Dibromomannitol in the Treatment of Chronic Granulocytic Leukemia: A Prospective Randomized Comparison With Busulfan

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Dibromomannitol (DBM) is a new agent for the treatment of chronic granulocytic leukemia. A prospective evaluation of the drug was undertaken in a randomized comparison with busulfan. Forty previously untreated, Philadelphia chromosome-positive cases were treated, with 20 patients in each treatment group. The protocol provided for continuous maintenance therapy after remission induction, with a crossover to the opposite drug in patients who became refractory to the primary agent but are without evidence of blastic transformation. There were 14 remissions in the DBM group and 15 in those treated with busulfan. The rate of decrease of the elevated leukocyte count was more rapid with DBM, but prolonged disease control off treatment occurred in only three of 14 cases as opposed to nine of fifteen busulfan-treated patients who required a median delay of 12 mo before maintenance could be initiated. Hypoplasia occurred in one DBM patient and two busulfan cases. Following recovery, crossover to the opposite drug in two cases again resulted in hypoplasia. Increased skin pigmentation, amenorrhea, pulmonary fibrosis, and cytologic dysplasia, commonly associated with busulfan administration, were also noted with DBM. The median duration of disease control with busulfan was 34 mo and 26 mo with DBM. There was no significant difference in the incidence of blastic transformation, and median survival for both groups was 44 mo. DBM appears to be as effective as busulfan in the treatment of the chronic phase of CGL but with a more predictable myelosuppressive action. The principal advantage of busulfan over DBM is the fact that more than half the busulfan-treated patients experienced prolonged disease control off treatment.

Dibromomannitol (DBM) is a brominated sugar alcohol with cytotoxic activity against a variety of experimental animal tumors. Although the mechanism of action is not completely known, some in vitro experimental evidence suggests that it behaves like an alkylating agent. Because of the demonstrated suppressive effect of this agent on myelopoiesis, initial clinical trials included patients with myeloproliferative diseases. The drug, which could be administered orally, was reported to be effective in inducing hematologic remissions in chronic granulocytic leukemia (CGL). Although the initial investigations demonstrated a response rate approaching 70%-80%, it was not apparent whether this drug could serve as a practical alternative to busulfan, or whether it could control CGL refractory to busulfan, and thus improve the survival of patients with CGL. Certain side-effects of busulfan such as bone marrow aplasia, cataracts, amenorrhea, rarely pulmonary fibrosis, and dysplastic cytologic abnormalities of
squamous and urothelial cells make a search for alternative therapies appropriate.\textsuperscript{4, 6}

The present report is the result of a prospective randomized trial in which DBM was compared to busulfan in previously untreated CGL patients. The trial was begun in July 1967 and ended June 1973 so that 7 yr follow-up information on the comparative effects of these drugs is now available.

MATERIALS AND METHODS

Patients with previously untreated, Philadelphia chromosome-positive CGL were randomized by the closed-envelope technique to receive either dibromomannitol or busulfan (Myleran) for attempted remission induction of the chronic phase of CGL. The dose of DBM was 250 mg/sq m by mouth daily for the first 3 days followed by reduction of the dose to 150 mg/sq m daily until remission. Busulfan was given as a daily oral dose of 4 mg/sq m and continued until the white blood count was reduced to one-half the initial level at which point the dose is decreased to 2 mg/sq m daily. After peripheral remission was achieved, a repeat bone marrow examination was performed. If the morphology coincided with the below mentioned criteria, the drugs were discontinued until there was evidence of reactivation of disease as evidenced by persistent leukocytosis above 15,000/cu mm and/or increase in spleen size or thrombocytosis. At that point, the protocol provided for continuous maintenance with the same drug until evidence of refractoriness or frank blastic transformation with either 2 mg/sq m busulfan or 150 mg/sq m of DBM. The clinical and hematologic criteria for blastic transformation in this trial include 30\% or more blasts in the marrow, refractory anemia and/or thrombocytopenia, splenomegaly, extramedullary myeloblastic infiltrations. Maintenance therapy was intended to keep the white blood count between 10,000 and 15,000/cu mm, provided the hemoglobin and platelet counts were sustained above 12.0 g/100 ml and 100,000/cu mm, respectively. Hematologic remission in CGL was considered complete if the patient fulfilled the following criteria: (1) return of peripheral blood counts to the normal range (Hgb, 12–16; WBC, 5,000–10,000/cu mm; platelets, 150,000–450,000/cu mm; absence of granulocytic precursor cells in the peripheral blood), (2) normal marrow cellularity and differential ratio, and (3) absence of splenomegaly.

Refractoriness to therapy in the absence of blastic transformation is defined as progressive leukocytosis with or without splenomegaly, <10\% blasts in the marrow despite increasing doses of the drug. In the above circumstance, patients were crossed over to the alternate drug. Periodic cytogenetic analysis of marrow specimens were performed usually at 6-mo intervals. The presence of myelofibrosis in Westerman-Jensen needle biopsy specimens was ascertained by histopathologic staining criteria previously described.\textsuperscript{7}

Complete follow-up is available on all patients, including complete autopsy material in 26 of 30 patients who have since died.

RESULTS

A total of 40 patients were treated and 20 patients were randomized to each drug. The presenting hematologic characteristics for each group are outlined

| Table 1. Chronic Granulocytic Leukemia: Hematologic Characteristics |
|----------------------|----------------------|
|                      | DBM                  | Busulfan             |
| Total cases          | 20                   | 20                   |
| Median age (yr)      | 34                   | 42                   |
| Blood counts         |                      |                      |
| (mean, range)        |                      |                      |
| Hgb g/100 ml         | 10.0 (5.7–15.5)      | 9.9 (6.1–15.4)       |
| White count (x 10\(^3\)/cu mm) | 214 (46–545) | 213 (83–492) |
| Platelet count (x 10\(^5\)/cu mm) | 525 (113–1200) | 554 (161–2030) |
| Median duration      | 1                    | 1                    |
| diagnosis to therapy (mo) |                      |                      |
Remission Induction

Both drugs were effective in inducing remission, but certain differences in the cytotoxic action was noted. Of the two drugs, DBM appeared capable of reducing the white counts more rapidly. Figure 1 illustrates the mean percentage reduction from initial levels during the first 4 wk of induction therapy. With both agents, the white blood count depression within the first 3 wk appeared to be more rapid in the DBM-treated group. The overall results and duration to response are shown in Table 2. The rate of remission was almost exactly the same for both drugs with 14 remissions with DBM and 15 with busulfan. Failures were due to early accelerated phase or blastic transformation and hypoplasia.

The median duration to complete hematologic remission was about 30 days shorter in the DBM-treated group (72 versus 100 days). Once remission was achieved, the protocol entailed continuous maintenance therapy to be instituted
after the white count rose above 10,000/cu mm. In the DBM-treated patients only three required any delay in instituting maintenance therapy (1, 4, 12 mo). Busulfan resulted in a far more prolonged period of white blood count suppression, with nine patients requiring a delay lasting a median of 12 mo (range, 2-24). Thus the over-all median duration of response was somewhat longer (34 > 26 mo) in the busulfan-treated group. In all cases the Philadelphia chromosome was present in 90%-100% of marrow cell metaphases during remission.

**Hypoplasia**

Severe but nonfatal hypoplasia manifested by peripheral platelet counts ≤20,000/cu mm occurred in three cases (two with busulfan, one with DBM). Following recovery from 6 mo of busulfan-induced thrombocytopenia, one patient crossed over to DBM and promptly had 13 mo of thrombocytopenia. The one case with DBM-induced thrombocytopenia of 3 mo experienced a further 6 mo of suppression after crossover to busulfan.

**Crossover**

Out of the 29 patients who achieved a complete remission with either drug, 24 have become refractory. In 19 of 24 cases, clinical and hematologic evidence of blastic transformation occurred requiring more intensive antileukemic treatment. In five cases, hematologic refractoriness to the primary drug, but without evidence of blastic transformation, permitted a crossover to the alternate drug. Four DBM patients crossed over to busulfan with two good partial responses lasting 6 and 15 mo. One busulfan patient received DBM for 1 mo without response.

**Survival**

Thirty of the 40 patients have died. The actuarial survival of the individual treatment groups is shown in Fig. 2. The median survival for both groups is about 45 mo, with 20% of the patients surviving up to 7 yr. There is no significant difference in the survival between the two agents. One patient died in the chronic phase of the disease of complications following an exploratory thora-
cotomy. Of the remaining patients, all 29 have died in blastic transformation. Ten patients are living, five in each group, but four have entered the blastic phase at this time. The median survival of nonresponders from both groups was 13 mo.

**Drug-related Abnormalities**

Skin pigmentation is a common side-effect of busulfan, and in this series eight of 14 patients who were maintained on the drug for at least 30 mo had some evidence of increased skin pigmentation. Interestingly, this was also seen in the DBM group where five of 11 patients had a similar degree of pigmentation when the drug was given for a similar period of time. Amenorrhea occurred in all premenopausal females who received at least 6 mo of continuous treatment with both agents.

Myelofibrosis occurred in nine patients treated with busulfan and in five patients treated with DBM.

Autopsy studies were available on 26 of 30 cases. Interstitial pulmonary fibrosis was noted at autopsy in three of the 14 cases who received busulfan. In no case was it severe or clinically detectable. Only one patient had evidence of dysplasia of the bladder mucosa, and in that case pulmonary fibrosis was also noted. No occult malignancies were noted in either group.

Amongst the DBM patients, only one of the 12 autopsied patients had any evidence of pulmonary fibrosis, and two cases had mild dysplasia of the bladder mucosa.

**DISCUSSION**

Since its introduction in 1953, busulfan has remained the standard chemotherapeutic agent to which all new drugs for the management of CGL are compared. In the past, randomized trials between busulfan and chlorambucil, 6-mercaptopurine, cyclophosphamide, and splenic irradiation have been reported, and in all of these trials busulfan emerged as the superior agent in remission induction and duration of disease control.

The initial clinical trials with dibromomannitol included a majority of patients who had been previously treated with other drugs and frequently with busulfan. Despite this, the complete and partial remission rates in these reports were in the order of 70%-80%, and it was proposed that DBM could serve as a second line drug in busulfan failures. The drug has similar toxicologic and hematologic effects as Mannitol-Myleran, and it is thought by some workers to share a common biochemical mechanism by its conversion to dianhydride in vivo. Since resistance to busulfan is most often associated with the onset of blastic transformation, the results of this trial confirm that dibromomannitol only rarely benefits the patient who is becoming refractory to busulfan. However, the use of busulfan itself is associated with a number of problems. The most serious is prolonged myelosuppression.

The results of the present study suggest that there is a cross sensitivity of CGL marrow cells to the marked suppressive effects of DBM and busulfan. However, myelosuppression with DBM appears to occur more rapidly with a faster recovery than busulfan. The prolonged remission of CGL off treatment
which can follow a course of busulfan was not seen with DBM. Thirteen of the DBM patients required continuous maintenance with no extended period off treatment, whereas nine of 14 busulfan patients had required no therapy and remained under good control for periods up to 24 mo.

The occurrence of myelofibrosis and skin pigmentation was also noted with DBM. This suggests that these complications are not unique to busulfan and raises the question that these effects may be more related to the disease activity rather than any single medication.

Dysplasia of bladder mucosa and pulmonary fibrosis were only detected at autopsy and had no clinical significance in either group. Some of the long-term cytologic complications of busulfan treatment may be more related to host factors than total dosage, since there appeared to be no correlation with duration of treatment.

DBM is a useful agent in the treatment of CGL and may be equally effective in other myeloproliferative disorders, especially since its myelosuppressive effect appears to be more predictable than busulfan. However, in a randomized comparative trial it was associated with a similar rate of remission and no significant difference in incidence of blastic transformation or survival with either 2 mg/sq m busulfan or 150 mg/sq m of DBM. The clinical and hematologic criteria for blastic transformation in this trial include (a) 30% or more blasts in the marrow, (b) refractory anemia and/or thrombocytopenia, (c) splenomegaly, (d) extramedullary myeloblastic infiltrations. Refractoriness to DBM, however, without definite evidence of blastic transformation, may still warrant a trial of busulfan. Recent investigations in busulfan-resistant CGL and blastic crisis confirms the lack of effectiveness of DBM in these circumstances. One European cooperative trial which was not controlled nonetheless demonstrated a median survival of 43 mo for patients who received only DBM of the chronic phase of CGL.

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