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# THE EXPERIMENTAL USE OF ORAL PHENYLALANINE MUSTARD IN THE TREATMENT OF MALIGNANT MELANOMAS

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Melanoma has been recognized as one of the most devastating malignant tumors encountered in medicine. Yet observations in recent years have indicated that a vigorous attack on this disease will decrease the mortality rate and increase the 5-year survival rate. To obtain added information on this point and to determine whether a chemotherapeutic attack in widespread metastatic disease may not give the patient some symptomatic relief during the terminal phase of the disease, a study of oral phenylalanine mustard therapy was undertaken in patients who had microscopically proved malignant melanoma.

## Pharmacology of Drug

*p*-Di(2-chloroethyl)-amino-L-phenylalanine is a phenylalanine derivative of nitrogen mustard formed by conjugation of the 2-chloroethyl amino group of the mustard with the L-isomer of the amino acid phenylalanine. The drug is well absorbed from the gastrointestinal tract and is thought to remain active in the blood for some 6 hours.

Toxicity from the drug affects primarily the gastrointestinal and hematopoietic systems. Soon after its oral administration, nausea, vomiting, and sometimes diarrhea may occur. Later (1 to 2 weeks after administration) a suppressive effect on the marrow may be reflected in decreased hemoglobin and in decreased leukocyte (especially polymorphonuclear) or platelet counts or both. Alterations in the results of renal or hepatic function tests have not been observed.

After its synthesis the antimetabolic effect of this chemical against some tumors in animals was recognized. Luck (3) reported on its cytostatic effect on Harding-Passey mouse melanoma. In clinical studies, Holland and Regelson (2) found that 2 of 16 patients with malignant melanoma were benfitted by its administration. Papac and colleagues (4) observed no clinical benefit in three patients with melanoma they treated with oral medication. Clifford and colleagues (1) have subsequently reported dramatic response in two patients with melanoma: macroscopic regression of tumor for periods of 3 and 7 months respectively.

## Present Study

*Material and Procedure.* Beginning in 1960, patients with malignant melanoma seen in the Section of Dermatology of the Mayo Clinic were considered candidates for possible additional therapy with *p*-di(2-chloroethyl)-amino-L-phenylalanine (melphalan, Alkeran).[1] Since 1960, treatment consisted of oral administration of 2 mg of the drug per kilogram of body weight in divided doses. Because our prepared capsule contained 50 mg, patients usually received 100 or 150 mg in two or three doses over 36 to 72 hours according to tolerance. Recent ex-

[1] The melphalan used in this study was kindly supplied as Alkeran by Donald S. Searle, M.D., Ph.D., of Burroughs Wellcome & Co., Inc., Tuckahoe, N. Y. 10707.

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perience with commercially prepared 2-mg tablets indicates 1.5 mg/kg should be the top dose. To prevent the nausea and vomiting attending oral melphalan therapy, prochlorperazine (Compazine), 25 mg, was given orally 30 to 60 minutes prior to each dose of the drug. When the medication was given in the morning, breakfast was withheld; with nighttime administration the drug was given at bedtime, after at least 4 hours had elapsed since the previous meal. When nausea or vomiting occurred despite these precautions, chlorpromazine (Thorazine), 50 mg by intramuscular injection, and secobarbital (Seconal), 0.1 gm by mouth, were given instead 1/2 to 1 hour before administration of melphalan.

Hemoglobin concentration and leukocyte and platelet counts were determined weekly beginning after 2 weeks of therapy and continuing for a total of three counts, if no abnormalities were noted. If hematopoietic suppression occurred, as evidenced by the lowered peripheral counts, the counts were continued until they returned to normal.

The patients were classified according to the extent of their disease, as follows: (1) primary lesion excised, regional lymph nodes apparently not involved; (2) primary lesion excised, regional lymph nodes involved; and (3) metastatic disease (cutaneous, bony, pulmonary, cerebral, or other [specified]).

The concept of chemotherapy as an adjunct to the surgical therapy already instituted was discussed with patient and the drug was administered in the courses outlined above. Patients seen during 1964 and 1965 were more likely to have had repeated courses of the drug administered at approximate intervals of 1 month or 6 weeks, in contrast to patients seen earlier whose medications were limited to one or two courses of the drug.

*Results.* Tables 1 and 2 give the pertinent follow-up data on the patients seen during the years 1960 through 1965, with the last follow-up available that of December 1967. In Table 1 the results are given by year and treatment group. In Table 2 the results are given solely according to treatment group, irrespective of when the patients were seen.

Table 1. *Distribution of Melanoma Patients Treated With Melphalan, by Group and Year*

| Year | Group | Patients treated: Total | Status as of Dec. 1967: Alive | Status as of Dec. 1967: Dead |
|---|---|---|---|---|
| 1960 | 1 | 0 | | |
| | 2 | 1 | | 1 |
| | 3 | 6 | | 6 |
| 1961 | 1 | 1 | 1 | |
| | 2 | 4 | 1* | 3 |
| | 3 | 8 | | 8 |
| 1962 | 1 | 2 | 1 | 1 |
| | 2 | 3 | 1 | 2 |
| | 3 | 15 | | 15 |
| 1963 | 1 | 0 | | |
| | 2 | 4 | | 4 |
| | 3 | 7 | | 7 |
| 1964 | 1 | 3 | 3 | |
| | 2 | 1 | | 1 |
| | 3 | 12 | 2 | 10 |
| 1965 | 1 | 0 | | |
| | 2 | 3 | 2 | 1 |
| | 3 | 6 | | 6 |
| Total | | 76 | 11 | 65 |

* Last follow-up, August 1967.

Table 2. *Distribution of Melanoma Patients Treated With Melphalan, by Group Alone*

| Group | Patients treated: Total* | Alive | Known dead |
|---|---|---|---|
| 1 | 6 | 5 | 1 |
| 2 | 16 | 4 | 12 |
| 3 | 54 | 2 | 52 |
| Total | 76 | 11 | 65 |

* All patients were traced.

Five of the six patients in group 1 were alive as of December 1967. A fourth of the patients of group 2 were alive even though they had regional metastasis when treated. By contrast, of 54 group 3 patients (with widespread metastasis on initial clinical examination), only 2 are known to be alive.

Outstanding among the therapeutic re-

sults achieved was that of the following patient:

A 45-year-old white man was first seen at the Mayo Clinic on Nov. 1, 1955, because of redness of the eyes, photophobia, pain, and gradual loss of vision of the right eye of 3 months' duration. Examination showed that the cornea of the right eye was markedly cloudy and that tactile tension was increased. The pupils were round and regular and reacted to light and accommodation. Slit-lamp examination disclosed grade 3 edema of the right cornea and a "melanoma" of the iris in the inferior temporal region. The patient was treated symptomatically. By the end of the year he had secondary glaucoma of the right eye and underwent an iridectomy of that eye on Jan. 4, 1956, and a cyclodialysis operation on Mar. 1, 1956. Because of the increased intraocular pressure, another cyclodialysis operation of the right eye was performed in late December 1956. Because of the lack of responsiveness to these measures, the right eye was enucleated on July 15, 1957. Histologic studies of the orbital contents revealed a malignant melanoma of the ciliary body and iris with implantation of tumor cells in the chamber angle and on the anterior surface of the iris.

The patient was seen intermittently thereafter; on each occasion the left eye was normal. In late 1961, however, because sharp pain had developed in the left eye after a change of glasses, he was seen once again; he then had mild early papilledema of the left eye. In addition, he complained of head and eye pain not characteristic of any specific disease. He underwent neurologic examination. After bilateral carotid angiography and fractional encephalography, both of which gave negative results, he underwent left transfrontal craniotomy, in March 1962. On exploration of the left orbit, pathologic tissue from the brain and from the left orbit was interpreted as that of metastatic malignant melanoma. Roentgen therapy was administered to the involved sites.

In July 1963, the patient presented a painful mass, 10 by 6 cm, of the left buttock. It was excised and proved histologically to be a melanoma. A chest roentgenogram did not show any abnormality.

In October 1963, he had a nodule 1 cm in diameter at the base of the right lung, and in December he had a second nodule 6 mm in diameter in the right costophrenic angle.

On limited right thoracotomy, the two metastatic nodules were palpable in the pulmonary tissue. A hard mass palpable in the liver was shown on needle biopsy through the diaphragm to be a metastatic nonmelanotic malignant melanoma. Melphalan was administered orally according to the schedule given in Table 3.

Table 3. *Schedule of Melphalan Therapy in Case of Melanoma Reported*

| Date | Mg/dose | No. of doses | Total mg |
|---|---|---|---|
| 1964 | | | |
| Jan. 6–7 | 50 | 3 | 150 |
| Mar. 25 | 50 | 3 | 150 |
| May 14 | 50 | 3 | 150 |
| Oct. 25–26 | 50 | 3 | 150 |
| 1965 | | | |
| Apr. 23–24 | 50 | 3 | 150 |
| May 21 | 50 | 3 | 150 |
| Sept. 24 | 50 | 3 | 150 |
| 1966 | | | |
| Jan. 14 | 50 | 3 | 150 |

When the patient returned on Mar. 25, 1964, he complained of an asymptomatic anal mass of 1 week's duration. The mass was seen in the subcutaneous tissue of the posterior part of the anus, was firm, but was not visibly inflamed. Further sarcolysine therapy was given (Table 3). Three months later (May 1964) the anal mass had enlarged and further melphalan therapy was given. When the patient returned in October 1964 the rectal mass had disappeared. Figure 1 compares roentgenograms of the chest made at a 1-year interval during which the patient received three courses of melphalan orally (50 mg every 12 hours for three doses). Stereoscopic films demonstrated more clearly that there had been resolution of the pulmonary metastatic lesions, estimated at 50 %.

In August 1966 the patient's local physician removed a cutaneous nodule from the right upper arm and this was interpreted histologically as being a malignant melanoma. General physical examination during September 1966 failed to reveal any evidence of metastatic disease.

In November 1966 another nodule removed from the anterior part of the chest proved histologically to be metastatic melanoma. During December, jaundice, ascites, and dyspnea developed. Hepatosplenomegaly was present and a roentgenogram showed multiple nodules

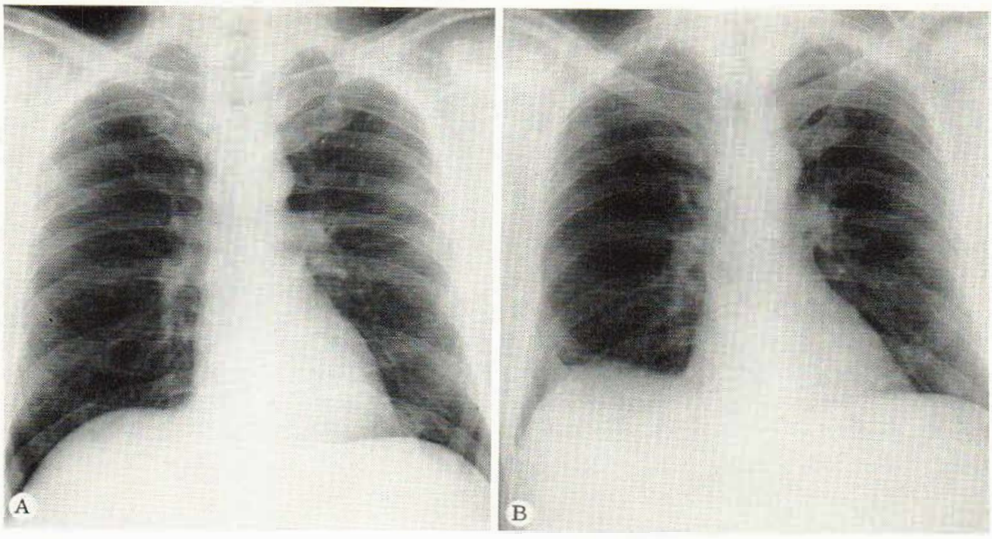


Fig. 1. *A* and *B*, Roentgenograms made at an interval of 1 year during which the patient received melphalan orally. There has been some resolution of the pulmonary masses.

in the lung fields. The patient's physical condition deteriorated and he died on Feb. 6, 1967.

Autopsy revealed widespread metastatic disease throughout the body, including the lungs, liver, kidneys, and adrenal glands.

## Discussion

Melanoma is recognized generally as highly malignant and capricious in its response to various treatments. After recognition of the inhibitory effects of phenylalanine mustard on this tumor, it was desired to embark on a program of oral chemotherapy using this drug. It was hoped that treatment of those patients with early disease could spare them of late devastating effects of this tumor and that those patients who already had metastasis could be given amelioration of their symptoms or, hopefully, could even be cured of their disease.

From Tables 1 and 2 it is apparent that follow-up data on the patients treated are particularly complete, with none of the 76 lost to follow-up. This study, therefore, represents a considerable experience with oral melphalan therapy under the conditions outlined.

Five of the six patients of group 1 (no metastasis) are still alive. The survival periods so far in this group have varied from 43 to 93 months following treatment. Lack of metastasis may be due to the primary operation or it may be only fortuitous. The relatively short period of follow-up for some patients may partially account for these survival times. The one patient with progressive disease did not respond to oral sarcolysin therapy but did have involution or his widespread melanoma after thiotepa therapy on a weekly basis. He subsequently succumbed to widespread metastatic disease.

Survival times for patients in group 2 (metastasis to regional lymph nodes) have varied so far from 3 to 72 months. Of the four patients still alive, one treated in 1961 is still alive and well, having survived 72 months at the time of this writing.

Of the group 3 patients (widespread metastasis when first seen), only two, both treated in 1964, are alive. Their survival times are 36 and 40 months. Recurrent cutaneous metastasis has been present in one of these.

The survival data for groups 2 and 3 again confirm the poor outlook for survival of patients with metastatic melanoma, particularly when lesions are present beyond the local draining lymph nodes. It is obvious that phenylalanine mustard therapy

has not increased total survival time for such patients.

Twenty-eight of the 54 patients in group 3 lived 6 months or less, and 4 of the 28 died within a month of therapy. These deaths were attributed to progression of the disease and were indicative of its far-advanced nature when therapy was undertaken. Four patients survived 13 to 24 months. Three survived 24 to 36 months, and one for 37 months. As mentioned above, the two patients of this group who are still alive have survived 36 and 40 months respectively. The survival of 10 patients for periods varying from 13 to more than 40 months might suggest that increased survival time may sometimes be ascribed to the use of melphalan, inasmuch as more than half the patients in the group as a whole survived 6 months or less.

Survival time for patients with melanoma is expressed in such a varied manner that it cannot be used for comparison of our study with the studies of others. Under the conditions of this study, no statistical analysis is possible, but it would seem probable that the use of melphalan did increase longevity in a few who survived for more than 2 years and probably was responsible for the increased longevity of others who survived more than a year.

The patients tolerated therapy well, and complications from therapy were negligible. No deaths were attributed directly to the therapy. Hematopoietic suppression requiring transfusion and due to melphalan therapy did not occur in any patient.

Patients with far-advanced melanoma, particularly with bony lesions, obtained some relief of pain with melphalan therapy. This was also true of patients with symptoms from diffuse pulmonary disease. Such therapy may be palliative at times, even if cure is not possible.

It seems significant that five of the six patients in group 1 are living: two for 36 months, one for 44 months, one for 64 months, and one for 80 months. Thirty to 50 % of such patients (no metastasis) may be expected to develop metastasis after present surgical therapy alone. If sarcolysin were to destroy a few remaining foci of melanoma cells, it could thereby increase survival in this group. A larger series of patients will have to be studied for a longer period to answer this question, and such a study is being undertaken.

Melphalan seems to be a safe chemotherapeutic agent when administered in the manner used in this series of patients. It has some limited effectiveness in advanced disease. It may prove to be of value in patients without metastasis.

## SUMMARY

A 7-year experience with phenylalaine mustard given orally to 76 patients with various stages of malignant melanoma is reported. The drug (2 mg/kg of body weight) was given in divided doses in one or more courses of treatment. Patients tolerated the therapy well and no deaths were attributed to it. It provided palliative relief for patients with advanced melanoma, and definite signs of tumor involution in some, particularly in those who had repeated courses of the drug.

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