Effect of Imidazole-4-carboxamide, 5-(3,3-Dimethyl-1-triazeno) on Immunity in Patients with Malignant Melanoma

Howard W. Bruckner, Margalit Birnbaum Mokyr, and Malcolm S. Mitchell

SUMMARY

Imidazole-4-carboxamide, 5-(3,3-dimethyl-1-triazeno), NSC 45388 (DTIC), was administered for 5 consecutive days as a rapid 150-mg/sq m or 250-mg/sq m infusion to 13 patients with melanoma. DTIC did not interfere with induction of a cellular immune (delayed hypersensitivity) response to dinitrochlorobenzene in 7 of 12 patients tested or with established delayed hypersensitivity reactions in 8 of 8 patients. The 5 nonresponders to dinitrochlorobenzene were unable to manifest a cellular immune response to skin test antigens even before treatment with DTIC. DTIC did not suppress the primary humoral response to Vi antigen in 7 of 12 patients. The secondary response to tetanus toxoid was normal in 5 of 7 patients. These results indicate that DTIC at these dosage schedules was only moderately immunosuppressive and inhibited humoral immune responses slightly more than the cellular responses tested.

INTRODUCTION

DTIC is a chemical agent of benefit in the palliation of malignant melanoma (12). DTIC has the structural characteristics of a purine antagonist and biological characteristics of an alkylating agent (6, 12). Both classes of drug inhibit immune responses (5, 13, 14), yet little is known about the immunosuppressive effects of DTIC. Since immunological mechanisms may be important in determining the clinical course and response to therapy of melanoma (4, 10-12), we have studied the immune response of 13 patients with disseminated melanoma receiving DTIC. Our results indicate that DTIC at the dosages studied was only variably immunosuppressive, much less so than effective doses of most other anticancer agents reported.

MATERIALS AND METHODS

DTIC was administered as a 10-min infusion to each of 13 patients with disseminated melanoma. The course of therapy usually consisted of 150 or 250 mg/sq m for 5 consecutive days (Table 1).

Patients were accepted for treatment regardless of their functional status (A, normal; B, symptomatic; C, less than 50% bedridden; D, more than 50% bedridden). The majority had a satisfactory nutritional status at the initiation of therapy.

As previously described (8, 9), the primary humoral immune response was tested with 70 μg of Vi antigen from Escherichia coli 5396/38 and the secondary (anamnestic) response with a 7.5-Ld dose of tetanus toxoid. Passive hemagglutination titers were estimated on serial specimens of serum drawn at weekly intervals (7, 15, 16). The primary cellular immune response was tested with DNCB (8, 9).

Challenge doses were not reapplied. Established skin reactions were normal in 5 of 7 patients. These results indicate that DTIC at these dosage schedules was only moderately immunosuppressive and inhibited humoral immune responses slightly more than the cellular responses tested.

RESULTS

Primary Humoral Response. Seven of 12 patients tested showed a primary response to Vi antigen, while 5 showed no response. The 7 had a mean titer of 4, similar to that of controls studied previously (8). One of the 7 (P. D.) had a delayed response, achieving a peak titer on Day 14. Untreated controls (8) and other patients treated with DTIC achieved a peak titer by Day 7. One other patient (J. McH.) who had a preexisting titer to Vi that could not be removed by absorption with red blood cells showed a secondary response to the antigen. The simultaneous use of corticosteroids and DTIC did not inhibit the response in 2 of 2 cases (H. B., J. W.).

Secondary Humoral Response. Five of 7 patients with a previous exposure to tetanus toxoid showed a normal sec-
Response to exogenous antigens during treatment with DTIC for disseminated melanoma

Description of the clinical status of patients in the study, with their individual responses to administered antigens.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Functional status*</th>
<th>Distribution of disease</th>
<th>DTIC* (mg/sq m)</th>
<th>Antibodies‡</th>
<th>Skin tests‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. S.</td>
<td>29</td>
<td>M</td>
<td>A</td>
<td>Skin-lungs</td>
<td>150 × 5</td>
<td>Vi: 0</td>
<td>0</td>
</tr>
<tr>
<td>C. L.</td>
<td>62</td>
<td>F</td>
<td>D</td>
<td>Lungs-liver</td>
<td>250 × 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A. J.</td>
<td>60</td>
<td>F</td>
<td>D</td>
<td>Skin-nodes</td>
<td>150 × 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>A. M.</td>
<td>58</td>
<td>F</td>
<td>B</td>
<td>Liver-hones</td>
<td>80 × 10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>M. N.</td>
<td>45</td>
<td>F</td>
<td>D</td>
<td>Liver</td>
<td>150 × 5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>H. B.</td>
<td>62</td>
<td>F</td>
<td>B</td>
<td>Brain-lungs</td>
<td>150 × 5</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>P. D.</td>
<td>52</td>
<td>F</td>
<td>A</td>
<td>Skin-brain</td>
<td>150 × 5</td>
<td>5*</td>
<td>2+</td>
</tr>
<tr>
<td>A. H.</td>
<td>45</td>
<td>M</td>
<td>B</td>
<td>Intestines-nodes</td>
<td>250 × 5</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>J. W.</td>
<td>40</td>
<td>F</td>
<td>D</td>
<td>Brain-liver</td>
<td>250 × 5</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>A. L.</td>
<td>30</td>
<td>M</td>
<td>A</td>
<td>Skin</td>
<td>80 × 10</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>R. K.</td>
<td>48</td>
<td>M</td>
<td>D</td>
<td>Liver-lungs</td>
<td>150 × 5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>J. P.</td>
<td>55</td>
<td>M</td>
<td>A</td>
<td>Skin</td>
<td>150 × 5</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>J. McH.</td>
<td>40</td>
<td>F</td>
<td>A</td>
<td>Skin-nodes</td>
<td>250 × 5</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* A, normal; B, minor decrease; D, more than 50% bedridden.
‡ mg of DTIC per sq m × no. of consecutive injections.
‡ Rise in titer in log₂; 0, no response; (S), secondary response to Vi; (P), primary response to tetanus. All responses to Vi were primary and to tetanus secondary unless designated by (S) or (P), respectively.
‡ 0, no induration; 2+, erythema and induration; 3+, vesicles; 4+, bullae.
‡ M, mumps; C, Candida; P, purified protein derivative; T, Trichophyton; positive during treatment but less so than before treatment.
‡ Corticosteroid used in addition to DTIC; equivalent to prednisone 20 mg 3 times a day.
‡ Reaction delayed compared to normal control.

DISCUSSION

It was possible to elicit primary and established delayed hypersensitivity responses in most of the patients and primary and secondary humoral immune responses in one-half of the patients given DTIC. In only 3 of 11 patients was there no primary or secondary immune response; the 3 appear to have been anergic. In general the incidence of cellular immunocompetence in advanced melanoma was higher than in one study which found that 75% of patients with unresectable disease had no response to DNCB (4). Recent reports support our data, however, showing that the majority of melanoma patients with metastatic disease had intact skin reactivity to DNCB (2) and to antigens derived from melanoma cells (1).

The objective of this clinical study was to ascertain whether patients with malignant melanoma were able to respond to exogenous antigens during treatment with DTIC. Since intact responses were demonstrated in many patients, internal controls for immunocompetence of the group were not obligatory. Nevertheless we recognize the desirability of using a battery of different antigens before and, if possible, after treatment to assess immunocompetence, in addition to the tests performed during treatment. This could avoid a failure to distinguish a patient’s intrinsic inability to respond from immunosuppression by the durg or to identify a possible augmentative effect on immuno-responsiveness (14).

The general lack of immunosuppression by DTIC is uncommon among cancer chemotherapeutic agents but is a property of mithramycin in man (M. S. Mitchell, unpublished data) and bleomycin in mice (A. Dlugi, K. Robie,
Cellular immunity appeared to be somewhat more resistant to DTIC than was humoral immunity.

Other evidence, to be reported in detail shortly, indicates that the relative sparing of immunity by DTIC, particularly cell-mediated immunity, extends to the response to tumor-associated antigens in melanoma as measured by microcytotoxicity in vitro (M. S. Mitchell, M. B. Mokyr, J. M. Davis, and H. W. Bruckner, manuscript in preparation). Six of the patients reported here were studied; 4 showed no decrease and 2 showed only a transient decrease after DTIC. Suppression of cellular immunity to tumor antigens was also absent or transient in 10 of 12 patients treated with DTIC who were studied by other investigators (3).

Minimal or selective immunosuppression with sparing of cellular immunity is desirable therapeutically, since increase in lysis of tumor cells should result from immune mechanisms and chemotherapy acting in concert. The observation that DTIC frequently does not impair immune responses further suggests that chemotherapy with DTIC would not interfere with concomitant active immunotherapy in melanoma.

ACKNOWLEDGEMENTS

We would like to thank Dr. Marion Webster, NIH, for the generous gift of Vi antigen.

REFERENCES

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