Effect of Vincaleukoblastine on Metastatic Choriocarcinoma and Related Trophoblastic Tumors in Women

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SUMMARY

An alkaloid, Vincaleukoblastine, has suppressed tumor growth and activity in five of eight women with methotrexate-resistant, metastatic trophoblastic disease. In three of these patients the urinary gonadotropin excretion reached normal levels, and in two other patients there was a decrease in pulmonary metastases. Reversible toxic effects have included bone marrow depression with severe leukopenia, alopecia, and neurotoxicity.

We have previously described our observations on the chemotherapeutic effects of a folic acid antagonist, methotrexate, upon choriocarcinoma and related trophoblastic tumors in women (4-6). In these studies the development of drug resistance after initial response to methotrexate has been observed.

We have reported elsewhere (3) that Vincaleukoblastine, an alkaloid originally derived from *Vinca rosea* by Cutts, Beer, and Noble (1, 7), has a remarkable inhibitory effect upon the growth of human choriocarcinoma maintained in heterologous transplant in the hamster cheek pouch (2). We now wish to report initial studies on the clinical effect of Vincaleukoblastine1 in eight women with methotrexate-resistant trophoblastic tumors. The methods and criteria for evaluation of these effects have been previously detailed (4). The level of urinary excretion of gonadotropin has provided a quantitative index of the initial activity of the tumor and of the therapeutic response obtained.

MATERIALS AND METHODS

The Vincaleukoblastine sulfate (VLB) was supplied as a dry sterile powder. The amount to be injected was dissolved in 10-20 ml. of saline just prior to use and injected into the tubing of a rapidly running infusion of normal saline. These precautions were taken because the material proved locally irritating and extravasation was found to be very painful. However, actual thrombophlebitis was rarely observed. Successive courses were given only after complete subsidence of the toxic effects of a preceding course.

The salient clinical features of these eight cases and the results of treatment are presented in Table 1.

It is apparent from the behavior of the gonadotropin titers that in five cases the tumor proved sensitive to VLB. In three of these (Nos. 1, 3, and 6), the gonadotropin titers fell to within the normal range for ovariectomized women (3). The effect of VLB on the gonadotropin titer has been consistently noted 2-3 weeks after the course. None of these three patients had pulmonary metastases at the start of therapy. The response of the urinary gonadotropin levels to VLB in patient No. 1 is presented in Chart 1. This patient's titer has remained normal for the past 6 months.

Two patients, Nos. 2 and 7, have shown some regression in pulmonary metastases associated with a decrease in gonadotropin excretion.

In three patients (Nos. 4, 5, and 8) VLB has apparently not affected the course of the disease, although the drug has been given to tolerance.

The administration of VLB has invariably been associated with suppression of the bone marrow. The most notable effect is a profound leukopenia with almost complete disappearance of the polymorphonuclear leukocytes from the peripheral blood. In Chart 2, the lowest absolute

1 The Vincaleukoblastine used in these studies as well as the specific alkaloids derived therefrom were kindly furnished by Dr. Irving Johnson and Dr. G. H. Svoboda of the Eli Lilly Company, Lilly Research Laboratories, Indianapolis, Ind.

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granulocyte count has been plotted against the dose of VLB for each course of therapy. Although the tumor response varied widely after each 3-day course, at a total dose of 30 mg. of VLB severe granulocytopenia was uniformly noted.

The suppression of white blood cells was apparent within a few days following the initiation of therapy, and maximal suppression occurred 7–11 days after therapy. The platelet count decreased by 30–60 per cent in from 3 to 6 days after treatment. Reticulocytes were absent from the peripheral blood by 2–9 days after treatment. The data representing typically severe toxicity in patient No. 1 are charted in Chart 3. Complete recovery of all the bone marrow elements as manifested by the peripheral blood findings occurred within 3 weeks, and there has been neither evidence of cumulative toxicity with successive courses of treatment nor decreasing effects in the bone marrow.

VLB also produced a number of additional toxic side-effects. Five of the eight patients exhibited a partial or complete suppression of deep tendon reflexes associated with each course of therapy. Two patients complained of numbness and paresthesias in the fingers. These changes proved to be reversible.

In addition to these apparent neurotoxic effects, there was suggestive evidence of parasympatholytic action of the drug. All patients, during at least one course of therapy, experienced marked constipation for 3–11 days. Bowel sounds were present during this time. There was one episode of urinary retention. Six patients had bilateral pain and tenderness of the parotid glands, usually associated with marked dryness of

<table>
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<tr>
<th>Table 1</th>
<th>Response to Vincaleukoblastine in Methotrexate-Resistant Patients</th>
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<tr>
<td>Patient</td>
<td>Salient clinical features</td>
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<tr>
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<tr>
<td>1 W.F. 31</td>
<td>After 3 remissions in 3 years, rising titer</td>
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<tr>
<td>2 W.F. 19</td>
<td>After 3 mos.' remission with MTX, increasing titer and pulmonary metastases</td>
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<td>3 W.F. 22</td>
<td>Rising titer after 2 mos.' remission with MTX</td>
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<tr>
<td>4 W.F. 16</td>
<td>Rising titer and increasing lung metastases after 2 mos. with MTX</td>
</tr>
<tr>
<td>5 W.F. 35</td>
<td>Rising titer and persistent lung metastases after 3 mos.' MTX remission</td>
</tr>
<tr>
<td>6 W.F. 26</td>
<td>Titer rose after 5 mos.' remission with MTX</td>
</tr>
<tr>
<td>7 C.F. 28</td>
<td>After 4 mos.' remission with MTX, lung and CNS metastases persisted unchanged</td>
</tr>
<tr>
<td>8 C.F. 28</td>
<td>After 4 mos.' regression with MTX, advancing pulmonary and pelvic metastases</td>
</tr>
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*V.L.B. = Vincaleukoblastine sulfate; given in six divided doses, a.m. and p.m. of three consecutive days.
†Expressed as mouse uterine units excreted per 24 hours.
‡MTX = Methotrexate therapy.
the mouth. Two patients developed sinus tachycardia in the absence of fever or other apparent cause. The electrocardiogram in one of these cases showed S-T depression, and in the other a prolonged Q-T interval was noted. The electrocardiogram of both of these patients subsequently reverted to normal.

Two patients developed total alopecia, and all had increased hair loss following VLB therapy. There was no other evidence of dermal response, and only one patient developed a small oral ulcer covered with grayish exudate.

Severe mental depression was uniformly noted during the toxic phase, and this was more marked than would be accounted for by the respective general clinical status of each of the patients. These mental changes usually occurred at the height of the systemic reaction and quickly disappeared as the general malaise receded.

Fever occurred in six patients during the leukopenic phase, and this was accompanied by a positive blood culture in two of them. Hence, a febrile response was interpreted as evidence of infection, and vigorous antibiotic therapy was instituted.

These observations provide quantitative and qualitative evidence that an alkaloid, VLB, possesses antitumor activity in women with metastatic trophoblastic disease. The full range of effectiveness of this agent, which represents a new chemical class of oncolytic drug, remains to be determined by further clinical trials. However, it should be emphasized that the effects reported here have been observed in patients who had become clearly resistant to methotrexate. Our prior efforts in the treatment of such methotrexate-resistant patients with a variety of
chemotherapeutic agents have been uniformly unsuccessful.

ACKNOWLEDGMENTS

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