PROCARBAZINE (NATULAN) IN THE TREATMENT OF HODGKIN'S DISEASE AND OTHER LYMPHOMAS

S. K. SPIES,* M.MED. (INT.) (PRET.) AND H. W. SNYMAN,† M.D. (GRON.), *Department of Internal Medicine, University of Pretoria*

Procarbazine (Natulan; Ro 4-6467; N-isopropyl-a-[2-methyl-hydrazino]-p-toluamide hydrochloride) is a synthetic compound which belongs to a new class of anti-tumour agent, the methyl hydrazine derivatives. Bollag and Grunberg[1] reported on the inhibitory effects of these agents on various transplantable rodent tumours. Clinical studies have been under way since 1962. It has generally been concluded that these compounds are of 'considerable' value in the treatment of Hodgkin's disease.[2-5] Beneficial effects have also been noted in other lymphomas,[3-5] malignant melanoma[5] and oat-cell carcinoma of the lung.[6]

The mode of action of this group of compounds has not yet been completely elucidated. The effect has been compared to the indirect effect of ionizing radiation. In cytological studies 1-methyl-2-benzyl hydrazine has been shown to inhibit mitosis by prolonging the interphase of cell division.[7] This evidently results from a disintegratory effect (depolymerization) of the methyl hydrazine on desoxyribonucleic acid (DNA), the main constituent of the chromosomes.[8]

MATERIALS AND METHODS

Twenty-eight patients with malignant lymphoma were selected for therapy with Natulan. The diagnoses were as follows: Hodgkin's disease in 21; reticulum-cell sarcoma in 5; lymphosarcoma in 1; and mycosis fungoides in 1. All patients had features of systemic disease and chemotherapy was a clear indication. Only 6 cases had not received previous treatment; for the rest, all had been treated by radiotherapy and/or at least 1 cytotoxic agent; 5 cases had been resistant to all available methods of treatment, i.e. radiotherapy, one or more of the alkylating agents and vinblastine sulphate.

Histological confirmation of disease was obtained in every case before treatment was started.

The patients' ages varied between 12 and 70 years; the majority being males between the ages of 21 and 50 (Table I).

TABLE I. AGE AND SEX DISTRIBUTION IN 28 CASES OF LYMPHOMA

Total	*Sex*		*Age*		*Over 50*
	M	*F*	*0–20*	*21–50*	
28	21	7	4	18	6

The drug (supplied in capsules containing 50 mg. and ampoules containing 250 mg.) was administered intravenously in isotonic saline (1 case only) or orally (27 cases). In most patients a dose of 300 mg. per day was aimed at and, depending on the white cell count, maintenance dosage was instituted at 50 - 150 mg./day. Total dosage varied between 1·25 and 60·4 G. In the initial stages blood counts were obtained twice a week, but after stabilization these were done as infrequently as once every 4 - 6 weeks. Treatment on an outpatient basis presented no special problems.

RESULTS OF TREATMENT

Of the 28 patients treated, 19 showed 'worth-while' clinical improvement while receiving the drug. Treatment was considered successful only in the presence of measurable objective improvement, i.e. regression of 50% or more of demonstrable pathological lymph nodes or a measurable reduction in size of an enlarged liver or spleen, lasting for 1 month or longer. Non-specific and subjective improvement, such as a fall in sedimentation rate, relief from itching, etc., although valuable as complementary signs of remission, alone were not considered an indication of successful treatment.

TABLE II. SUMMARY OF CASES TREATED WITH NATULAN

Neoplasms	*Total*	*No. improved*
Hodgkin's disease	21	16
Reticulum-cell sarcoma	5	2
Lymphosarcoma	1	0
Mycosis fungoides	1	1
	28	19

The response symbols used in individual cases in Table III are those suggested by Karnofsky,[9] viz.:

Category O:
- O - O : No clinically useful effect on course of disease.
- O - O : Disease progresses; no subjective benefit.
- O - A*: Disease progresses; subjective benefit without favourable objective changes.
- O - B*: Favourable objective changes without subjective benefit.
- O - C : Subjective benefit and favourable objective changes in measurable criteria, but of less than 1 month's duration; then the disease progresses.

Category I: Clinical benefit with favourable objective changes in all measurable criteria of disease.
- I - A*: Distinct subjective benefit with favourable objective changes in all measurable criteria for 1 month or more.
- I - B*: Objective regression of all palpable or measurable neoplastic disease for 1 month or more in a relatively asymptomatic patient who is able to carry on his usual activities without undue difficulty.
- I - C : Complete relief of symptoms, if any, and regression of all manifestations resulting from the active disease for 1 year or more.

Category II: Interruption or slowing in progression of disease without definite evidence of subjective or objective improvement.

*Superscript is time in months of duration of response.

Hodgkin's disease. Of 21 cases, 16 improved with regression of enlarged lymph nodes, reduction in the size of an enlarged liver or spleen, disappearance of fever or itching and improvement of general condition as evidenced by weight gain, improvement of appetite, etc. In one patient there was marked improvement of bilateral pleural effusions within 3 weeks of commencing treatment. This patient incidentally had previously responded poorly to cyclophosphamide.

Reticulum-cell sarcoma. There was definite improvement in 2 patients with diffuse skin lesions, although in one of these remission lasted for only about 3 months. The other was still in good remission, at the time of writing, 8 months after treatment was started.

Lymphosarcoma. In one patient treated, no objective response was seen.

*Member and †Head of the Cancer Chemotherapy Section. supported by a grant from the National Cancer Association of South Africa.

TABLE III. SUMMARY OF PATIENTS TREATED WITH NATULAN

Patient			Diagnosis and duration of disease	Dominant clinical features	PS*	Dosage		Lowest WBC count	Previous treatment	Response† category	Comment
No.	Sex	Age				Period (days)	Total (mg.)				
1	M	19	Hodgkin's disease 4 yrs.	Fever, anaemia, lymphadenopathy and splenomegaly	B	491	60,400	2,600	Cyclophosphamide. Radiotherapy	I–C	Complete resolution of all lesions. Drug temporarily stopped because of agranulocytosis. Still in remission after 18 months on maintenance treatment
2	F	63	Hodgkin's disease 6 mths.	Bilateral pleural effusions. Anaemia. Diffuse lymphadenopathy. Hepatosplenomegaly	C	31	5,250	4,500	Trisethylene-iminobenzo-quinone (Trenimon). Cyclophosphamide	I–A[1]	Marked improvement of dyspnoea as effusions cleared. Other lesions regressed partially. Then developed paraplegia and died 3 months later
3	M	45	Hodgkin's disease 2½ yrs.	Mesenterial lymphadenopathy (large epigastric mass). Hepatosplenomegaly	B	25	7,100	5,600	Radiotherapy. Cyclophosphamide	O–O	No improvement noted. Vinblastine sulphate given subsequently, likewise had no effect
4	M	16	Hodgkin's disease 4 mths.	Diffuse lymphadenopathy. Hepatomegaly. Fever	B	55	9,400	8,100	None	I–A[2]	Very good response. Still in remission on maintenance treatment
5	M	45	Lymphosarcoma 5 yrs.	Diffuse lymphadenopathy. Hepatosplenomegaly	B	41	8,850	14,000	Cyclophosphamide. Radiotherapy. Trisethylene-iminobenzo-quinone (Trenimon)	O–A	Subjective improvement only. Responded well to subsequent radiotherapy
6	M	12	Hodgkin's disease 5 mths.	Hepatosplenomegaly. Enlarged glands neck and right axillary region	B	50	7,350	4,200	None	I–A[2]	Complete disappearance of lymphadenopathy and marked shrinkage of spleen. Still on maintenance treatment
7	M	42	Hodgkin's disease 7 mths.	Hepatomegaly. Skin and rectal infiltration	C	502	52,950	3,000	None	I–C	Complete remission. Still on maintenance treatment
8	M	45	Hodgkin's disease 3 mths.	Hepatosplenomegaly. Generalized lymphadenopathy. Severe oedema of penis and scrotum due to lymphatic obstruction	B	43	11,700	2,600	None	I–A[1]	Complete remission. Treatment temporarily stopped because of leucopenia
9	F	21	Hodgkin's disease 7 yrs.	Progressive anaemia for 4 years. Also fever, hepatomegaly and mild jaundice	C	71	5,150	2,900	Cyclophosphamide. Radiotherapy	I–A[3]	Steady rise in haemoglobin. Fever subsided. Jaundice cleared as hepatomegaly regressed. Treatment temporarily stopped because of leucopenia. PS improved from C to A. Still in remission on maintenance treatment
10	M	42	Reticulum cell sarcoma 2 mths.	Skin lesions	B	138	16,800	3,300	Radiotherapy (to enlarged lymph glands)	I–A[5]	All lesions markedly improved
11	M	45	Mycosis fungoides 13 mths.	Diffuse skin lesions (ulcerating lesions on feet)	B	159	32,300	800	Radiotherapy	I–A[3]	Marked improvement of lesions on feet. Remission lasted for 3 months
12	M	29	Hodgkin's disease 3½ yrs.	Severe backache. Splenomegaly. Cervical lymphadenopathy	B	56	16,300	3,500	Cyclophosphamide. Chlorambucil	O–A	Some improvement in backache occurred but measurable lesion did not regress. Responded favourably to subsequent administration of vinblastine sulphate
13	F	70	Hodgkin's disease 9 mths.	Nodular lesions on skin of face and scalp (histologically proved). Cervical lymphadenopathy. Splenomegaly. Cachexia	C	29	9,000	5,200	Radiotherapy	I–A[1]	All lesions regressed but neurological side-effects (disorientation and drowsiness) precluded further treatment
14	M	35	Hodgkin's disease 1 mth.	Jaundice and anaemia. Hepatic and peritoneal infiltration (laparotomy)	B	98	8,900	1,900	None	I–A[7]	Good response. Jaundice disappeared. Steady rise in haemoglobin. No palpable lesions in abdomen. Still in remission
15	M	36	Hodgkin's disease 14 mths.	Fever. Hepatomegaly. Lymphadenopathy. Lung infiltration	B	119	24,150	3,100	Cyclophosphamide. Radiotherapy	I–A[4]	Measurable lesions improved, but this lasted for only 4 months. Thereafter steady downhill course and patient died 31 days after treatment was stopped
16	F	31	Hodgkin's disease 2½ yrs.	Lung infiltration. Lymphadenopathy neck and mediastinal glands	C	123	12,650	2,900	Cyclophosphamide. Radiotherapy. Vinblastine sulphate	I–A[2]	Lung infiltration cleared and performance status improved to A. Treatment stopped because of side-effects (leucopenia, nausea and vomiting)
17	M	17	Reticulum cell sarcoma 1 mth.	Anaemia. Massive enlargement cervical and mediastinal lymph glands. Hepatomegaly	C	11	1,800	10,000	None	O–O	No effect noted. Died 22 days after start of treatment
18	F	23	Hodgkin's disease 4 yrs.	Anaemia. Lung infiltration. Lymphadenopathy	B	71	8,500	3,300	Radiotherapy. Cyclophosphamide. Vinblastine sulphate	I–A[3]	Lung infiltration cleared. Performance status improved to A. Remission lasted for 3 months only
19	M	61	Hodgkin's disease 17 mths.	Fever. Hepatosplenomegaly. Severe backache, generalized lymphadenopathy	B	322	29,750	2,300	Nitrogen mustard. Vinblastine sulphate. Radiotherapy	I–A[10]	Backache much better. Regression of all lesions
20	M	55	Reticulum cell sarcoma 4½ yrs.	Abdominal pain and haematemesis. Severe weight loss. Anaemia. Inguinal lymphadenopathy	C	41	7,350	3,700	Cyclophosphamide	O–A	Complained of severe nausea and vomiting. Treatment did not affect steady downhill course. Abdominal pain improved

TABLE III. (CONT'D.)

Patient No.	Sex	Age	Diagnosis and duration of disease	Dominant clinical features	PS*	Dosage Period (days)	Dosage Total (mg.)	Lowest WBC count	Previous treatment	Response† category	Comment
21	F	65	Hodgkin's disease ±6 mths.	Skin infiltration face and scalp. Lymphadenopathy. Infiltration lungs	C	38	10,950	800	Radiotherapy	O–O	Treatment stopped because of side-effects. Severe leucopenia occurred as well as thrombocytopenia and neurological symptoms (disorientation ++)
22	M	47	Hodgkin's disease 8 mths.	Liver infiltration. Marked splenomegaly. Lymphadenopathy	A	9	1,250	1,600	Radiotherapy	O–C	Lesions regressed, but treatment had to be stopped because of leucopenia and drowsiness. Then hepatomegaly and lung infiltration occurred
23	M	55	Hodgkin's disease 10 mths.	Lymphadenopathy (cervical and mediastinal). Anaemia	B	34	10,200	3,200	Cyclophosphamide. Vinblastine sulphate. Radiotherapy	I–A[1]	Improvement of lymphadenopathy noted but disease relapsed before white cells recovered completely
24	M	46	Hodgkin's disease 2 yrs.	Jaundice. Abdominal distension. Hepatomegaly	D	15	5,375 (IV)	7,800	Cyclophosphamide. Vinblastine sulphate	O–O	Treatment stopped because of severe drowsiness and disorientation. No improvement noted
25	M	29	Hodgkin's disease 6 yrs.	Lymphadenopathy. Backache. Pleuritic pain	B	452	67,200	2,900	Cyclophosphamide. Vinblastine sulphate. Radiotherapy	I–C	Complete remission which lasted for 15 months before disease relapsed
26	M	51	Reticulum cell sarcoma 2 yrs.	Pulmonary infiltration. Diffuse skin lesions	C	105	22,500	2,400	Cyclophosphamide. Chromomycin-A3. Radiotherapy	I–A[3]	Disappearance of skin lesions for 3 months before exacerbation of disease occurred
27	F	52	Reticulum cell sarcoma 1 yr.	Pulmonary metastases. Large mass of glands left side of neck. Anaemia	B	10	2,000	7,200	Cyclophosphamide. Radiotherapy ^{32}P	O–O	Died suddenly 18 days after start of treatment. No effect noted
28	M	41	Hodgkin's disease 2 yrs.	Splenomegaly. Diffuse lymphadenopathy. Recurrent pulmonary infections	B	107	20,500	2,300	Radiotherapy. Chlorambucil	I–A[3]	Marked improvement of all lesions. Still in complete remission

*PS: Performance status defined by the following symbols: A = normal activity; B = unable to work, but living at home and caring for most personal needs; C = Unable to care for personal needs; D = very ill, bedridden or paraplegic patient.
†Response category as suggested by Karnofsky.[9] See text.

Mycosis fungoides. The only patient treated showed well-marked improvement, although this lasted for only 3 months before resistance to cytostatics developed.

Previous Treatment

It is interesting to note the response with regard to previous treatment (Table IV). Of the 19 cases that improved no less than 14 had received previous treatment in the form of radiotherapy and/or at least one cytotoxic agent; 5 of these were resistant to both alkylating agents and the vinca alkaloids.

TABLE IV. EFFECT OF PREVIOUS TREATMENT (PT) ON RESPONSE TO METHYL HYDRAZINE IN 25 CASES OF LYMPHOMA

Neoplasms	Cases improved Total	Cases improved PT	Failures Total	Failures PT
Hodgkin's disease ..	16	11	5	4
Reticulum-cell sarcoma ..	2	2	1	1
Lymphosarcoma ..	0	0	1	1
Mycosis fungoides ..	1	1	0	0
Total	19	14	7	6

Toxicity (Table V)

TABLE V. SIDE-EFFECTS IN 28 PATIENTS TREATED WITH NATULAN

	No. of cases
1. Severe nausea and vomiting	5
2. Leucopenia (WBC lower than 4,000/cu.mm.)	19
3. Thrombocytopenia	2
4. Evidence of haemolysis	0
5. 'Flush syndrome'	2
6. Dry mouth	1
7. Skin rash	0
8. Epilation	0
9. Hyperglycaemia	0
10. Neurological symptoms (euphoria, psychosis, delirium, drowsiness, disorientation, coma)	4

1. *Gastro-intestinal.* Nausea and vomiting are the most frequent complications of treatment with this drug and occur in the majority of patients if the initial dosage is stepped up too rapidly. These side-effects can however be avoided almost completely by a slow increase of the daily dose, starting with 50 mg. a day and increasing by 50 mg. increments up to 300 mg./day. A dose of more than 300 mg. per day is hardly ever necessary.

In this series severe nausea and vomiting occurred in 5 cases, but in only 2 of these was it necessary to stop administration of the drug.

Judicious administration of anti-emetics, i.e. prochlorperazine, 1 - 2 mg./day, may be of considerable help in controlling nausea.

2. *Haematological.* Bone-marrow depression is a frequent complication of the administration of methyl hydrazine derivatives. In this series leucopenia (WBC less than 4,000) was observed in 19 cases. The lowest white cell count encountered was 800/cu.mm.; this occurred after a total dose of only 10·9 G. Frequent mention is made of the fact that leucopenia commonly occurs after the administration of approximately 6 - 8 G, unless damage has already been caused by previous X-ray treatment or administration of other cytostatics. In this respect it is of note that one patient in this series showed no signs of bone-marrow depression whatsoever, even after the administration of 53·25 G of Natulan.

There did not seem to be a selective effect on polymorphs or other cells of the white cell series.

The red cell count and haemoglobin were on the whole unaffected by treatment.

Thrombocytopenia occurred in 2 cases, but this was not accompanied by purpura or haemorrhagic tendencies and disappeared after reduction in dosage or cessation of treatment.

As this drug is a hydrazine derivative, mention is made of haemolysis occurring during treatment with Natulan.[6] We have not observed overt haemolysis, although regular reticulocyte counts and other tests for occult haemolysis were not performed as a routine.

3. *Neurological symptoms* were observed in 4 patients, in 2 of these after the concurrent administration of phenothiazines. One patient, an elderly woman, became extremely restless and slightly confused, but this disappeared after withdrawal of phenothiazines and other sedatives. The other patient became very drowsy and would certainly have gone into a coma if we had not been aware of this disturbing side-effect.

4. *Other side-effects*. A 'flush syndrome' occurred in 2 patients after the intake of alcohol. One patient complained of a very dry mouth, but this improved after a reduction in the dose of Natulan.

Skin rashes, alopecia and hyperglycaemia were not encountered in any of the cases treated in this series.

DISCUSSION

Procarbazine has a very definite place in the treatment of Hodgkin's disease. It has already been mentioned by others[3,5] that the frequency of obtaining a remission with this drug is approximately the same as for vinblastine and the alkylating agents in common use. This applies also for the quality and duration of remissions and, if any, remissions obtained with procarbazine last longer than those seen with vinblastine.[3]

In view of these findings it seems quite logical that 'the order in which these agents are used in the treatment of Hodgkin's disease is likely to be governed by considerations such as ease of administration and freedom from side-effects'.[5] Oral administration is a distinct advantage over vinblastine, whereas alopecia, so frequently observed with cyclophosphamide (the alkylating agent mostly employed by us), has not yet been described in cases treated with procarbazine. Mathé *et al.*[3] also mention the fact that treatment with the drug is easier than with another effective alkylating agent—trisethylene melamine. Apart from troublesome nausea in some cases, patients have generally tolerated the drug very well.

We have been particularly impressed by the frequency of remissions in cases resistant to other cytostatics—notably the absence of 'cross-resistance' with the alkylating agents and vinblastine.

In the management of localized Hodgkin's disease radiotherapy remains the treatment of choice and neither procarbazine nor any other chemotherapeutic agent should replace it in these cases. Other diseases of the lymphoma-group respond more variably but even in these cases gratifying results may be obtained.

SUMMARY

Procarbazine (Natulan, Ro 4-6467), a new methyl hydrazine derivative, has been used in the treatment of advanced malignant lymphomas, with particularly good effect in cases of Hodgkin's disease. 'Worth-while' clinical improvement was noted in 16 of 21 cases with Hodgkin's disease, 2 of 5 patients with reticulum-cell sarcoma and in 1 case of mycosis fungoides.

An impressive feature has been the frequency of remissions in cases previously treated and resistant to radiotherapy, the alkylating agents and/or vinblastine.

It is concluded that Natulan should be considered in the primary treatment of generalized Hodgkin's disease, and that it is definitely indicated in cases resistant to other available agents, including radiotherapy.

The Natulan (Ro 4-6467) used in this study was kindly supplied by Roche Products Ltd., Johannesburg.

REFERENCES

1. Bollag, W. and Grunberg, E. (1963): Experientia (Basel), **19**, 130.
2. d'Alessandri, A., Keel, H. J., Bollag, W. and Martz, G. (1963): Schweiz. med. Wschr., **29**, 1018.
3. Mathé, G., Schweisguth, O., Schneider, M., Amiel, J. L., Berumen, L., Brule, G., Cattan, A. and Schwarzenberg, L. (1963): Lancet, **2**, 1077.
4. Sicher, K. and Backhouse, T. W. (1963): *Ibid.*, **2**, 1278.
5. Todd, I. D. H. (1965): Brit. Med. J., **1**, 628.
6. Martz, G., d'Alessandri, A., Keel, H. J. and Bollag, W. (1963): Cancer Chemother. Rep., **33**, 5.
7. Rutishauer, A. and Bollag, W. (1963): Experientia (Basel), **19**, 131.
8. Berneis, K., Kofler, M., Bollag, W., Kaiser, A. and Langemann, A. (1963): *Ibid.*, **19**, 132.
9. Karnofsky, D. A. (1961): Clin. Pharmacol. Ther., **2**, 709.