

the malignant cases multiple metastases were verified at the time of surgery. Homovanillic acid determination was by a modified fluorometric assay (Sato, 1965). As shown in the Table, the only finding of abnormality was a slightly increased homovanillic acid in one of the malignant cases.

It may certainly be concluded that the absence of elevated homovanillic acid does not rule out the possibility of a malignant tumour. Contrariwise, the presence of an increased urinary homovanillic acid does not necessarily indicate malignancy, though available data suggest this finding may be more common in malignant than in benign cases.

REFERENCES

- Page, L. B., and Jacoby, G. A. (1964). *Medicine (Baltimore)*, **43**, 379.
 Robinson, R., Smith, P., and Whittaker, S. R. F. (1964). *Brit. med. J.*, **1**, 1422.
 Ruthven, C. R. J., and Sandler, M. (1964). *Analyt. Biochem.*, **8**, 282.
 Sankoff, I., and Sourkes, T. L. (1963). *Canad. J. Biochem.*, **41**, 1381.
 Sato, T. L. (1965). *J. Lab. clin. Med.*, **66**, 517.
 Weil-Malherbe, H. (1956). *Lancet*, **2**, 282.

Preliminary Communications

Natulan (Procarbazine) Combined with Radiotherapy in Management of Inoperable Malignant Melanoma

Brit. med. J., 1965, **2**, 1473-1474

Natulan (N-isopropyl-alpha-(2-methylhydrazino)-p-toluamide hydrochloride) (procarbazine) is a benzyl-methyl hydrazine derivative with cytotoxic effect. It is rapidly metabolized *in vivo* with formation of the azo-compound through dehydrogenation.

The mechanism by which the cytotoxic effect is exerted has been claimed to be due to the formation of O and OH radicals. Berneis, Kofler, Bollag, Kaiser, and Langemann (1963), in their *in vitro* studies with Natulan under aerobic conditions, noticed a decrease in the viscosity of aqueous deoxyribonucleic acid solutions and explained this phenomenon by the formation of hydrogen peroxide by autoxidation. They pointed out that if Natulan is added immediately after irradiation of deoxyribonucleic acid the radiation effect is potentiated. It therefore seemed desirable to study the combined action of Natulan and ionizing radiation in patients with malignant tumours resistant to radiation therapy. Good results were obtained with this combination in treating malignant mesothelioma (Falkson and Jacobs, 1964; Falkson, de Villiers, and Falkson, 1965).

Todd (1965) reported improvement in two out of six cases of melanomatosis treated with Natulan. We have observed objective improvement in six out of ten cases of inoperable malignant melanoma treated with combined Natulan and radiotherapy (see Table).

CASE 1

A 52-year-old man presented with two satellite lesions near an operation scar over the sacrum. At the start of treatment with Natulan he had bilateral inguinal lymphadenopathy; on the left the glands measured 5 by 2 cm., and on the right 4 by 3 cm. There was also an enlarged lymph node in the right axilla. Three other distal metastases were also present—on the right leg, the left buttock, and the left posterior chest wall. He had lost 15 lb. (6.8 kg.) in weight. His general condition was good and he was able to carry out normal activities.

His first lesion had appeared 18 months previously over the sacral area. After surgery to this primary skin lesion he remained asymptomatic for more than a year.

All measurable tumour regressed after one month's treatment with Natulan; only a 1-cm. node remained palpable in the left inguinal area. The duration of remission has been 16 months.

CASE 2

A 38-year-old woman presented with an enormous pericardial effusion and cardiac tamponade. Malignant melanoma cells were found in the fluid, and a neck-gland biopsy confirmed the diagnosis of malignant melanoma. The primary site could not be determined. Other clinical findings at the start of treatment with Natulan were oedema pedis and ascites. She was very ill and bedridden.

Summary of Treatment

Case No.	Dosage of Natulan in mg.	Concomitant Radiotherapy	Lowest W.B.C./c.mm.
1	90,100 in 556 days	Telecobalt to both inguinal areas, each field 13 × 13 cm. Skin dose: 1,300 r in 13 days to each field	4,000
2	26,550 in 149 days	Telecobalt: anterior chest 13 × 13 cm., 1,500 r in 5 days. 15 × 15 cm. left supraclavicular and infraclavicular area, 1,000 r in 5 days. 15 × 15 cm. anterior chest, 1,000 r in 5 days	700
3	7,800 in 22 days	Telecobalt to abdomen, 17 × 17 cm., 500 r in 5 days	6,600
4	34,100 in 321 days	Telecobalt over sinus, 4 × 5 cm., 3,000 r in 2 weeks	2,700
5	38,350 in 282 days	Deep x-ray therapy: 1st 5 days, over lesions in front of ear, 2,000 r in 5 days. 4th month of treatment with Natulan: 7 × 5 cm. field over lesions right side of neck, 2,000 r in 5 days. 7th month of treatment with Natulan: 10 × 15 cm. field right side of head, 4,100 r in 4 weeks	2,300 3,200
6	19,400 in 262 days	None	3,200
7	14,050 in 146 days	Telecobalt to right breast, including chest wall from sternum to mid-axillary line. 250 r/day, to a total of 4,000 r	1,000
8	12,700 in 94 days	Telecobalt: 2 opposing fields 11 × 9 cm. over upper mediastinum, 4,300 r in 3 weeks. At same time: 17 × 11 cm. field to left supraclavicular and axillary area, 4,300 r	2,700
9	17,250 in 132 days	Deep x-ray therapy: 10 × 15 cm. left medial thigh, 2,000 r in 2 weeks. 3 months later: 10 × 10 cm. left inguinal area, 2,000 r in 2 weeks. 2.5 cm. circle left ankle, 4,800 r in 1 week	6,900
10	3,350 in 20 days	Deep x-ray therapy, 2 opposing fields 15 × 7 cm. over thoracic vertebra and mediastinum, 2,000 r in 2 weeks	6,900

Five days before the start of Natulan a pericardial paracentesis was done and 1,000 ml. of fluid was removed. Two days after the start of Natulan another 1,000 ml. of fluid was removed, followed 13 days later by 1,500 ml., and in 133 days by 1,500 ml. She improved sufficiently to walk about and go on holiday. The remission lasted for three months. The patient died 151 days after the beginning of treatment.

CASE 3

A 51-year-old woman had a history of local excision of a malignant melanoma from the right shoulder, which resulted in a symptom-free period of eight months. The lesion then recurred and was removed by broad excision; she was now readmitted with abdominal distension. The ascites was repeatedly tapped and bloody

fluid was removed. The duration of the disease from the start of the first lesion was 14 months. She died 23 days after Natulan was begun.

CASE 4

A man aged 57 was admitted for the removal of a polypoid protrusion from the nasal sinus. The histological diagnosis was malignant melanoma. He had had the polyp for five months. His general condition was good and he was able to carry on normal activities. Treatment with Natulan and telecobalt resulted in complete disappearance of measurable lesions, and he continued in remission 10 months after the start of treatment. He is now on maintenance therapy with Natulan.

CASE 5

A 67-year-old woman presented with multiple skin metastases on the right side of the face, as well as right-sided facial paralysis. The duration of the disease was 16 months. The previous treatment consisted of surgery (which resulted in three months' remission), intra-arterial triethylene-glycol diglycidyl ether, radiotherapy, and cyclophosphamide, none of which brought any favourable response. At this stage she was unable to work, but was living at home and supplying most of her personal needs.

The lesions, which had grown despite previous radiotherapy, responded well to combined radiotherapy and Natulan. When a new lesion appeared on the neck four months after treatment with Natulan was started, it also responded to radiotherapy. Four months later pulmonary metastases developed and grew rapidly. She died 10 months after the start of Natulan. Her remission had lasted for seven months.

CASE 6

A 32-year-old man who had had local surgery to the foot, plus block-dissection of the inguinal lymph node four years previously, was admitted with a recurrence of lesions on the foot as well as bilateral lung metastases. He was unable to work, but was living at home and dealing with most of his personal needs. The lesions have remained unchanged for nine months since the start of treatment with Natulan.

CASE 7

In this 40-year-old woman the following findings were made at the start of treatment with Natulan. A mass, 4 by 3 cm., in the right breast, and lymphadenopathy in the right anterior axilla: the history dated back four years. She had previously had local excision of a malignant melanoma from the medial aspect of the right lower leg, followed by removal of the inguinal glands. She was free of symptoms for more than a year after surgery. When the lesion recurred in the right inguinal area it was removed surgically, followed by post-operative radiotherapy. This again resulted in an asymptomatic period for more than a year. Three weeks before the start of Natulan a metastatic lesion was removed from the right intercostal space.

After three weeks of treatment with Natulan and radiotherapy the mass had disappeared. The patient has been in complete remission for four months and is still taking a maintenance dosage of Natulan.

CASE 8

A 74-year-old woman had had a broad local excision of a malignant melanoma in the left scapular region two years previously. She was readmitted with massive enlargement of lymph nodes in the left axilla, the left supraclavicular area, and mediastinum. She was unable to care for personal needs and complained of severe pain.

Treatment resulted in rapid decrease in size of all measurable lesions. The lesions became more than 60% smaller, then generalized metastases developed and the patient died four months after the start of Natulan. Her remission had lasted for two months.

CASE 9

A 58-year-old woman was admitted with metastases in the skin of the upper medial thigh, below the scar of a block-dissection. She complained of pain in the whole of the left leg, was unable to work, but was living at home and caring for most of her personal needs. The previous treatment was surgery on three occasions—first, excision of a lesion from the medial side of the left ankle, resulting in a symptomatic period of eight months; secondly, a block-dissection of the left groin, which again resulted in eight months' remission; the third surgical procedure (resection of a lesion from the left calf) had no favourable result. The lesions improved after Natulan and radiotherapy, but new lesions continued to appear on the left leg.

CASE 10

A 77-year-old woman had enucleation of the right eye for a malignant melanoma; she remained asymptomatic for more than a year. When lesions recurred exenteration of the right eye was performed.

When admitted for Natulan treatment she was bedridden, and severely ill with a paraplegia as a result of medullary metastases. She also had mediastinal metastases and a bedsore. She died one month after the start of treatment.

COMMENT

We feel that these results support the contention that Natulan (procarbazine) can sensitize tumour tissue to the damaging effects of ionizing radiations. We believe the response as well as the quality and duration of improvement to be significant, and feel that further investigations in the treatment of malignant melanoma with combined Natulan and radiotherapy are warranted.

GEOFFREY FALKSON,* M.D., M.B., CH.B.,
M.MED.(INT.).

P. C. DE VILLIERS, M.B., CH.B.

H. C. FALKSON, M.B., CH.B.

T. FICHARDT, M.D., D.SC., M.MED.(RAD.T.),
D.M.R.E., F.F.R.(R.C.S.I.).

Department of Radiotherapy, Pretoria General Hospital,
Pretoria, South Africa.

* In receipt of a grant from the National Cancer Association of South Africa.

REFERENCES

- Berneis, K., Kofler, M., Bollag, W., Kaiser, A., and Langemann, A. (1963). *Experientia (Basel)*, **19**, 132.
Falkson, G., and Jacobs, E. L. (1964). *Med. Proc.*, **10**, 452.
— de Villiers, P. C., and Falkson, H. C. (1965). *Cancer Chemother. Rep.*, **46**, 7.
Todd, I. D. H. (1965). *Brit. med. J.*, **1**, 628.