myeloma,[1] polycythemia vera,[2] and carcinoma of the breast.[5] During the treatment of these disorders, myelosuppression is the rule. Yet there is only one case report in the literature suggesting that this agent might be useful in the management of chronic granulocytic leukemia (CGL).[6] However, in the early 1960s Rundles et al.[7] introduced this drug for management of patients with CGL, and it has found continued use for this purpose at Duke Medical Center. This report reviews this experience from 1968 through 1976.

MATERIALS AND METHODS

Records of all patients with CGL who were initially treated with melphalan alone and diagnosed at Duke Hospital in the period 1968 1976 were reviewed. The first patient entered into this series was started on treatment January 15, 1968, and the last April 2, 1976; the observation period extended through February 26, 1977. Appropriate informed consent was obtained for all patients.

The illness was characterized by a careful evaluation of the symptoms, including the Karnovsky performance status and objective signs, spleen size, peripheral blood counts, and percentage of blast cells. During treatment with melphalan these features were repeatedly determined and other relevant clinical measurements carefully recorded. The clinical response in these measurements obtained within the first 3 mo of therapy was evaluated for each patient.

Treatment was initiated with melphalan tablets in a daily dose of 4-12 mg, depending upon the level of the white cell count. The induction dose was continued for 5-7 days and then gradually reduced to a maintenance dose according to the hematologic response. Most patients required 2-4 mg/day, and one required only 2 mg three times each week. If the white cell count fell below 5000×10^6/cu mm treatment was withheld until the count again became normal or increased. Allopurinol was usually given during the induction period and again during the period of exacerbation but generally was not used during the phase of the disease that required very little chemotherapy for control.

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Melphalan was continued until the disease could no longer be controlled with this agent. This endpoint was termed an exacerbation of the disease, and its description was reviewed and characterized by the symptoms, blood counts, differential count, bone marrow, lymph node enlargement, and spleen size. The term "blastic transformation" was reserved for that stage at which there were more than 10% blasts in the peripheral blood.

Side effects such as skin rash, allergies, nausea, lung disease, renal disease, and myelosuppression were recorded, as were other medical problems, including those that might be complications of chemotherapy.

The curve representing nonparametric estimates of survival was obtained using the Kaplan-Meier method.[8] The median reported was the time point at which the curve intersected the line representing 50% survival. "Censored" survival values refer to values for patients who were still alive at the time of last followup. Where the longest survival value is a censored one, the curve is divided into two parts, representing the upper and lower bounds on survival estimates beyond the last death.

Patients

Of 94 patients whose charts were reviewed, 33 were found to have CGL and were treated with melphalan alone. The broadest definition of CGL was applied when a patient had an unexplained leukocytosis of greater than 30,000 cu mm with a gradient of myeloid immaturity in the peripheral blood. Other supporting features were usually present, as described below. The mean age for the group was 53 yr (range 14–80); 19 were male, 14 females; 13 were black, 20 white. Symptoms were present in 78% of the patients. Twenty-two percent were asymptomatic, and the illness was discovered incidentally during a medical (e.g., insurance physical) or surgical (e.g., transurethral resection) screening examination. The most common symptom was fatigue; the next most common was splenic discomfort. The remaining symptoms included priapism, bruising, arthralgias, fever, or dizziness; these were rare.

Supportive objective features were noted. The white cell count was greater than 30,000/cu mm for all, and for 12 it was between 200,000 and 1,135,000/cu mm. The spleen was enlarged in 24 patients; in 17 of these it was more than 3 cm below the left costal margin. The peripheral blasts count was greater than 10% for 3 patients and 2%–10% for 13 patients. The Philadelphia chromosome was determined for 25 patients; it was present in 24. (The test was either not done or the laboratory received an inadequate sample for the remaining 8 patients.) In this retrospective study, the reasons for not doing the evaluation were not always clear, but many times it was not done in an elderly patient. Anemia was defined as present if the hemoglobin was less than 12 gm/dl for women or 14 gm/dl for men, and was present in 22 patients. The platelet count was less than 150,000/cu mm in two patients and greater than 600,000/cu mm in seven. Nine patients were without splenomegaly; six had the Philadelphia chromosome and the remaining three had presenting granulocyte counts greater than 100,000/cu mm.

RESULTS

Treatment, First 3 mo

Thirty-three patients received melphalan alone as initial therapy. Of the 26 symptomatic patients, 25 were subjectively improved. One patient with idiopathic congestive heart failure continued to experience fatigue despite correction of anemia. All but five patients became entirely asymptomatic.

The white cell count on all 33 patients was easily reduced to less than 15,000/cu mm, usually within 3 wk of therapy and invariably within 3 mo. The spleen usually decreased in size. This response was slower than the white cell count response but was completed within 3 mo. The spleen decreased below the level of palpation in 21 of the 24 patients with a palpable spleen. The 3 remaining patients each had a very large spleen, palpable 3 cm or more below the left costal margin: in 2, there was no reduction in splenic size despite complete correction of the granulocyte count, and in one there was a partial response; all 3 of these patients had Philadelphia chromosomes detected.

Following treatment the hemoglobin level was reviewed at least 1 mo subsequent to the last transfusion. For 13 patients, there was either complete correction of the anemia or an improvement by >1 g/dl. In 6 there was no change in the level of anemia, and in 3 the anemia became worse, with a decrease in the hemoglobin by >1 g/dl. One nonanemic patient developed mild anemia during treatment.

Few problems in clinical management were encountered during the early phase of the illness. Two patients developed transient leukopenia within the first month (total white cell count <2000/cu mm for each) and one developed fever. For both, treatment with melphalan was later resumed, and both lived more than 22 mo thereafter. One of the patients developed thrombocytopenia during the initial clinical response. Only 5 of the 33 patients experienced nausea during the first week of treatment. One patient experienced a pruritic, macular skin rash while taking allopurinol and melphalan, and this subsided when both drugs were stopped. He had a beneficial clinical response to melphalan but was subsequently treated with hydroxyurea.

Treatment, Chronic Phase

Following the initial response, maintenance therapy with other chemotherapeautic compounds was used in six patients. For four, this was in accordance with other pilot studies testing the effect of intensive consolidation treatment and was administered after 4–21 mo of therapy with melphalan. For one, busulfan was substituted at another institution after 19 mo of treatment with melphalan. A sixth patient developed a skin rash while receiving both allopurinol and melphalan; these were stopped and treatment was continued with hydroxyurea. As of this writing three of these six patients have lived for more than 34 mo; three have been followed for less than 16 mo. These six patients were not included in expressing the melphalan survival data.

The remaining 27 patients were maintained on melphalan alone. The dose of drug was usually titrated to keep the white cell count controlled, 5,000–20,000/cu mm; this usually required doses ranging from 2 mg on alternate days to 4 mg/day. Although maintenance therapy was sometimes withheld for from 1–3 mo, planned prolonged remissions of greater than 3 mo without drug therapy were not observed.

No complications developed during this period of disease control that might be directly attributed to the therapy, but three untoward events did occur. After 1½ yr of the disease, a nonthrombocytopenic patient developed an oozing, duodenal ulcer. This ulcer subsequently healed, and the patient was treated for an additional 37 mo with melphalan. One patient experienced transient pulmonary infiltrates and fever, unassociated with leukopenia. This complication resolved without difficulty, and melphalan was continued for 18 mo more. One patient felt well enough to stop his own therapy after 6 mo of treatment. Eventually his white cell count increased to 146,000/cu mm, his massively enlarged spleen ruptured spontaneously, and he required an emergency splenectomy. His illness was controlled for another year with melphalan alone. None of the remaining patients developed hyperpigmentation, skin disorders, pulmonary disease, or weight loss and cachexia. Nausea was not encountered with maintenance doses of the drug.

Eight patients were still clinically well when last observed, either at Duke or while under the care of their personal physician. One, treated for 31 mo with melphalan, then moved to another state where treatment was changed to busulfan, possibly because of mild thrombocytopenia; her present clinical status is unclear, although she was still alive at 48 mo. She was censored from study at 31 mo. For seven patients most recent observation was in the last 9 mo of the study.

Two patients died of nonhematologic disease during the chronic period; one, a 14-yr-old girl who committed suicide, was removed from further study on the date of her death. The other died of unknown causes and was removed from the study on the date of his last clinic visit, when he was in hematologic remission.

Disease Exacerbation and Survival

Of the 27 patients receiving the melphalan maintenance program, 17 eventually developed terminal exacerbation that the clinician felt could no longer be controlled with this agent. For these 27 patients the median time from diagnosis to this exacerbation was 25.3 mo.

The nature of the exacerbation for each patient was carefully defined from the record. For 14 of the 17 patients, symptoms were present (fever, 5; fatigue, 5; splenic discomfort, 2; bone pain, 1; sinusitis, 1). The platelet count was less than 50,000/cu mm for 2 patients. The spleen progressively increased in size in 13 of the 17. The blast count was elevated for 14; for 3 patients the peripheral blast count was less than 1000/cu mm. One of these three, a 23-yr-old male, developed massive enlargement of the liver, spleen, and lymph nodes, fever, and a pleural effusion. A second was a 72-yr-old female with thrombocytopenia and an enlarging spleen. The third, a 22-yr-old male, developed progressive eosinophilia to 40% while receiving melphalan after 3 yr of disease control. The drug was stopped and 5 mo later the blood and bone marrow blast counts had increased.

Of the 17 patients who entered this exacerbation, 14 had died and 3 were still living at this writing. Of these 17 patients, 15 received systemic chemotherapy including combinations of cytosine arabinoside, thioguanine, vincristine, prednisone, 6-mercaptopurine, or azacytidine. Two patients were not treated with other agents, the 72-yr-old female with thrombocytopenia described above and an 85-yr-old female with a white cell count of 150,000/cu mm with 70% blasts.

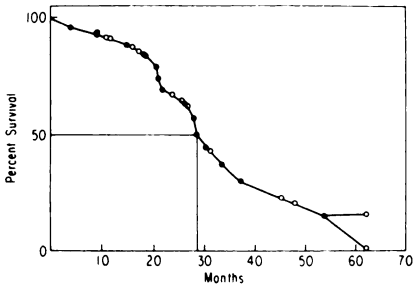

Fig. 1. Survival curve for 27 CGL patients from onset of treatment with melphalan. •, Deceased patients; ○, censored patients.

The survival curve for the 27 patients who received melphalan alone for induction and maintenance therapy is shown in Fig. 1. 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 28.6 mo.

DISCUSSION

A variety of therapeutic measures, including splenic or whole body irradiation, ^{32}P, 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.[9,10] 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.[10] 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.[9] 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.[11] The survival times obtained from two independent series of patients treated with hydroxyurea,[12,13] and now for melphalan, also fit 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.[14-16] 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.[17] Its frequency is low; possibly less than 1 in 50 patients develops the clinical syndrome of pulmonary insufficiency.[9] Cellular atypia, however, may be present in 30%–50% of autopsied cases.[10,16] The other severe, and fortunately even less frequent, toxicity is the wasting syndrome.[18] For both of these complications, the prudent course is to eliminate busulfan from the therapy. However,

dibromomannitol, for example, may not represent a useful second-line agent, since pulmonary fibrosis and cytologic dysplasia have been associated with its use.

Melphalan has found clinical use in the treatment of other neoplasms;[1-5] the median duration of therapy in these conditions ranged from 1 to 2 yr. Although a large number of patients have received melphalan for even longer periods, the complications of pulmonary fibrosis and a wasting syndrome have yet to be reported in other clinical situations. In this report of melphalan-treated CGL patients, the median duration of observation was 29 mo, and neither of these complications was seen. In addition, hyperpigmentation, a more common but less bothersome side effect associated with busulfan, was not observed.

This melphalan series included two patients with pancytopenia, predominantly marked by leukopenia. This effect was not associated with infections or bleeding complications and did not require platelet support, in contrast to the prolonged episodes of pancytopenia, lasting several weeks, for busulfan as illustrated by isolated cases.[9,19] The melphalan-treated patients who developed cytopenias were subsequently easily managed with reduced drug doses without developing another episode of marrow toxicity.

The beneficial clinical response obtained with melphalan is very predictable and consistently excellent. The clinical illness can be controlled for 2–3 yr. The severe busulfan-induced morbid side effects of pulmonary fibrosis, wasting, and prolonged cytopenia have not been seen with melphalan, it would seem to be a useful agent in the management of CGL. On the other hand, none of the currently available chemotherapeutic agents now used to treat this disease, including melphalan, appears to be effective in preventing hematologic exacerbation.

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