A Comparative Study of 1-(2-Chloroethyl)-3-cyclohexyl-1-nitroso-urea (NSC 79037) and Imidazole Carboxamide (NSC 45388) with Vincristine (NSC 67574) in the Palliation of Disseminated Malignant Melanoma

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SUMMARY

The effects of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) (NSC 79037) were compared to those of a combination of imidazole carboxamide (NSC 45388) and vincristine (NSC 67574) as treatment in 37 patients with disseminated malignant melanoma.

Objective remissions were observed in 4 of 18 patients who received the combination as primary therapy compared to 1 of 19 remissions after CCNU. Subsequent use of the alternate regimen resulted in 1 clinical remission in 11 cases with the combination and no remissions with CCNU among 7 cases. Thus, secondary therapy with either regimen was ineffective.

The toxicity observed with imidazole carboxamide and vincristine included hematological depression with leukocyte counts below 3,000/cu mm in 9 of 29 patients and platelet counts less than 100,000/cu mm in 8 of 29 patients, as compared to 8 of 26 patients with leukocytes below 3,000 and 13 of 26 patients with platelets less than 100,000 utilizing CCNU. Nausea and vomiting occurred in all patients who received the combination and in 17 of 26 patients who received CCNU. Parenteral fluids were not necessary in either group. Neurological toxicity including paresthesias and loss of deep tendon reflexes occurred in 9 of 29 patients after the combination therapy but was not observed with CCNU therapy. Moderate to severe hair loss occurred in 7 of 29 patients who received the combination therapy but did not occur with CCNU. One patient developed a papular dermatological reaction after imidazole carboxamide and vincristine.

INTRODUCTION

In a previous publication, we reported the clinical activity of 3 agents: imidazole carboxamide (NSC 45388), phenylalanine mustard (NSC 8806), and hydroxyurea (NSC 32065) in patients with disseminated malignant melanoma (1). Objective remissions were observed only with the use of imidazole carboxamide; 2 of 23 patients had clinical benefit. As an extension of the previous study, the present report concerns the evaluation of CCNU (NSC 79037) and of imidazole carboxamide with vincristine (NSC 67574) in a group of 37 patients with Stage IV (disseminated) malignant melanoma.

CCNU is one of a group of nitrosoureas that is lipid soluble, can be advantageously administered p.o., and has shown activity in the melanoma B-16 tumor system (2). CCNU is related to BCNU which, in earlier clinical trials, has shown activity against human malignant melanoma (3).

Experience previously reported with combination chemotherapy with the 3 drugs, imidazole carboxamide, vincristine, and BCNU (NSC 409962), has resulted in 12 of 27 (44%) remissions reported by Luce et al. (4). Moon (5) reported 9 of 20 regressions utilizing a combination of BCNU and vincristine; the series included 3 patients with visceral-dominant disease.

The present study was designed to observe the clinical effects of 2 agents, imidazole carboxamide and vincristine, as a combination program previously not reported and a new nitrosourea, CCNU, in patients with disseminated malignant melanoma.

MATERIALS AND METHODS

Thirty-seven patients in our series had disseminated malignant melanoma. Thirty-five patients had the skin as the site of origin of their malignant melanoma, whereas 2 patients had choroidal primary lesions. Prior to randomization and treatment, the patients were classified as to the presence or absence of visceral disease. Thirty-four of the 37 patients had visceral-dominant disease; this characterization of severity of disease is essential in reporting therapeutic effectiveness of chemotherapy in patients with malignant melanoma.

None of the patients had had chemotherapy with any of the drugs utilized in this study, and only 5 had had previous anticancer chemotherapy of any kind; all 5 had had alkylating drugs.

All patients were maintaining a reasonable state of nutrition, and none had received radiation therapy either in an area or in an amount that would compromise bone marrow.
function. A frank discussion with the patient concerning the limitations and possible toxicity of the proposed investigative chemotherapeutic study was held prior to treatment. Every patient had a hematological status that did not preclude vigorous cytotoxic chemotherapy, that is, a leukocyte count greater than 4,000/cu mm and a platelet count greater than 100,000/cu mm.

After classification as to the presence or absence of visceral disease, the patients were randomly assigned to 1 of 2 treatment programs, either CCNU or a combination of imidazole carboxamide with vincristine.

Imidazole carboxamide was given at a dose of 300 to 350 mg/sq m (mean 315 mg/sq m) on each of 5 successive days by rapid i.v. infusion. The vincristine in this program was administered i.v. at a dose of 1.4 mg/sq m (not to exceed 2 mg) on the 1st and 5th days of the treatment schedule. CCNU was given as a p.o. dose of 130 mg/sq m on 1 day.

After treatment, the leukocyte count and the platelet count were obtained twice weekly for 3 weeks on the patients who received imidazole carboxamide and vincristine and for 6 weeks on the patients who received CCNU. All of the patients were reevaluated at 6 weeks, and therapy was repeated, if toxicity permitted.

Objective improvement was defined as a measurable reduction in the size of the indicator lesions by at least 50% of the product of the perpendicular diameters of any given lesion. A patient was classified as having progressive metastatic disease if the size of any malignant lesions had increased or if new lesions had developed since he was last seen. Any patient whose disease had regressed or remained stable was retreated with the same chemotherapeutic program until objective evidence of progressive disease became manifest. Any patient who failed the initial chemotherapeutic effort was treated with the other therapeutic regimen on a crossover arrangement.

Of the 37 patients entered on study, 10 were females and 27 were males; the mean age was 51.1 years (median, 54 years).

RESULTS

Six of 35 patients (17%) had objective clinical remissions (Table 1). Five of the 6 had received a combination of vincristine and imidazole carboxamide, and 4 of these had their remission after primary treatment. As with the previous study, subsequent treatment with either of the programs was associated with little clinical activity. Only 1 remission occurred on the subsequent treatment program, and this was with the combination of imidazole carboxamide and vincristine.

CCNU provided only 1 objective clinical remission, which occurred as initial therapy.

Five patients who received imidazole carboxamide and vincristine had remissions: the lengths of remission were 36, 36, 14, and 13 weeks for the 4 patients whose remission has ended and 36 weeks for the 1 patient whose remission continues. The CCNU remission lasted 13 weeks. Table 2 outlines the quality and length of objective regressions.

The toxicity associated with imidazole carboxamide and vincristine included nausea and vomiting, hematological depression, alopecia, neurological disturbances, and a papular dermatological reaction in 1 patient (Table 3). As was true in the previous report, imidazole carboxamide was associated with nausea and vomiting in all patients, but in none of the patients was this of such severity as to warrant the use of parenteral fluids. Nine of 28 patients had symptomatic neurological toxicity, mainly peripheral paresthesias and loss of deep tendon reflexes; in these, the dose of vincristine was modified on subsequent occasions. Alopecia occurred in 7 of 29 patients who received imidazole carboxamide and vincristine. The platelet depression after this program occurred on the average of 19 days after treatment and lasted for 7 days. The leukopenic episodes occurred on an average of 15 days after treatment; the mean length of the depression was 9 days.

CCNU, as was previously reported with BCNU, is a mellow suppressant. At a dose of 130 mg/sq m, one-half of the patients had hematological depression. The thrombocytopenic episodes occurred on an average after 24 days and lasted on an average of 13 days. The leukopenic episodes occurred on the average of 30 days after treatment, with the depression lasting an average of 9 days. There was initial transient upper gastrointestinal toxicity in 17 of 25 patients, but this was not severe.

DISCUSSION

The program utilizing imidazole carboxamide and vincristine as outlined seems to be fairly well tolerated and associated with appreciable antitumor activity exceeding, in our experience, the use of imidazole carboxamide alone. However, the number of patients entered on each series was not large enough to prove this statistically. The morbidity associated with imidazole carboxamide and vincristine seems to be no greater, however, than with imidazole carboxamide alone.

**Table 1**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Imidazole carboxamide and vincristine</th>
<th>CCNU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>4/18</td>
<td>1/19</td>
</tr>
<tr>
<td>Subsequent</td>
<td>1/11</td>
<td>0/7</td>
</tr>
<tr>
<td>Total</td>
<td>5/29</td>
<td>1/26</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Toxic reaction</th>
<th>Imidazole carboxamide and vincristine</th>
<th>CCNU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (&lt;3,000)</td>
<td>9/29</td>
<td>8/26</td>
</tr>
<tr>
<td>Platelets (&lt;100,000)</td>
<td>8/29</td>
<td>13/26</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>29/29</td>
<td>17/26</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1/29</td>
<td>0/26</td>
</tr>
<tr>
<td>Neurological</td>
<td>9/29</td>
<td>0/26</td>
</tr>
<tr>
<td>Alopecia</td>
<td>7/29</td>
<td>0/26</td>
</tr>
</tbody>
</table>
Table 2

Regressions on treatment programs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Drug</th>
<th>Parameter before treatment</th>
<th>Parameter after treatment</th>
<th>Length of regression (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>M</td>
<td>CCNU</td>
<td>Skin nodules 1.5 x 1.5 cm</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>M</td>
<td>Imidazole carboxamide and vincristine</td>
<td>Pulmonary lesion 3/2.5 cm</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>F</td>
<td>Imidazole carboxamide</td>
<td>Liver RSCM 7 cm; xiphoid 7.5 cm</td>
<td>Lung 1</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>M</td>
<td>Imidazole carboxamide and vincristine</td>
<td>Lung Node 2.5/1 cm</td>
<td>Lung 1</td>
<td>36; remission continues</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>F</td>
<td>Imidazole carboxamide and vincristine</td>
<td>Liver RSCM 8 cm; xiphoid 7.5 cm</td>
<td>Lung 1</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>M</td>
<td>Imidazole carboxamide and vincristine</td>
<td>Abdominal mass 2.5 x 8 cm</td>
<td>Urine melanin negative</td>
<td>14</td>
</tr>
</tbody>
</table>

* RSCM, right subcostal margin; alk. phos., alkaline phosphatase; SGOT, serum glutamic oxalpyruvic transaminase; BSP, sulfobromophthalein.

alone, with the exception of mild neurological toxicity and moderate hair loss.

Disappointingly, CCNU showed a very low level of antitumor activity with this group of patients at the dose selected (130 mg/sq m). The drug was extremely well tolerated in this group of patients, but unfortunately its antitumor effect was not great enough to consider it a helpful chemotherapeutic agent in this neoplasm as a single treatment.

Secondary treatment, as was previously shown with other agents, to date is of little benefit in malignant melanoma.

Continued Phase II clinical trials are necessary with new agents in patients with disseminated malignant melanoma in hopes of finding agents with increasing activity for this disease.

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REFERENCES

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