Procarbazine (Natulan; Ro 4-6467: N-isopropyl-a-[2-methyl-hydrazino]-p-toluidine hydrochloride) is a synthetic compound which belongs to a new class of antitumour agent, the methyl hydrazine derivatives. Bollag and Grunberg 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. Beneficial effects have also been noted in other lymphomas and oat-cell carcinoma of the lung.

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. This evidently results from a disintegratory effect (depolymerization) of the methyl hydrazine on deoxyribonucleic acid (DNA), the main constituent of the chromosomes.

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 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

<table>
<thead>
<tr>
<th>Category</th>
<th>Neoplasms</th>
<th>Hodgkin’s disease</th>
<th>Reticulum-cell sarcoma</th>
<th>Lymphosarcoma</th>
<th>Mycosis fungoides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>21</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No. improved</td>
<td>16</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**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

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

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.

The response symbols used in individual cases in Table III are those suggested by Karnofsky, viz.: Category 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.
TABLE III. SUMMARY OF PATIENTS TREATED WITH NATULAN

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis and duration of disease</th>
<th>Dominant clinical features</th>
<th>Dosage</th>
<th>Lowest WBC count</th>
<th>Previous treatment</th>
<th>Response category</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>F</td>
<td>63</td>
<td>Hodgkin’s disease 6 mths.</td>
<td>Bilateral pleural effusion, anaemia, diffuse lymphadenopathy, Hepatosplenomegaly</td>
<td>C 31</td>
<td>5,250</td>
<td>4,500</td>
<td>Triethylene-imino-benzio-quinoine (Trenimon), Cyclophosphamide</td>
<td>I-A</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>45</td>
<td>Hodgkin’s disease 2 yrs.</td>
<td>Mesenterial lymphadenopathy (large engorged mass), Hepatosplenomegaly</td>
<td>B 25</td>
<td>7,100</td>
<td>5,600</td>
<td>Radiotherapy, Cyclophosphamide</td>
<td>O-O</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>42</td>
<td>Hodgkin’s disease 7 mths.</td>
<td>Hepatospleno-megaly, Skin and regional lymphadenopathy</td>
<td>C 302</td>
<td>52,950</td>
<td>3,000</td>
<td>None</td>
<td>I-C</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>45</td>
<td>Hodgkin’s disease 3 mths.</td>
<td>Hepatospleno-megaly, Generalized lymphadenopathy, Severe oedema of penis and scrotum due to lymphatic obstruction</td>
<td>B 43</td>
<td>11,700</td>
<td>2,600</td>
<td>None</td>
<td>I-A</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>42</td>
<td>Reticulum cell sarcoma 2 mths.</td>
<td>Skin lesions</td>
<td>B 138</td>
<td>16,800</td>
<td>3,300</td>
<td>Radiotherapy (to enlarged lymph glands)</td>
<td>I-A</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>45</td>
<td>Mycosis fungoides 13 mths.</td>
<td>Diffuse skin lesions (ulcerating lesions on feet), Severe backache, Splenomegaly, Cervical lymphadenopathy</td>
<td>B 159</td>
<td>32,300</td>
<td>800</td>
<td>Radiotherapy</td>
<td>I-A</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>70</td>
<td>Hodgkin’s disease 9 mths.</td>
<td>Nodular lesions on skin of face and scalp (histologically proved), Cervical lymphadenopathy, Splenomegaly, Cachexia</td>
<td>C 29</td>
<td>9,000</td>
<td>5,200</td>
<td>Radiotherapy</td>
<td>I-A</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>36</td>
<td>Hodgkin’s disease 14 mths.</td>
<td>Fever, Hepatomegaly, Lymphadenopathy, Lung infiltration</td>
<td>B 119</td>
<td>24,150</td>
<td>3,100</td>
<td>Cyclophosphamide, Radiotherapy</td>
<td>I-A</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>17</td>
<td>Reticulum cell sarcoma 1 mth.</td>
<td>Anaemia, Massive enlargement cervical and mediastinal lymph glands, Hepatomegaly</td>
<td>C 11</td>
<td>1,800</td>
<td>10,000</td>
<td>None</td>
<td>O-O</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>55</td>
<td>Reticulum cell sarcoma 4 yrs.</td>
<td></td>
<td>C 41</td>
<td>7,350</td>
<td>3,700</td>
<td>Cyclophosphamide</td>
<td>O-A</td>
</tr>
</tbody>
</table>
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.

Toxicity (Table V)

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.

10. Neurological symptoms (euphoria, psychosis, delirium, drowsiness, disorientation, coma)...... 4
As this drug is a hydrazine derivative, mention is made of haemolysis occurring during treatment with Natulan. If 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 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.

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. 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. 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**


**VENOUS LIGATION FOR SEPTIC PULMONARY EMBOLI FOLLOWING SUPPURATIVE PELVIC THROMBOPHLEBITIS**

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Ligation of the inferior vena cava, for pyaemic metastatic abscesses due to septic emboli from suppurative pelvic thrombophlebitis, is not a new procedure. Despite the control and eradication of pyaemia in obstetrical and gynaecological practice, there exists a small number of cases where ligation of the venous drainage from the pelvis may be a life-saving measure.

In cases of puerperal pyaemia, Trendelenburg and Miller demonstrated the presence of palpable thrombosed veins at operation. They ligated these individual veins proximal to the thrombus. Uninvolved branches of the inferior vena cava and ovarian veins were not ligated. As their mortality rates were only slightly better than those following expectant therapy, this method fell into disrepute.

However, it was Collins et al. who showed that surgical ligation could be highly successful in cases of pyaemia, even though medical treatment had failed. This they achieved, by completely interrupting the venous return from the uterus and ovaries by ligating the inferior vena cava and the ovarian vessels, irrespective of the site of the venous thrombophlebitis.

Five cases of septic pulmonary emboli following suppurative pelvic thrombosis are presented. Conservative treatment had failed, and ligation of the inferior vena cava was considerably beneficial and a life-saving procedure.