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Clinical Studies on the Antitumor Action of Mecaphane*

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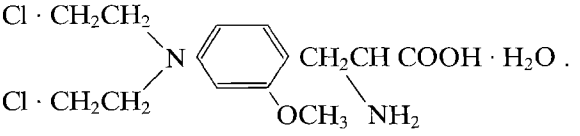
Summary. *Over a period of 4 years, 241 patients with advanced cancer were treated with mecaphane alone in 11 hospitals. Effective objective responses were obtained in 100 patients (41.4%). The response was most conspicuous in chronic granulocytic leukemia, with remission in 37 of 40 patients; in Hodgkin's disease and lymphosarcoma response rates were 60% and 47.3%, respectively. Mecaphane had an analgesic action in metastatic osteolytic bone cancer, and two patients with such metastases even attained recalcification of the osteolytic destructive lesions.*

The common toxic manifestations of mecaphane were leukopenia (33.6%), gastrointestinal upsets (28.2%), and thrombocytopenia (12.8%).

It is concluded, therefore, that mecaphane could be a good antitumor agent in clinical use. It is less expensive and can be taken orally. Further trials of this drug are recommended.

Introduction

In the course of studying the relationship between structure and antitumor action in derivatives of phenylalanine nitrogen mustard, the Institute of Materia Medical Academia Sinica found mecaphane [dl-o-methoxy-p-bis-(2-chloroethyl)-amino-phenylalanine] [1]. It possesses a markedly significant antitumor activity, exhibiting 98%–100% effectiveness on Jensen sarcoma, Yoshida sarcoma, and Walker carcinosarcoma 256 in rat [4]. Its structural formula is as follows:



Clinical trials have demonstrated that mecaphane is quite effective against chronic granulocytic leukemia, malignant lymphoma, and other malignant solid tumors [5]. Thus it was introduced for phase II clinical studies from January 1962. Up to the end of December 1965, a total of 241 patients with very advanced cancer had been treated in 11 hospitals. The results of this cooperative clinical study and long-term follow-up data are reported here.

Materials and Methods

The diagnoses recorded for these 241 patients are listed in Table 1. All patients' diagnoses were confirmed pathologically or hematologically. The patients fulfilled the following four requirements: 1. for at least 2–3 weeks prior to the institution of mecaphane therapy the patients did not receive any other chemotherapy or radiotherapy; 2. the patients' clinical condition had become progressively worse during the course of previous treatment; 3. they were treated solely with mecaphane, and a minimum dosage of 500 mg mecaphane must have been given, except in a few children and elderly debilitated patients; and 4. the tumors were accessible for direct measurement or there were other means of comparison (e.g., blood or marrow changes in cases of leukemia).

Mecaphane was given p.o. with an initial daily dose of 25–50 mg. When the total dosage reached 500 mg, the daily dose was reduced to 25 mg and continued until a full course of 1,000–1,500 mg had been given. In some cases a maintenance dose of 25 mg was given once, twice, or three times a week, depending upon the white blood cell count and individual tolerance. The initial daily dosage for chronic granulocytic leukemia was usually 50–100 mg, and it was reduced to 25–50 mg per day when the white blood cell count had fallen below 20,000/mm^3. After the white blood cell count had reached the normal range, mecaphane was either completely withdrawn or given in the reduced, maintenance dosage.

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Table 1. The clinical efficacy of mecaphane

Diagnosis	No. of patients	Complete remissions	Partial remission	Improvement	No response	Response rate %
Chronic granulocytic leukemia	40	10	23	4	3	92.5
Acute leukemia	17	–	–	5	12	29.4
Multiple myeloma	2	–	–	1	1	1/2
Hodgkin's disease	25	3	10	4	8	68.0
Lymphosarcoma	19	–	4	5	10	47.3
Reticulum cell sarcoma	11	–	–	2	9	2/11
Seminoma	5	–	2	–	3	2/5
Ovarian carcinoma	5	–	1	1	3	2/5
Carcinoma of breast	30	2	1	4	23	23.3
Carcinoma of lung	29	–	–	8	21	27.5
Other malignancies	58	1	1	8	48	17.2
Total	241	16	42	42	141	41.4

During the treatment, routine blood examinations were carried out once or twice a week. Hepatic and renal function tests and bone marrow examination were performed before, during, and after the treatment in some of the cases.

The results of therapy of solid malignant tumors were eveluated according to the criteria put forth by the Second National Symposium on Cancer Research in China, held in 1965 [2], and those obtained leukemia according to the National Hematological Congress in China held in 1964 [3].

Results and Discussion

1. Clinical Response

As seen in Table 1, a total of 241 patients analyzed showed an overall objective response in 100 cases (41.4%). It is noted also that in patients who had an effective result, an average of 500 mg mecaphane was usually required in the course of 10 days.

In the present series, the best results were observed in patients with chronic granulocytic leukemia. Of the 40 patients treated, 37 showed remission (92.5%). Among them, complete remission had occurred in ten, with remission periods varying from 6–36 months. The period of remission was over 6 months in two cases, over 12 months in three, and over 18 months in five patients (average duration 15.6 months). Partial remission was noted in 23 and improvement in four patients. The average period of remission of the 37 effective cases was 8.6 months. Ten patients developed terminal blastic crisis during or after the treatment. The relationship between the development of terminal blastic crisis and mecaphane treatment is as yet unclear.

Five of the 17 patients with acute leukemia obtained only minor responses with very short duration, usually less than 1 month.

In 55 cases of malignant lymphoma, good results were observed in Hodgkin's disease. Seventeen of the 25 cases (68%) with Hodgkin's disease had good responses. Of these, three attained complete remission, ten partial remission, and four improvement only. The remissions lasted over 6 months 5 cases, 4 cases for 45 months, 75 months, 12 years (died with other disease), and 12 years (still alive) respectively. However, the remission period for nine of the 19 cases of lymphosarcoma (47.3%) did not exceed 3 months. Only two of the 11 patients with reticulum cell sarcoma showed any slight response. Two of the five patients with seminoma had good responses to mecaphane. The periods of complete remission were 6 and 57 months, respectively. In the five patients with ovarian cancer two had objective improvements, with remission periods of 2 and 10 months, respectively. In 117 patients with other kinds of cancer, responses of various degree were noted in 25. Among these patients, two patients with breast cancer and one with retroperitoneal anaplastic carcinoma had complete remission for 7.9 months, 10 months, and 14 months, respectively. In the present series, there were eight cases of metastatic cancer of bone; after treatment two of these patients had recalcification of the oesteolytic lesions with remission of 9 years and 5 months, respectively, and the other five patients experienced marked reduction of pain do spite persistence of the bone lesion. Therefore, it seems that further trials of this drug in the management of cases with bony metastases are warranted.

2. Toxicity

Leukopenia was observed in 81 cases (33.6%). Gastrointestinal reactions were present in 68 cases (28.2%). Thrombocytopenia was noted in 31 patients (12.8%), seven of whom showed subcutaneous or submucosal bleeding (2.9%). Other toxic manifesta-

tions, such as stomatitis (six cases, 2.4%), skin eruption (six cases, 2.4%), and jaundice (two cases, 0.8%), were mild and rare. According to our observations, mecaphane had a comparatively marked depressive effect on the white blood cell count, as one-third of the patients developed leukopenia. The incidence of leukopenia seemed to be related to the daily dosage of the drug, since in cases with white cell counts below 1,000/mm^3 the daily dosage was mostly over 75 mg. Consequently an

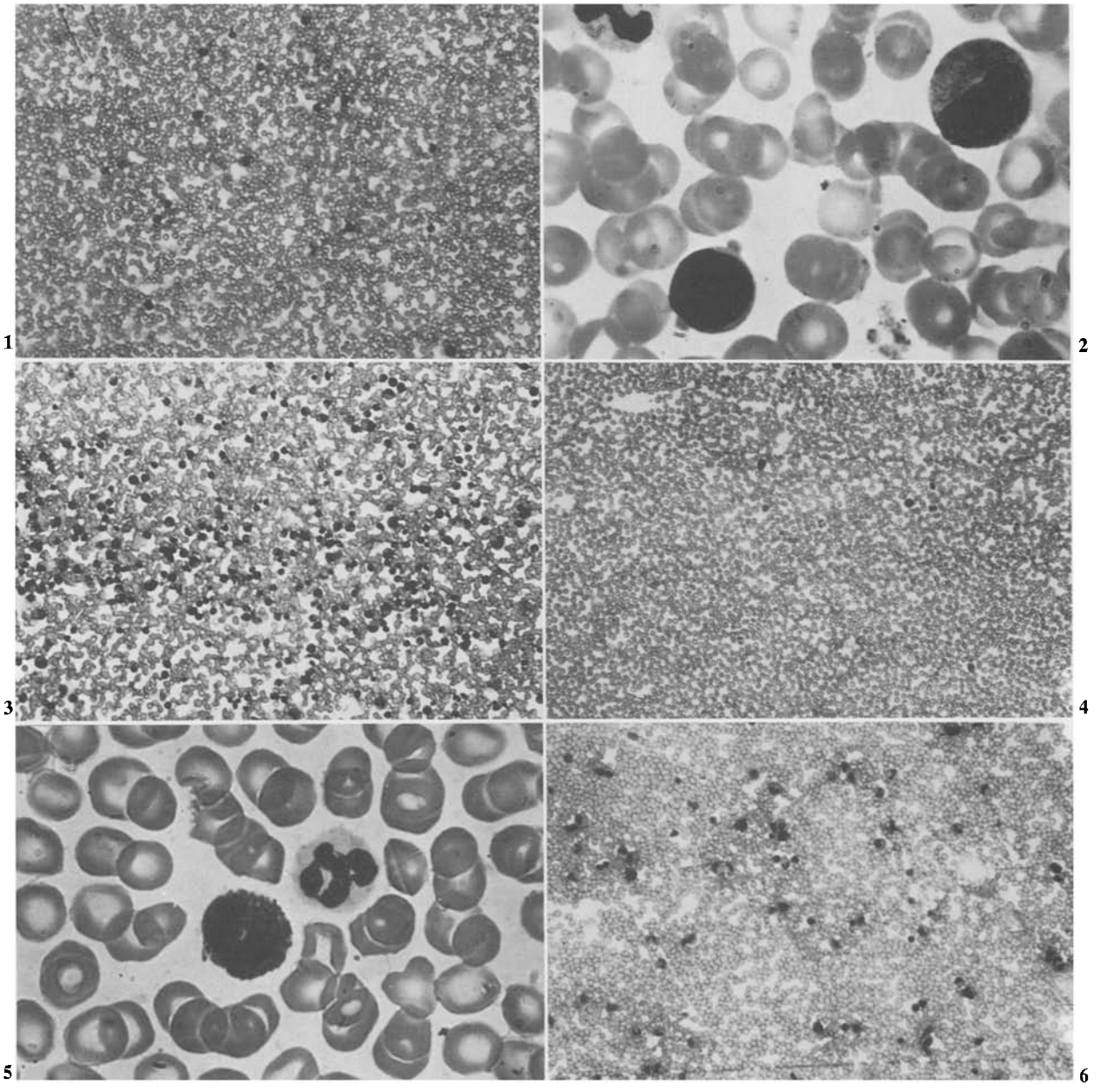


Fig. 1. Case 1: Chronic myelogenic leukemia before mecaphane treatment. Blood smear (× 400)

Fig. 2. Case 1: Before treatment. Blood smear (× 1,000)

Fig. 3. Case 1: Before treatment. Bone marrow smear (× 400)

Fig. 4. Case 1: After treatment. Blood smear (× 400)

Fig. 5. Case 1: After treatment. Blood smear (× 1,000)

Fig. 6. Case 1: After treatment. Bone marrow smear (× 400)

initial dose of 25–50 mg daily is recommended. There were two deaths in our series which could be attributed to the toxicity of mecaphane; these patients died of gastrointestinal bleeding and severe infection subsequent to marked bone marrow depression. In addition, it is note worthy that there were 11 patients who developed leukopenia as late as 6–30 days after discontinuation of the drug. This might possibly be due to a delayed depressive effect of mecaphane upon the bone marrow. The low white cell count usually returned to a normal level within 6–45 days (average 14 days) after discontinuation of the drug.

Undesirable effects on the gastrointestinal tract, such as anorexia, nausea, vomiting, and diarrhea, were usually mild and transient, and nearly all could be alleviated by the concomitant administration of sodium bicarbonate without diminishing the therapeutic effect of mecaphane. In some cases liver and kidney function tests were performed before, during, and after the treatment. No marked changes that could be attributed to mecaphane were observed.

Illustrative Cases

Case 1. A 38-year-old woman was admitted to our hospital in April 1964 with the chief complaint of a 'mass' on the left upper abdomen for the previous 6 months. Laboratory examinations showed RBC, 3.5 million/mm^3; Hgb, 10.2 mg and platelets, 102,000/mm^3; white blood cell count 152,000/mm^3, with myeloblasts 2%, premyelocytes 4%, myelocytes 22%, and metamyelocytes 10% (Figs. 1–3). Physical examination revealed an enlarged spleen, which was palpable 15 cm below the left costal margin. Mecaphane treatment was started with 25 mg T.I.D. Two weeks later the white cell count dropped to 37,200/mm^3, and the dosage of mecaphane was therefore reduced to 25 mg twice daily. Two days later the white cell count dropped further to 12,500/mm^3, when the dose was reduced to 25 mg per day. Four days later, after 21 days of mecaphane treatment, the white cell count dropped to 5,050/mm^3, with myelocytes 3%, metamyelocytes 3%; RBC 4.5 million/mm^3; Hgb, 12 g and platelets 240,000/mm^3; there was shrinkage of the spleen and it was palpable 7.4 cm below the costal margin. The total mecaphane dose was 1,100 mg. Only 2 weeks later, however, the white cell count rose again to 46,400/mm^3, with premyelocytes 1%, myelocytes 7%, and metamyelocytes 9%. A further course of mecaphane was then given. Fortunately, the response was as good as before. Two weeks later, the white cell count dropped to the normal range, without any

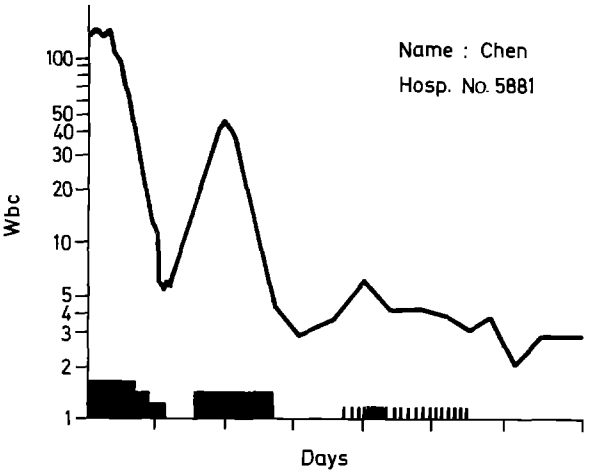


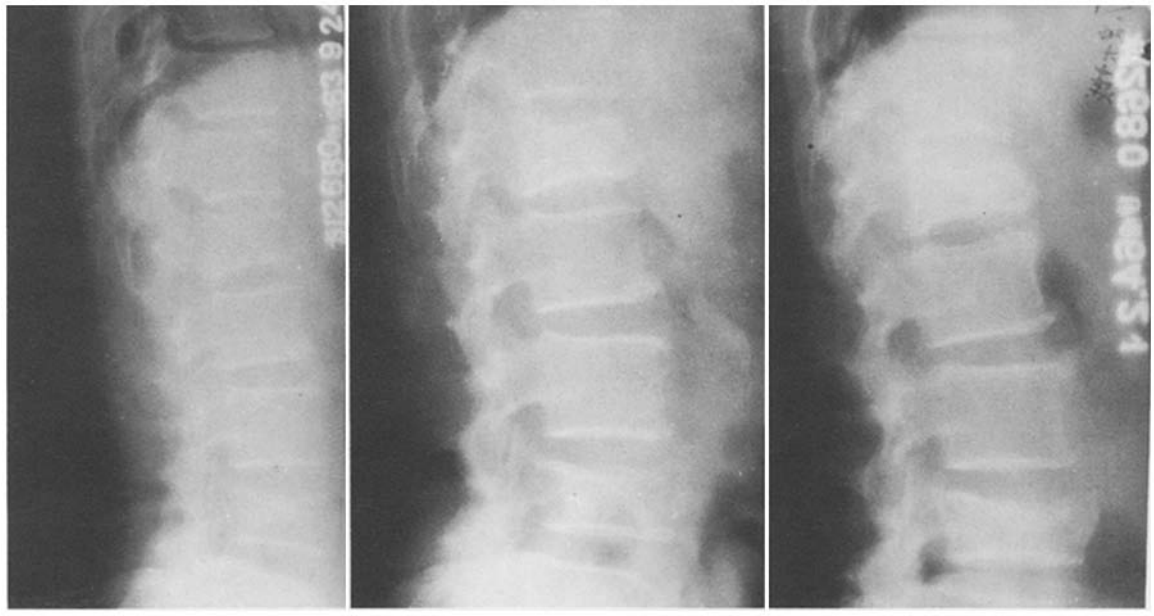
Fig. 7. Case 1: Relationship between mecaphane dosage and white cell count

immature white cells in the peripheral blood, and bone marrow slides also showed a normal picture (Figs. 4–6). A maintenance dose of mecaphane 25 mg every other day or twice weekly was continued for a long time. The patient was living and still without any evidence of disease 20 months later.

Fig. 7 shows the relationship between mecaphane dosage and white blood cell count.

Case 2. A 25-year-old woman was admitted to our hospital in January 1963 with Hodgkin's disease of the ileocecal region. Many enlarged mesenteral lymph nodes were discovered during exploratory laparotomy for a mistaken diagnosis of appendicitis. G.I. series revealed marked induration of the ileum wall. There was a cord-like mass about 8 × 3 × 3 cm in the right lower abdomen and there were enlarged inguinal lymphnodes on each side. Treatment was started with mecaphane 25 mg daily. When the total dose of this drug reached 540 mg the mass in the right lower abdomen was no longer palpable, but the inguinal lymph nodes remained the same. The enlarge lymph nodes did not disappear until the total dose reached 1,200 mg. Meanwhile all symptoms disappeared. Then a maintenance dose of mecaphane, 25 mg every other day, twice weekly or weekly (according to the white blood cell count) was continued for a long time. On follow-up at 29 months the patient was still alive and had already returned to work, after a total dose of 4,600 mg mecaphane. At the last follow-up in December 1975 she still alive without any evidence of disease.

Case 3. A 43-year-old man was admitted to hospital in July 1963 with the chief complaint of enlarged liver. He had an past history of an enlarged testis, which



8 9 10

Fig. 8. Case 4: Cancer of bone metastasis before treatment. X-ray revealed L_1 and L_4 had osteolytic destruction

Fig. 9. Case 4: During mecaphane treatment. The destructive bone lesions were slightly recalcified. Lumbago was relieved

Fig. 10. After mecaphane treatment. The destructive bone lesions had been affected by more recalcification

was over 9 × 7 × 7 cm in size; in February 1962 he had undergone a left orchiectomy and pathological examination proved that a seminoma had caused the enlargement. Postoperative radiation to the whole abdomen was given for 49 days, with a total tumor dose of 1,800 rad. Physical examination revealed that the liver was palpable 5 cm below the costal margin and 7 cm below the xiphoid process. Biochemical data showed AKP 33 u and LDH 1414 u, while radioactive isotope scanning and ultrasonic detection revealed liver metastasis. He then received mecaphane treatment with 25 mg daily. When the total dose of mecaphane reached 440 mg the liver had shrunk markedly and was no longer palpable. AKP had dropped to 15.3 u, LDH to 416 u. The ultrasonic scan did not show any abnormal wave. More than 1,295 mg mecaphane was given within 6 months. When medication was stopped, the patient's liver became enlarged again. The course of mecaphane was repeated and his enlarged liver ceased to increase in size. As soon as the medication was stopped the liver gradually enlarged again. Owing to a low white blood cell count chemotherapy was stopped, so after a good remission lasting about 1 year he was then subjected to radiotherapy. When followed up in August 1966 he was still alive and in good health.

Case 4. A 73-year-old man was admitted to hospital in August 1963 with the chief complaint of lumbago for 2 months. X-ray examination revealed osteolytic destruction in L_1 and L_4 (Fig. 8). The primary lesion was unknown. Treatment was started with mecaphane 25 mg daily. One week later he felt a marked decrease of his lumbago and after 2 weeks he was up and about without any pain. After the total dose reached 625 mg this patient received a maintenance course of mecaphane, 25 mg every other day for a long time. Five months later the follow-up X-ray film revealed recalcification of the osteolytic lesion (Figs. 9 and 10). Finally, the patient died of gastric cancer 6 months later.

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