The Clinical Use of Epoxypiperazine, a New Alkylating Agent, in the Treatment of Lymphomas and Other Neoplasms*

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The use of diepoxides as cytotoxic alkylating agents was described in 1950 by Ross (8) and by Everett and Kon (3). Epoxypiperazine—1,4-bis(2,3-epoxypropyl-piperazine) was synthesized by Johnson and Wright (4) and shown to be active in animal tumors. This was corroborated by Burchenal et al. (1), who tested the efficacy of this agent against a spectrum of mouse leukemias. Krakoff et al. (7) established the dose of this agent in patients with malignant diseases and described improvement in some cases.

It is the purpose of this paper to report the effects of this member of a new class of clinically useful alkylating agents in the treatment of 60 patients with malignant lymphomas and other neoplastic diseases.

MATERIALS AND METHODS

Epoxypiperazine was supplied in 50-mg. vials as a white crystalline powder. A suitable quantity of physiological saline was added to each vial to provide a concentration of 25–50 mg/cc. At room temperature the powder dissolved readily. Administration was begun immediately after the solution was prepared. It was given by intermittent injection into the tubing of a free-running intravenous infusion of 5 per cent glucose in distilled water over a 3-minute period.

Krakoff et al. (7) have determined that a total dose of 60 mg/kg regularly induces reversible leukopenia in patients whose marrow has not been compromised by their disease or prior therapy. This was the maximum total dose that we employed for such patients; however, others received less. The daily dose was 15 mg/kg or multiples thereof. As more experience was gained with the agent, more patients received the total dose at one administration. Treatment was given to hospitalized patients and to selected out-patients. Sixty patients were treated with epoxypiperazine. The types of diseases and the number of patients with each are outlined in Table 1.

A response was recorded after treatment with epoxypiperazine when the diameter of palpable disease decreased by one third or more, provided no other area of disease was increasing at this time. Temperature response, x-ray and blood cell changes were also used in appropriate situations as objective evidence of response. The response of the disease was correlated with the response of the patient by an estimation of his performance status.

Hodgkin's disease.—Since patients with Hodgkin's disease vary widely in their clinical condition and the disability resulting therefrom, we found it desirable to divide them into three categories in order to evaluate the effects of the treatment.

Category 1: Able to carry on normal activity; no special care is needed.

Category 2: Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed.

Category 3: Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.

TABLE 1

<table>
<thead>
<tr>
<th>Classification by Diagnoses of the 60 Patients Treated with Epoxypiperazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin's disease</td>
</tr>
<tr>
<td>Lymphosarcoma</td>
</tr>
<tr>
<td>Reticulum-cell sarcoma</td>
</tr>
<tr>
<td>Chronic lymphatic leukemia</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Bocck's sarcoi</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td>Breast carcinoma</td>
</tr>
<tr>
<td>Renal-cell carcinoma</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
</tr>
<tr>
<td>Chordoma</td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
</tr>
<tr>
<td>Malignant melanoma</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

* This work was supported by grant CY-3215 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

Received for publication June 5, 1959.
These categories and the performance status upon which they are based have been previously defined by Karnofsky and Burchenal (5). The same procedure was followed for patients with other diagnoses. In Table 2 are listed the number of patients in each category and the number responding to treatment.

With regard to the extent of disease, no patient was treated with this systemic chemotherapeutic agent who had only one clinical focus of disease and no generalized symptoms attributable to Hodgkin's disease. These patients were considered candidates for radiation therapy. All patients had disease in more than one area or had symptoms generally associated with widespread active disease, e.g., pruritus, night sweats, fever. In this group of 27 patients only two had disease which had never extended beyond one anatomical region, i.e., only two patients had Class II disease as defined by Diamond (2); the remainder were Class III.

Category I: Ten of the eleven patients in this category showed some response to treatment. Of these ten patients, in eight the duration of response was more than 1 month. Two patients with particularly good responses and with notable clinical improvement are described below.

A 9-year-old white female with Hodgkin's disease for 8 years: Previous treatment had been radiation therapy to the mediastinum and peripheral nodes. She was seen in the outpatient clinic 1 month after delivery of a normal infant, complaining of fatigue, night sweats, and pruritus. The edge of the liver was palpable, the spleen was palpable 4 cm. below the left costal margin, and para-aortic nodes were evident. She was given 60 mg/kg of epoxypiperazine in one dose as an out-patient. There were no untoward effects. Symptoms subsided completely, and 8 weeks later the liver, spleen, and para-aortic nodes were no longer palpable. The patient remained completely free of signs or symptoms of her disease for 9 months. Slight hepatomegaly has recurred recently, but the patient remains without symptoms.

A 38-year-old white female with Hodgkin's disease for 2½ years: Previous therapy consisted of radiation therapy to mediastinal and peripheral nodes. The patient was hospitalized because of dyspnea and was found to have extensive bilateral pulmonary infiltrates. The vital capacity was 88 per cent and the maximum breathing capacity 59 per cent. She was treated with epoxypiperazine, 15 mg/kg daily for 4 days, without any untoward effect. In 1 week her dyspnea had decreased. Two weeks later, her vital capacity was still 88 per cent, but her maximum breathing capacity had increased to 98.4 per cent. The chest x-ray film at that time showed slight improvement. Her improvement persisted for about 2 months. Her disease then became slowly progressive again, both symptomatically and on x-ray examination. Re-treatment with epoxypiperazine did not lead to further improvement. It is now 10 months later, and she has not returned to the degree of disability that prevailed before the treatment with epoxypiperazine.

Category II: Four of the eleven patients in this category responded in some parameter of their disease. Of the four patients responding, the duration was greater than 1 month in three (and one of these had radiation therapy added after response to epoxypiperazine had begun). One patient in this category received 30 mg/kg of epoxypiperazine intrapleurally as treatment for a recurrent pleural effusion without any improvement. A favorable response of the fever of Hodgkin's disease to treatment with epoxypiperazine is shown in Chart 1.

Category III: Three of the five patients in Cate-
gory 3 had some response to treatment. In only one patient was the response of more than 1 month’s duration and of any clinical significance. This patient was also treated with radiation therapy but only after a clear-cut response to epoxypiperazine had been noted. This case is described below.

A 15-year-old white female with an 8-month diagnosis of Hodgkin’s disease: The patient had received no previous therapy. She was admitted to the hospital with fever, profuse diaphoresis, pruritus, and dyspnea. There was marked peripheral lymphadenopathy with some node masses measuring 5 and 7 cm. in diameter. In addition, there was mediastinal lymphadenopathy with left pleural effusion and hepatosplenomegaly. The performance status was 80. She received epoxypiperazine, 15 mg/kg daily for 4 days. At the end of 1 week, the night sweats, fever, and pruritus had completely subsided; and there was a measurable decrease in lymphadenopathy. Dyspnea, mediastinal adenopathy, and left pleural effusion had improved somewhat, but it was felt that radiation therapy should be given to the enlarged mediastinal and hilar lymph nodes. One month later peripheral lymphadenopathy had subsided completely except for for a few cm. residuals of the largest node masses. The areas treated with radiation therapy had improved also, and the patient left the hospital with a performance status of 70.

In Chart 2 the responses of various manifestations of Hodgkin’s disease following treatment with epoxypiperazine are summarized.

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**Lymphadenopathy:** Eight patients with lymphosarcoma were treated with epoxypiperazine. Seven of these showed improvement in some parameter of response. Table 2 lists the patients by category and responses. The only patient whose disease showed no response was a 39-year-old male in terminal condition. Despite the fact that 15 mg/kg daily for 4 days caused no clinical improvement, the administration of this agent caused the serum uric acid level to rise from 16.3 mg. per cent to 32.8 mg. per cent. No further epoxypiperazine was given, and the serum uric acid value fell to 7.7 mg. per cent. Hydration or other factors that might have altered the uric acid levels were unchanged during this period.

With regard to specific parameters of response, all seven patients showed a measurable decrease in lymphadenopathy; in three out of five there was decreased hepatosplenomegaly; in one out of two, pulmonary disease improved. A third patient with pulmonary disease showed no improvement after epoxypiperazine despite the fact that lymphadenopathy and hepatosplenomegaly decreased. She was treated with nitrogen mustard and radiation therapy to the lungs with no benefit. This patient died, and at post-mortem examination the pulmonary disease thought to be lymphosarcoma was chronic pneumonitis and pleurisy.

No comment can be made about the duration of the improvement observed, since, with the exception of one patient, all had radiation therapy given to significant residual disease after the maximum effect of the epoxypiperazine had been observed. The fact that these patients required supplemental therapy attests to the incompleteness of the remission achieved. The one patient who did not receive supplementary radiation therapy is of particular interest and will be described in detail.

A 60-year-old white male with lymphosarcoma for 8 years: Previous therapy had been by irradiation and triethylene melamine. He was admitted to the hospital because of severe dyspnea due to lymphosarcomatous infiltration of his lungs superimposed upon chronic fibrosis and emphysema (Fig. 1a). Treatment with epoxypiperazine, 15 mg/kg for 4 days, produced moderate improvement in the pulmonary parenchymal infiltrations (Fig. 1b) and marked decrease in dyspnea. This improvement lasted for about 6 weeks. Re-treatment with 15 mg/kg for 2 days again caused symptomatic improvement. The patient remains partially incapacitated because of dyspnea, but there has been no progression of his disease for the last 10 months.

**Reticulum-cell sarcoma:** Ten patients with reticulum-cell sarcoma were treated with epoxypiperazine. Table 2 outlines the number of patients and responses in each category. These responses consisted of the following features: In four out of five instances when lymphadenopathy was used as a criterion of response, there was measurable regression; in two out of six patients, hepatosplenomegaly regressed; in one patient neurological signs of disease improved. A patient with reticulum-cell sarcoma had decreased in fever, night sweats, and bone pain but no decrease in measurable disease. In only three patients was the response complete enough to eliminate the need for supplementary radiation therapy. The duration of response in two of these patients was 1 month and 6 weeks. However, in neither case was the decrease of measurable disease of clinical benefit to the patient. There was significant clinical improvement in two other patients with abdominal disease, but in these cases radiation therapy was added, and the effect of epoxypiperazine could not be evaluated. Two patients treated with epoxypiperazine had sig-

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**Lymphadenopathy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>80.0%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>76.9%</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>75.0%</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>70.0%</td>
</tr>
<tr>
<td>Lung Infiltration</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

**Chart 2.**—Incidences of response of specific signs and symptoms in Hodgkin’s disease following treatment with epoxypiperazine.
significant clinical improvement and will be described in detail.

A 69-year-old white male diagnosed as having reticulum-cell sarcoma: The patient was referred to Memorial Center because of a painful neck mass of 1 month's duration. He was found to have an 8 x 6 cm. right cervical mass and splenomegaly. He was treated in the out-patient clinic with the injection of epoxypiperazine, 30 mg/kg daily for 2 days. One week later the neck mass was one half the original size, and in 2 weeks the mass was no longer palpable; neither was the spleen palpable. It is now 5 months after treatment, and the patient is free of cervical and other lymphadenopathy. The splenomegaly has recurred and the liver is slowly enlarging, but the patient is without symptoms or disability.

A 35-year-old white male with reticulum-cell sarcoma: The patient developed pain in his neck after jumping off a truck. Progressive weakness of the extremities led to hospitalization and the discovery of a pathological fracture of the second cervical vertebra and a retropharyngeal mass. Biopsy of this mass was inconclusive. Anaplastic carcinoma and plasma-cell myeloma were considered. The patient's condition deteriorated rapidly, and he was admitted to Memorial Center in coma with a temperature of 101°F. and Cheyne-Stokes respiration. Death was considered imminent. He was given epoxypiperazine, 30 mg/kg, as a measure of desperation. Twenty-four hours later he was conscious. Forty-eight hours later he was alert, eating, and drinking, and improvement in neurological signs was evident. Radiation therapy was then started, and after its completion the patient was able to go home in head traction, alert, free from pain, and in control of his extremities. The patient died at home a few months later, and an autopsy at a local hospital revealed reticulum-cell sarcoma.

Miscellaneous.—The results in this group of patients are summarized in Table 3.

Two patients with chronic lymphatic leukemia were treated with epoxypiperazine. For one patient, whose disease was of 1 month's duration, this was the first course of therapy. The second patient had this diagnosis for 4 years and had been treated with radiation therapy and triethylene melamine with poor results. Because of the known sensitivity of the bone marrow of patients with this diagnosis to alkylating agents, these patients were treated with one-half the usual dose, that is, a total of 30 mg/kg. In each patient there was a 30-40 per cent decrease in lymphadenopathy and a marked fall in the white blood cell count. However, there was sufficient residual lymphadenopathy to be symptomatic (despite retreatment in one patient). Fall in white blood cell count was not accompanied by a fall in the per cent of lymphocytes in the peripheral blood, and the platelet count decreased. In these two patients with chronic lymphatic leukemia, the response did not lead to any clinical improvement.

Krakoff et al. (7) described a fall in leukocyte count and decrease in spleen size in two patients with chronic granulocytic leukemia.

Treatment with epoxypiperazine did not result in any response in the patients with Boeck's sarcoid, carcinoma of the lung, carcinoma of the ovary, hemangiosarcoma, or malignant melanoma. A patient with renal-cell carcinoma who received 60 mg/kg had a decrease in pulmonary disease thought to be metastases. She also felt stronger and had less anorexia for about 2 weeks. However, her persistent fever did not abate; other parameters of disease progressed. Treatment with nitrogen mustard did not lead to any improvement, and the patient died 6 weeks later.

One of the three patients with carcinoma of the breast had a decrease in two clusters of skin nodules and also of liver size after full courses of epoxypiperazine. Retreatment 4 weeks later did not cause any further improvement, and the disease has been very slowly progressive.

TABLE 3
MISCELLANEOUS NEOPLASMS: RESULTS OF TREATMENT WITH EPOXYPIPERAZINE

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. patients</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lymphatic leukemia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Renal-cell carcinoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Boeck's sarcoïd</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chordoma</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Unexpectedly good results were obtained in a patient with mycosis fungoides and will be described in detail.

A 69-year-old white male with a 4-year history of mycosis fungoides: The patient's initial response to radiation therapy had been good, but recently resistance had developed. He was treated with epoxypiperazine, 15 mg/kg on each of 4 consecutive days. By the time the last injection had been given, some of the lesions began to fade, and 1 week later there was marked regression of disease. This improvement is shown in Figures 2a, 2b, 3a, and 3b. Since this effect was accomplished with little depression of the leukocytes or platelets, he was given 15 mg/kg at weekly intervals in an effort to maintain the remission. However, 1 month after the first course of therapy a rapid relapse occurred. He was then treated with nitrogen mustard, 0.4 mg/kg, with improvement of the same order and for the same duration as had been obtained with epoxypiperazine.

DISCUSSION

The results obtained with epoxypiperazine compare favorably with those reported for nitrogen mustard and triethylene melamine with regard to the spectrum of activity and the degree of results. A critical note, however, must be injected into interpretation of the results obtained. In
evaluating this agent, what was noted and tabulated was response of specific and, for the most part, objective criteria of disease. A decrease in lymphadenopathy or the elimination of a specific pulmonary lesion does not always mean real clinical improvement. The discrepancy between response of the disease per se and clinical improvement as determined by estimating the patient's performance status may be noted in Table 4. Thirteen of the 35 patients (or more than one-third) who showed response of some specific parameter did not improve clinically. Nor has the duration of improvement been longer than what might reasonably have been expected from conventional therapy. This is not mentioned to depreciate the effects of this agent but only to view the results obtained in the proper perspective. The brevity of some of the responses was, in each instance, similar to that noted on subsequent trial of conventional agents. There was no patient who failed to respond to epoxypiperazine who did respond to subsequent treatment with another alkylating agent. We were not able to follow the duration of results of some of the most favorable responses, because it was felt that the patients could not be deprived of the possible additional benefit that would accrue from the use of radiation therapy.

There was one patient who had a favorable response to epoxypiperazine who had previously not responded to nitrogen mustard or triethylene melamine. This was a 31-year-old white female with Hodgkin's disease with hepatosplenomegaly and lung infiltration whose chief complaint was pruritus. Previous treatment with triethylene melamine and nitrogen mustard to leukopenic levels did not affect this complaint. After treatment with epoxypiperazine, the pruritus subsided completely for 6 weeks. None of these agents had any influence on the visceral disease which was progressive and fatal. Before it is concluded that this compound has an effect on pruritus that cannot be achieved with other alkylating agents, a large number of cases would have to be accumulated. The alternate possibility would be the development of tumor sensitivity to alkylation in a patient previously resistant. Such a situation has been reported (7).

Toxicity.—Fifty per cent of the patients had some side effects. The nature of these reactions is listed in Table 5. Of 71 courses administered, ten were accompanied by vomiting (14.1 per cent). The incidence of vomiting is apparently related to the size of the dose injected. Table 6 contrasts the incidence of vomiting when the total dose was divided (4.4 per cent) as compared with the incidence prevailing when the patient received 60 mg/kg in one dose (50 per cent). This is in contrast to our experience with nitrogen mustard whereby we have found that there is very little difference in the incidence of vomiting between a course of 0.4 mg/kg given at once and when the same total dose is divided over 4 days.
FIG. 1a.—A 60-year-old male with lymphosarcoma. Appearance of chest film before treatment with epoxypiperazine.
FIG. 1b.—Appearance after treatment.

FIG. 2a.—A 62-year-old male with mycosis fungoides. Appearance of face before treatment with epoxypiperazine.
FIG. 2b.—Appearance after treatment.
Fig. 3a.—A 62-year-old male with mycosis fungoides. Appearance of hands before treatment with epoxypiperazine.

Fig. 3b.—Appearance after treatment.
FIG. 3a.--A 6'2-year-old male with mycosis fungoides. Appearance of hands before treatment with epoxypiperazine.

FIG. 3b.--Appearance after treatment.
The visual aberrations are also apparently related to the amount of epoxypiperazine injected at once, since six of the seven patients with such disturbances received injections of more than 15 mg/kg at one time.

One patient with far advanced carcinoma of the breast and widespread metastases was to have received 60 mg/kg in one dose. After the injection of approximately 8 mg/kg, profuse diaphoresis and hypotension occurred. She was found to have a ventricular tachycardia and died 1 hour later despite vigorous supportive therapy. The patient had extensive intrathoracic disease, and an abnormal electrocardiogram was noted before this therapy. This fatality was not thought to be due directly to treatment with epoxypiperazine, but that possibility could not be definitely excluded. A second patient with carcinoma of the breast who received 15 mg/kg daily for 4 days experienced flushing of the face and constriction of the throat and chest during the injection. With the next injection an electrocardiogram was taken, and continual blood pressure, pulse, and respiration rate determinations were made. No changes were noted. With the third injection, a placebo solution was used. The same symptoms noted at the time of the first injection recurred.

At a total dose of 60 mg/kg, a significant depression of white blood cells and platelets occurs (Chart 1). The degree of depression in most cases and the time of its maximum effect (7–14 days) and the recovery (approximately 1 month) after injection were similar to what is seen with 0.4 mg/kg of nitrogen mustard. No prolonged or irreversible leukopenia or thrombocytopenia was observed in patients who did not have subsequent treatment with other marrow-depressant agents. In none of these patients were there any serious sequelae to the thrombocytopenia or leukopenia. However, in three other patients who were being treated with epoxypiperazine in combination with other marrow-depressant agents serious hemorrhagic diatheses occurred.

Although the paired control technic was not employed, it would appear that the effectiveness of this drug is comparable to that of nitrogen mustard. However, no therapeutic advantage over nitrogen mustard was apparent. The low incidence of nausea and emesis at the dose levels indicated is not sufficient reason to supplant alkylating agents already in clinical use.

The use of epoxypiperazine by mouth in dogs led to nausea and vomiting, and oral administration has not been attempted clinically. However, analogs of this compound have been prepared, and further investigation with this class of compounds will continue in an effort to explore their full range of clinical usefulness. Other epoxide compounds are biologically active, and Stenderup, Bichel, and Jensen have reported on the therapeutic effects of diepoxybutane (9).

SUMMARY

1. Epoxypiperazine—1,4-bis(2,3-epoxypropyl)piperazine—an intravenously administered alkylating agent, was used in the treatment of 48 patients with lymphoma and twelve patients with miscellaneous malignant tumors.

2. Significant clinical improvement (in contrast to response of disease per se) was seen in patients with Hodgkin's disease, lymphosarcoma, reticulum-cell sarcoma, and mycosis fungoides.

3. The types of response seen, the duration of its effect, and the spectrum of diseases affected were similar to what might have been expected with the use of other alkylating agents.

4. The same precautions regarding depressant effect on the white blood cells and platelets obtain with epoxypiperazine as with other alkylating agents.

ACKNOWLEDGMENTS

The authors wish to thank Eli Lilly & Company of Indianapolis, Indiana, who provided the epoxypiperazine used in this investigation.

REFERENCES


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