Clinical Experience with Vincaleukoblastine Sulfate in the Treatment of 11 Patients with Hodgkin’s Disease

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ABSTRACT

Eleven patients with established Hodgkin’s disease were treated with vinblastine sulfate. Each patient received from 0.15 to 0.20 mg./kg. of body weight intravenously in 10 divided doses over a five-hour period as initial therapy. All had received one or more of the more established forms of treatment before being given vinblastine. The response to treatment with vinblastine was excellent in three patients, good in one, and poor in three; there was no response in four. The longest remission was 15 months. Two of the patients were father and son. The side effects of treatment in this series included alopecia, leukopenia, and septicemia.

VINCA ROSEA Linn is a flowering plant commonly known as the periwinkle. It has been used empirically in primitive medical practice in many parts of the world, e.g. to control hemorrhage and scurvy in Brazil,1 to suppress milk flow in Europe,2 to treat diabetic ulcer in the British West Indies,3 and as an oral hypoglycemic agent in the Philippines.4 In 1958 Noble, Beer and Cutts5 working at the University of Western Ontario, isolated a new alkaloid from this plant which they named vincaleukoblastine (VLB). VLB is a dimeric alkaloid; its empirical formula is C_{46}H_{66}O_{6}N_{4} but its actual structural formula is not known. It was observed that this material produced a striking leukopenia in normal rats used in the bioassay of this compound. Subsequently, in 1959, both Noble, Beer and Cutts5 at Western Ontario and Johnson et al.6 at the Lilly Research Laboratories were able to demonstrate suppression of P-1534 acute lymphocytic leukemia in DBA/2 mice following administration of VLB. These workers proposed that its site of action may be in the metabolic pathways from glutamic acid to urea, and from glutamic acid to the citric acid cycle. In vitro, the growth-inhibitory effect of VLB could be prevented by glutamic acid, coenzyme A, aspartic acid, and alpha keto-glutaric acid, as well as by citrulline, arginine and ornithine.

The effects of VLB on cells have been studied both in vivo by Cutts7 and in vitro by Cardinali, Cardinali and Blair.8 Their experiments indicate that VLB is a metaphase poison. Arrest of normal bone marrow cells in metaphase in DBA/2 mice was maximal in six hours, and in DBA/2 mice with L1210 leukemia (asctic form) in 20 hours; both series of animals received 1 mg./kg. of VLB. VLB in doses of 0.25 mg./kg. per day has been shown to prolong the life of rats inoculated with experimental tumors, while twice this dose (0.5 mg./kg./day) did not prolong life to the same extent and, in addition, produced marked loss of weight and diarrhea.

Because of the clinical manifestations of loss of deep tendon reflexes and leg pain following treatment with this agent, Woodhall et al.9 studied the effects of VLB on the sciatic nerve of dogs. They applied pledgets soaked in Ringer’s solution containing VLB, following which demyelination and axis-cylinder fragmentation was demonstrated at the sites where the VLB-Ringer’s solution had been applied.

From 1960 up to the present the drug has been used in the treatment of a variety of malignant disorders.10-15 It soon became apparent that VLB had a greater effect on Hodgkin’s disease than on other tumors.

At St. Michael’s Hospital, Toronto, VLB has been used in the treatment of 11 patients with Hodgkin’s disease. All had received other forms of therapy prior to receiving VLB. The diagnosis, established by biopsy in all, was Hodgkin’s disease, granuloma type, except in one case of Hodgkin’s sarcoma.

All patients were treated initially with a dosage of VLB varying between 0.15 and 0.20 mg./kg. of

SOMMAIRE

Onze malades atteints de maladie de Hodgkin ont été traités au sulfate de vincaleukoblastine. Comme traitement d’attaque, chaque malade reçut une dose variant de 0.15 à 0.20 mg./kg. de poids corporel, en 10 injections intraveineuses séparées. Avant d’être traités avec ce produit, tous avaient reçu au moins un mode de traitement classique. Trois malades réagirent de manière excellente au sulfate de vincaleukoblastine, alors que la réaction fut bonne chez un malade, médiocre chez trois autres et nulle chez les quatre derniers. La plus longue rémission enregistrée fut de 15 mois. Deux des malades étaient le père et le fils. Parmi les réactions secondaires au traitement, figuraient alopecie, leucopénie et septicémie.
body weight. The drug was administered in the following manner. The estimated dosage of lyophilized VLB powder was dissolved in 10 c.c. of distilled water in a 10-c.c. syringe. The needle used to dilute the material was removed and replaced with a No. 25 hypodermic needle in order to minimize the loss of VLB from the syringe by leakage during the initial multiple-injection schedule. An intravenous infusion of 5% glucose in distilled water was set up to run at approximately 60 drops per minute. One cubic centimetre of the diluted VLB was injected into the side arm of the intravenous tubing at intervals of one-half hour until all 10 c.c. had been given.

**CASE REPORTS**

**CASE 1.—**The presence of Hodgkin's granuloma was recognized in a 27-year-old man in 1951 following an inguinal node biopsy. In 1948, in Austria, another inguinal node had been removed for examination but the patient did not know the result of this biopsy.

For nine years, from 1951 onward, he received periodic therapy, first with radiation and later with nitrogen mustard. By March 1960 he was seriously ill. A course of cyclophosphamide and prednisone did not help. He was feeble, tired and cachectic, and was running a daily fever to 103°F. Cervical nodes were enlarged. Abdominal nodes were palpable. The liver was felt 5 cm. below the costal margin. By April 30, 1960, his hemoglobin had fallen to 7.4 g. %. The red cells were hypochromic. Obstructive jaundice, hypoproteinemia and edema had developed. The patient was nauseated and vomiting. His weight was 135 lb.

On that date 12.5 mg. of VLB was administered into the tubing of an intravenous drip in 10 divided doses at half-hour intervals (0.2 mg./kg. body weight). His temperature fell abruptly to normal four days later, and the deep tendon reflexes at both the knees and the ankles were absent. The plantar responses, touch, vibration and position senses were normal. Seven days after VLB administration, his edema cleared but by the end of that year was again quite ill. His hemoglobin was then 8.2 g. %; his weight was 122 lb. and his spleen was palpable 4 cm. below the left costal margin. From March 1961 on, this man received 10 mg. VLB intravenously every two weeks. (The initial dose was 0.18 mg./kg./body weight.) At the onset of this treatment he complained of increasing shortness of breath, and a chest radiograph showed a large number of round densities in both lung fields. However, except for a bout of pneumonia at the end of March, he steadily improved. His appetite improved and his shortness of breath decreased. The hemoglobin rose to 10 g. %. All lymph nodes decreased in size, as did the spleen and pulmonary nodules. The patient remained well for seven months before entering hospital with fever, wasting and neck rigidity. At that time his blood and cerebrospinal fluid grew *Listeria monocytogenes*. The patient died on October 1, 1962. Postmortem examination showed widespread Hodgkin's sarcoma and, as well, focal brain abscesses and hemorrhages.

**CASE 3.—**A 29-year-old Englishman, 6 ft. 3 in. tall and 240 lb. in weight, became almost explosively ill with high fever, malaise, unusually profuse sweating, splenomegaly, and a mass of large glands on the right side of his neck. Biopsy of the neck glands revealed Hodgkin's granuloma. A cautious course of radiation produced only an incomplete remission and 14 weeks after the onset of the symptoms, he was given VLB 20 mg. intravenously in 10 divided doses at half-hour intervals (0.19 mg./kg. of body weight). The patient had a very marked improvement in well-being. There was reduction in spleen size, a fall in temperature and a fall in the leukocyte count from 9000 to 2000 cells/c.mm. Symptoms recurred in three weeks. Further therapy with prednisone, blood transfusions, radiation and nitrogen mustard produced no benefit and the patient ran a steady downhill course, dying of widespread Hodgkin's disease eight and one-half months after the onset of symptoms.

**CASE 4.—**A 62-year-old French-Canadian woman was febrile for an entire year before her inguinal glands became enlarged. Biopsy of these glands revealed Hodgkin's granuloma. She responded well to three courses of nitrogen mustard. By February 1962, the patient was again pale, anemic and tired. Her hemoglobin was 6.4 g. %. Twenty-five months after the onset of symptoms, 10 mg. of VLB was given intravenously in 10 divided doses at half-hour intervals. Beta methasone (Celestone) 0.5 mg. three times a day was begun at the same time. VLB 10 mg. in single doses was given every two weeks for the next six months. Her appetite returned, the fever fell, her weight increased, and her hemoglobin rose to 10.3 g. %. The spleen became smaller and the patient led a useful life at home for six months before again entering hospital and dying of widespread Hodgkin's disease. The remission was not complete in that the patient always tired easily and had some degree of anemia.

**CASE 5.—**A 55-year-old Irish woman had hepatosplenomegaly and enlarged lymph nodes in multiple
areas when first seen in 1960. A biopsy of her inguinal nodes revealed Hodgkin's granuloma. Her response to two courses of nitrogen mustard was incomplete. Twenty-five months after the onset of symptoms the patient received three injections of VLB, each of 10 mg., at intervals of two weeks. This treatment produced no response. The patient continued a slow but steady downhill course. Pancytopenia developed and persisted. Further cautious attempts at treatment with nitrogen mustard and VLB were made, with no response. The patient became increasingly cachectic and died.

Case 6.—A 60-year-old Italian man developed large right cervical nodes in 1953. Biopsy of these revealed Hodgkin's granuloma. He had one course of radiation therapy in 1954. He remained well except for several admissions to hospital with hypochromic microcytic anemia attributed to a large hiatus hernia. Otherwise, he was well until early 1962, when he again became pale and tired. His hemoglobin was 8.2 g. %. There were no hypochromic red cells on that occasion. The stools were negative for occult blood. His peripheral blood showed polychromasia and some spherocytosis. Both direct and indirect Coombs tests were positive and the spleen was felt a hand's breadth below the left costal margin. On May 31, 1962, he was given 10 mg. of VLB in 10 divided doses at half-hour intervals and two weeks later he received another 10 mg. in a single intravenous injection in 10 c.c. distilled water. His temperature fell to normal the day after the first injection. The spleen decreased in size and was no longer palpable. The hemoglobin rose to 7.1 g. %, and his weight increased from 135 to 165 lb. The autoimmune hemolytic anemia from which he suffered had partly responded to steroid therapy, and the steroids had been discontinued; this anemia now disappeared and did not recur. The indirect Coombs test became negative but the direct Coombs test remained positive. The patient remained free of symptoms for almost 15 months before readmission was necessary. At that time he received injections of 12.5 mg. of VLB two weeks apart and responded. His hemolytic anemia did not recur. To date, this second remission has lasted five months.

Case 7.—A 27-year-old Englishman developed enlarged lymph nodes in the posterior triangle of the neck on the right side in October 1957. Biopsy of these showed Hodgkin's granuloma. Over the next five years, two courses of radiation and three courses of nitrogen mustard were given. On December 7, 1962, 10 mg. VLB was given intravenously in 10 divided doses at half-hour intervals. A further 5 mg. was given as a single injection on December 31, 1962. The temperature fell, the spleen decreased in size, the white blood count fell from 9000 to 3000 per c.mm., and the hemoglobin rose from 6.4 to 8.3 g. %. However, this treatment was given only two weeks after a partial course of radiation. The improvement cannot be clearly attributed to VLB. Four weeks after the first dose, the patient again became ill and he steadily deteriorated and died.

Case 8.—A 40-year-old Irishman developed crampy abdominal pain in November 1962. A mass could be felt in the ileocecal region. On laparotomy on November 30, 1962, large masses of tumour were noted on the surface of the terminal ileum. Other retroperitoneal masses of tumour could also be felt. Nitrogen mustard was given in December 1962, with some improvement. During March 1962, the patient's bowel perforated at the site of a tumour and a shunting operation was carried out. On March 29, 1962, a left sixth cranial nerve palsy developed. On April 9, he was given 10 mg. of VLB intravenously in 10 divided doses at half-hour intervals. On April 12, a right seventh nerve palsy developed, followed shortly by a right sixth nerve palsy. Radiation treatment was administered, with some improvement. He survived in an unsatisfactory state of health until September 1963, when he developed paresis of both legs, and intractable diarrhea, and died. The radiation was given right after the VLB, and it is impossible to assess the effects of VLB in this case.

Case 9.—In November 1962, a 74-year-old man (the father of Case 2) developed weakness, fever, large glands in the left axilla and left groin, and also noted a persistent, aggravating, dry unproductive cough. He was admitted first in March 1963. Biopsy of a node confirmed the clinical impression of Hodgkin's disease. Radiographs of the chest showed diffuse infiltration of both lungs. A course of nitrogen mustard relieved the patient's cough and he felt somewhat better, but no objective change in his condition occurred. By late April the patient was again in hospital, and on April 29, 1963, 10 mg. of VLB was given. A mass of nodes in the right inguinal region melted away in the next 48 hours. Other nodes remained unchanged. The patient's general state did not improve. The white blood cell count fell from 19,000 to 3100 per c.mm. By May 10 the patient was very ill. Both his sputum and his stool grew hemolytic Staphylococcus aureus on culture. He died suddenly a few days later.

Case 10.—In April 1961, a 31-year-old male French Canadian first developed large nodes in the right posterior triangle of the neck. Biopsies of one of these showed only lymphadenitis. The remaining nodes then became smaller and disappeared, only to enlarge again a few weeks later. A second node was removed and the diagnosis of Hodgkin's granuloma was established. He received a course of radiation therapy and remained well until December 1962, when he was again admitted, complaining of weakness, sweating, and crampy abdominal pain. This pain required morphine for relief. He improved after a course of nitrogen mustard and returned home, but was readmitted to hospital a few weeks later. Abdominal pain was once more the most prominent symptom. On March 20, 1963, 10 mg. of VLB was given in 10 divided doses, intravenously, at half-hour intervals. A single intravenous dose of 10 mg. was given eight days later. His temperature fell to normal the day after the first dose. The abdominal pain decreased, and the patient seemed to improve for four weeks. Then his pain increased and ureteral obstruction developed. Radiation was administered to both flanks and the lower back over the period of July 11 to July 28, 1963. All his symptoms cleared and the patient has been at home and well since that time. VLB produced no really useful benefit for this patient.
Vincaleukoblastine produced a worthwhile remission in six of these 11 patients (Table I). In Case 3 the remission was very short. In Case 10 the chief benefit was relief of pain. In Cases 1, 2, 4 and 6 the remissions were quite long and compare favourably with the length of remissions obtained with other forms of therapy. The results in Case 4 are difficult to determine because the patient was on steroid therapy at the same time.

Case 1 is remarkable because of the spectacular degree of his remission. He recovered from a "terminal" cachectic state to have five and one-half months of useful life. Case 6 is remarkable because of the length of the remission (15 months) and because of the fact that the patient is now enjoying a second remission associated with reduction in the size of the spleen, a rise in hemoglobin and an increase in weight. Cases 2 and 9 are of interest in that they were father and son. The son died of his

### TABLE I

<table>
<thead>
<tr>
<th>Case and sex</th>
<th>Age and year of onset of disease</th>
<th>Duration of disease prior to VLB (months)</th>
<th>Other therapy prior to VLB</th>
<th>Date and dosage of first course of VLB</th>
<th>Date and remission duration attr. to VLB</th>
<th>Date of death or present status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. M</td>
<td>27 1948</td>
<td>144</td>
<td>R. N. M.</td>
<td>Apr./60 12.5*</td>
<td>Excellent 5½ months</td>
<td>26- 4-61</td>
</tr>
<tr>
<td>2. M</td>
<td>42 1959</td>
<td>24</td>
<td>R. N. M.</td>
<td>Mar./62 20.0</td>
<td>Excellent 7 months</td>
<td>10-12-62</td>
</tr>
<tr>
<td>3. M</td>
<td>29 1961</td>
<td>4</td>
<td>R. N. M.</td>
<td>June/61 20*</td>
<td>Poor 3 weeks</td>
<td>19-11-61</td>
</tr>
<tr>
<td>5. F</td>
<td>55 1990</td>
<td>25</td>
<td>N. M.</td>
<td>Feb./62 30</td>
<td>None</td>
<td>22-6-62</td>
</tr>
<tr>
<td>6. M</td>
<td>60 1953</td>
<td>108</td>
<td>R.</td>
<td>May/62 20</td>
<td>Excellent 15 months</td>
<td>Well</td>
</tr>
<tr>
<td>7. M</td>
<td>27 1957</td>
<td>60</td>
<td>R. N. M.</td>
<td>Dec./62 15</td>
<td>None</td>
<td>14- 4-63</td>
</tr>
<tr>
<td>8. M</td>
<td>40 1962</td>
<td>5</td>
<td>N. M.</td>
<td>Apr./63 10</td>
<td>None</td>
<td>6-10-63</td>
</tr>
<tr>
<td>9. M</td>
<td>74 1962</td>
<td>6</td>
<td>N. M.</td>
<td>Apr./63 20</td>
<td>Poor 1 month</td>
<td>Fair</td>
</tr>
<tr>
<td>10. M</td>
<td>31 1961</td>
<td>23</td>
<td>R. N. M.</td>
<td>Mar./63 20</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>11. F</td>
<td>77 1963</td>
<td>3</td>
<td>N. M.</td>
<td>Sept./63 20</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*Single dose only.

**Note:** Case 2 is the son of Case 9

- R. = Radiation.
- N. M. = Nitrogen mustard.
- C. = Cyclophosphamide.

### TABLE II—OBJECTIVE IMPROVEMENT

<table>
<thead>
<tr>
<th>Case</th>
<th>Spleen smaller</th>
<th>Lymph nodes smaller</th>
<th>Temperature reduced</th>
<th>Rise in Hb.</th>
<th>Weight gain</th>
<th>Loss of edema</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>5.9 g.</td>
<td>29 lb.</td>
<td>*</td>
<td>Lung densities smaller</td>
</tr>
<tr>
<td>2</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>1.8 g.</td>
<td>Marked sweating ceased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.6 g.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.0 g.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.0 g.</td>
<td>30 lb.</td>
<td></td>
<td>Hemolysis stopped; Coombs test became negative</td>
</tr>
<tr>
<td>6</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.0 g.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.0 g.</td>
<td></td>
<td>Abdominal pain decreased</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.0 g.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.0 g.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.0 g.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>3.0 g.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**DISCUSSION**

The details of this study are summarized in Tables I and II. The series included eight men and three women whose ages ranged from 27 to 77 years at the time of onset of their disease. For the purposes of this study, a remission was taken as the time between the administration of the initial dose of VLB and the date at which the patient again required admission to hospital because of Hodgkin's disease.

The objective changes following VLB are recorded in Table II. The most common change was a fall in temperature, noted in seven patients. This response usually occurred the day after the first dose of VLB had been given. The spleen became smaller in six patients, becoming impalpable in three. A rise in hemoglobin after VLB was recorded in five patients. An autoimmune hemolytic anemia disappeared following treatment in Case 6; direct

and indirect positive Coombs tests became negative in this patient at the same time.

Cases 3, 7 and 9 developed a leukopenia following VLB; in none of these three did the white blood count fall below 2000/0 e/mm. Even in these three patients the neutrophil was the predominant cell. One patient (Case 9) developed staphylococcal pneumonia and enteritis and died, but he was ill enough to develop these complications even before VLB was given.

**Canad. Med. Ass. J.**

mustard in the treatment of the more generalized forms of the disease. Neither VLB nor nitrogen mustard should be used before radiation when the disease is restricted to a local group or local groups of nodes with minimal evidence of systemic disease. When no evidence of generalized disease is present, surgical excision of a local node or group of nodes followed by radiation still provides the only hope of permanent cure. The side effects of VLB are no more severe than those of other chemotherapeutic agents. No patient in this series experienced any gastrointestinal symptoms after the administration of this agent.

The reason or reasons why VLB benefits patients with Hodgkin's disease more than those with other lymphomas are not known.

I wish to thank Dr. O. H. Warwick, formerly of the Princess Margaret Hospital, Toronto, for the VLB used in the initial treatment of Case 1, and for his help and advice regarding the mode of administration. My thanks are also due to Eli Lilly & Co. Ltd. for the VLB used in the remainder of the treatment of all 11 patients, and for data concerning VLB supplied at the outset of this study and during the time that the study was carried out. Thanks are extended to Mr. A. Smialowski for the preparation of the photographs of Tables I and II.

REFERENCES


PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE OCHSNER METHOD IN APPENDICITIS

A visit to the Ochsner clinic in Chicago convinced me that it is a mistake to be rash in operating, at sight, on many cases and that at times the statement "that the operation was too late" might be qualified by the addition "or the time for operation badly chosen".

In reporting two hundred consecutive cases of appendicitis without a death the points of interest are:
1. Sixty-four cases were not treated surgically during the acute attack.
2. One hundred and thirty-six were operative cases. Of these forty-nine were acute cases operated on as soon as they came under observation—twelve were pus cases of whom eight had an abscess drained only, and four had both abscess drainage and removal of appendix, while eighty-four were of the chronic type or were operated after the acute attack had well subsided.
3. Principles of treatment. The medical treatment if it can be called such was prohibition of food, physic, and generally of water. Lavage at times. Rest in bed. Mild heat locally. All cases seen in the first forty-eight hours were operated on at once if willing, a few were operated on the third day, but cases from the fourth to ninth days, were, especially if very ill, treated medically and a safer time waited for.

When one states that the cases were divided between country practice, private hospital, and city hospital work the Ochsner treatment can be commended as a safe and practical outline for guidance even under such varying conditions.—E. S. Hicks, Canad. Med. Ass. J., 5: 767, 1915.