Prognostic Correlations and Response to Treatment in Advanced Metastatic Malignant Melanoma

Lawrence H. Einhorn, M. Andrew Burgess, Carlos Vallejos, Gerald P. Bodey, Sr.,
Jordan Gutterman, Giora Mavligit, Evan M. Hersh, James K. Luce,
Emil Frei, III,
Emil J Freireich, and Jeffrey A. Gottlieb

Department of Developmental Therapeutics, M. D. Anderson Hospital and Tumor Institute at Houston, Houston, Texas 77025

SUMMARY

Four-hundred twenty-six patients with disseminated melanoma were analyzed, all of whom were treated with chemotherapy. There was a high correlation with hepatic metastases and elevated lactic dehydrogenase levels. Although there were frequent false-positive lactic dehydrogenase levels, normal lactic dehydrogenase levels were consistently associated with a normal liver.

Central nervous system disease was a major cause of morbidity and mortality in metastatic melanoma. Eleven percent of the patients in this study had evidence of central nervous system disease at onset. The only treatment that was proven to be effective in these patients was whole-brain radiotherapy with concomitant dexamethasone administration.

There were certain areas of anatomical involvement that correlated with an improved survival. These were patients that had pulmonary metastases only (median survival, 10 months) and patients with disease limited to the skin and s.c. tissue (median survival, 11 months). The median survival for all patients was 4.7 months.

The response rate to a variety of treatment regimens with 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide was 18% (75 of 426) for all patients and 23% for evaluable patients only. There was an increased response to 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide for nonvisceral involvement (28%), compared with visceral involvement (13%). The addition of 1,3-bis[2-chloroethyl]-1-nitrosourea appeared to have an increased response rate for pulmonary and other visceral involvement, compared with 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide alone.

INTRODUCTION

Although malignant melanoma comprises only 1 to 3% of all tumors, it remains a disease that has attracted the attention of surgeons, internists, oncologists, and immunologists. There is no tumor that disseminates more widely or involves more organs than malignant melanoma (1). Similarly, no tumor is more unpredictable than melanoma with its relatively high rate of spontaneous regression (5), as well as the well-documented long intervals between removal of the primary and the development of metastases. This is especially true of choroidal melanoma; it is not unusual in this disorder to have a 10- to 15-year latency period between removal of the primary by enucleation and the development of hepatic metastases (4).

During the 6-year period between March 1967 and March 1973, 426 patients were referred to the Department of Developmental Therapeutics, M. D. Anderson Hospital and Tumor Institute at Houston, for chemotherapy of disseminated melanoma. This report (a) examines the accuracy of staging procedures used to assess metastatic involvement, (b) evaluates the prognostic implication of various clinical parameters, and (c) evaluates the effect of different chemotherapeutic regimens.

MATERIALS AND METHODS

Four-hundred twenty-six patients with disseminated malignant melanoma treated with chemotherapy were analyzed. All of these patients were seen by the Department of Developmental Therapeutics at M. D. Anderson Hospital and Tumor Institute at Houston between March 1967 and March 1973. All patients treated were no longer considered to be candidates for surgical procedures. Most of these patients were thoroughly evaluated as to extent of disease by careful history and physical examination, chest X-ray, liver function studies, liver scan, brain scan, EEG, and bone marrow aspiration. There were 241 men and 185 women in this study. The median age was 52 years with a range of 13 to 86 years. All patients were treated with chemotherapy. The different treatment regimens are shown in Table 1.

Complete response was defined as a complete disappearance of all discernible disease for a minimum of 1 month, and partial response was defined as a greater than 50% regression (5), as well as the well-documented long intervals between removal of the primary and the development of metastases. This is especially true of choroidal melanoma; it is not unusual in this disorder to have a 10- to 15-year latency period between removal of the primary by enucleation and the development of hepatic metastases (4).

The different treatment regimens are shown in Table 1.

Complete response was defined as a complete disappearance of all discernible disease for a minimum of 1 month, and partial response was defined as a greater than 50% regression (5), as well as the well-documented long intervals between removal of the primary and the development of metastases. This is especially true of choroidal melanoma; it is not unusual in this disorder to have a 10- to 15-year latency period between removal of the primary by enucleation and the development of hepatic metastases (4).

The different treatment regimens are shown in Table 1.

Complete response was defined as a complete disappearance of all discernible disease for a minimum of 1 month, and partial response was defined as a greater than 50% regression (5), as well as the well-documented long intervals between removal of the primary and the development of metastases. This is especially true of choroidal melanoma; it is not unusual in this disorder to have a 10- to 15-year latency period between removal of the primary by enucleation and the development of hepatic metastases (4).

The different treatment regimens are shown in Table 1.

Complete response was defined as a complete disappearance of all discernible disease for a minimum of 1 month, and partial response was defined as a greater than 50% regression (5), as well as the well-documented long intervals between removal of the primary and the development of metastases. This is especially true of choroidal melanoma; it is not unusual in this disorder to have a 10- to 15-year latency period between removal of the primary by enucleation and the development of hepatic metastases (4).

The different treatment regimens are shown in Table 1.

Complete response was defined as a complete disappearance of all discernible disease for a minimum of 1 month, and partial response was defined as a greater than 50% regression (5), as well as the well-documented long intervals between removal of the primary and the development of metastases. This is especially true of choroidal melanoma; it is not unusual in this disorder to have a 10- to 15-year latency period between removal of the primary by enucleation and the development of hepatic metastases (4).

The different treatment regimens are shown in Table 1.

Complete response was defined as a complete disappearance of all discernible disease for a minimum of 1 month, and partial response was defined as a greater than 50% regression (5), as well as the well-documented long intervals between removal of the primary and the development of metastases. This is especially true of choroidal melanoma; it is not unusual in this disorder to have a 10- to 15-year latency period between removal of the primary by enucleation and the development of hepatic metastases (4).

The different treatment regimens are shown in Table 1.
reduction in the sum of the products of 2 diameters of measured lesions without the appearance of new lesions. Survival was measured from onset of chemotherapy to death, unless otherwise stated. Patients were considered evaluable if they completed 2 courses of therapy.

All patients were treated with DIC, alone or in combination. DIC was initially evaluated in a Phase I study, showed promise in melanoma, and was therefore pursued in that disease (10). The early promising results with the combination of BCNU and vincristine (12) in metastatic malignant melanoma prompted the creation of the BVD regimen described in Table I. Although the usefulness of procarbazine in malignant melanoma was uncertain, there was evidence that the drug was active (7), and this led to the DIC + procarbazine regimen described in Table I. At the present time, we are evaluating the combination of DIC chemotherapy with BCG nonspecific active immunotherapy (Table 1).

Many of these patients were treated in cooperation with the Southwest Cancer Chemotherapy Study Group, and detailed analysis of the various studies on which these patients were participants will be forthcoming in the future.

RESULTS

Correlation of Liver Function Studies with Liver Involvement

During the years 1967 and 1969, most patients were evaluated for metastases involving the liver with SGOT, alkaline phosphatase, and bilirubin determinations, as well as liver scans. An abnormal liver scan with definite cold area(s) was felt to represent liver metastases in these patients. No attempt was made to confirm the scan by open or needle biopsy. Liver scans were performed in 338 patients in this series, and 107 (32%) were interpreted as being positive for hepatic metastases. The results of all liver function tests determined as part of the evaluation prior to initiation of chemotherapy are shown in Table 2. The serum bilirubin was rarely elevated in metastatic melanoma to the liver (17 of 275 determinations), but when elevated was always associated with hepatic involvement. Alkaline phosphatase had the best correlation of the 3 above-mentioned liver function studies, in that it had the lowest percentage of false negatives (Table 2); however, there were numerous patients with metastatic melanoma in the liver and completely normal liver function studies. After 1969, simultaneous multiple analysis was routinely done which included an LDH as well as an SGOT, alkaline phosphatase, and bilirubin. It soon became apparent that LDH was elevated in essentially every case of metastatic melanoma of the liver, and usually the elevation was greater than twice the upper range of normal. Similarly, if the LDH was normal, the likelihood of hepatic metastases was remote (Table 2).

Brain Scan and EEG

In this series, 47 patients (11%) had CNS metastases demonstrated by brain scan during their prechemotherapy evaluation. Thirteen of the 47 (27%) had no signs or symptoms of CNS disease. All 13 had evidence of a space-occupying lesion demonstrated on a brain scan, and 3 of them also had abnormal EEG’s. There were 4 patients who were reported as having abnormal brain scans with space-occupying lesions who did not have CNS melanoma. Two of these patients died shortly after the brain scan was done and had no CNS disease at autopsy. The other 2

<table>
<thead>
<tr>
<th>Name</th>
<th>Regimen</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DIC</td>
<td>DIC, 250 mg/sq m i.v., for 5 days every 21 days</td>
<td>3/67-8/69</td>
</tr>
<tr>
<td>2. BVD</td>
<td>BCNU, 150 mg/sq m i.v., on Day 1 every 28 to 42 days</td>
<td>8/69-8/71</td>
</tr>
<tr>
<td></td>
<td>Vincristine, 2 mg i.v., on Days 1 and 5 every 28-42 days</td>
<td></td>
</tr>
<tr>
<td>3. DIC-procarbazine</td>
<td>DIC, 250 mg/sq m i.v., for 5 days every 28 days</td>
<td>8/71-3/72</td>
</tr>
<tr>
<td></td>
<td>Procarbazine, 100 mg/sq m p.o., for 10 days every 28 days</td>
<td></td>
</tr>
<tr>
<td>4. DIC-BCG</td>
<td>DIC, 250 mg/sq m i.v., for 5 days every 21 days</td>
<td>3/72-3/73</td>
</tr>
<tr>
<td></td>
<td>BCG (6 x 10^6 organisms by scarification on Days 7, 12, and 17 of each treatment course) every 21 days</td>
<td></td>
</tr>
</tbody>
</table>

Table 1

Major treatment regimens

<table>
<thead>
<tr>
<th>No. done</th>
<th>Normal</th>
<th>Elevated</th>
<th>False positives</th>
<th>False negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT</td>
<td>332</td>
<td>268</td>
<td>64</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>LDH</td>
<td>282</td>
<td>134</td>
<td>148</td>
<td>68 (46%)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>336</td>
<td>218</td>
<td>118</td>
<td>37 (31%)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>275</td>
<td>258</td>
<td>17</td>
<td>0</td>
</tr>
</tbody>
</table>
Advanced Metastatic Malignant Melanoma patients were demonstrated by arteriography to have an aneurysm and an A-V malformation.

Bone Marrow

Prior to the start of chemotherapy, a bone marrow examination was performed on 254 patients in this series to assess the adequacy of hematopoiesis and to determine if melanoma had invaded the marrow. In 24 (9%), cytological evidence of metastatic melanoma was detected. In addition, of the 96 patients examined at autopsy, 15 (16%) had bone marrow involvement.

Small Bowel Involvement

An upper gastrointestinal series with a small-bowel follow-through was not routinely done as part of the prechemotherapy work-up, and thus we cannot report on the incidence of involvement of the small bowel with melanoma at the initiation of chemotherapy. However, we were impressed by the frequent occurrence of symptomatic gastrointestinal bleeding or abdominal pain attributable to small bowel melanoma. An upper gastrointestinal series which included an examination of the small bowel frequently revealed submucosal defects characteristic of small bowel melanoma, while involvement of the stomach and duodenum was rare. Intussusception was a common operative finding in those patients who underwent a laparotomy due to gastrointestinal bleeding.

Prognosis Related to Site of Metastatic Involvement and Other Parameters

Nonvisceral Involvement

It has been appreciated for a long time that some patients, although they have disseminated disease, appear to exert some immunological control over their disease and live in a symbiotic-like relationship with their malignancy. This is most evident in patients with nonvisceral metastases who often undergo repeated surgical removal of metastatic melanoma and yet do not develop visceral involvement. In this series, there were 90 patients who presented with nonvisceral metastases. Their survival, by extent of involvement, is shown in Table 3. The median survival for all 90 patients was 8 months. Patients with disease limited to the skin and s.c. tissue fared the best, with a median survival of 11 months.

Pulmonary Metastases

The survival for patients in whom pulmonary involvement represented the sole manifestation of metastatic disease was better than anticipated. Although many of these patients had bilateral pulmonary parenchymal disease, and often had massive disease, the median survival for this group of patients was 10 months, compared with a median survival for all patients of only 4.7 months. This increased survival cannot be attributed to responsiveness to chemotherapy, as the response rate in this group of patients was only 18%, which is identical to the response rate seen in all 426 patients. There were 39 patients in this category representing 9% of the total population. No patients in this series underwent surgical removal of metastatic disease. Patients with a solitary nodule as their only evidence of metastatic disease were referred to the thoracic surgery service for consideration of thoracotomy (13) and did not receive chemotherapy.

CNS Disease

Brain metastases were the most devastating manifestation of disseminated malignant melanoma. Although the incidence of CNS disease at the initiation of chemotherapy was only 11%, the autopsy incidence was 54% (46 of 85), and CNS melanoma was the major cause of death in the 46 patients. This autopsy incidence of CNS melanoma is similar to that reported by Beresford (37 of 85, or 44%) (2). The median survival for the 47 patients who had CNS melanoma at the onset of chemotherapy was 2.75 months from the initiation of chemotherapy.

Lymphocyte Counts

Absolute and relative lymphocyte counts were examined at the time of diagnosis, at the start of chemotherapy, and after 3 courses of chemotherapy. There was no significant relationship between absolute lymphocyte count or change in the count and response rate to chemotherapy, nor was there a relationship between lymphocyte count and survival.

Sex

There are several studies that have demonstrated increased survival for females with all stages of malignant melanoma (3). This was also seen in this study, as there was an increased survival for females both from the time of diagnosis and from the initiation of chemotherapy to death.
L. H. Einhorn et al.

(Tables 4). While not statistically significant, we have not yet observed in any of our therapeutic regimens a greater response rate in men than in women.

Metastatic Spread from Different Anatomical Primaries

All patients were analyzed as to area(s) of metastatic spread from different anatomical primaries. The only primary that had a consistent anatomical pattern was ocular melanoma; in this category 17 of 23 patients (74%) developed hepatic metastases as their initial metastatic spread.

The pattern of metastatic spread with other primaries is listed in Table 5.

Unknown Primary

Sixty-five patients (15%) had metastatic melanoma with an unknown primary. The data on this group of patients are shown in Tables 6 and 7. Most of these patients had s.c. or nodal metastases at the time of diagnosis. It is unknown whether these represented spontaneous regression of a cutaneous primary. The unusual and unique biological behavior of melanoma is exemplified by some of these patients. There were 4 patients who initially had a laparotomy and were found to have metastatic melanoma involving the small bowel, rectum, kidney, and gall bladder, respectively, which was completely excised. There were no other areas of melanoma found in these patients at the time of surgery or during extensive evaluation by physical examination and laboratory tests. The patient with metastatic melanoma of the small bowel remained asymptomatic with no evidence of disease for 2.5 years and then developed CNS
metastases. These other 3 patients developed widely disseminated disease at 14, 10, and 7 months, respectively, following laparotomy, and all 3 died within 20 months of diagnosis. Also of interest were 2 patients who presented with metastatic pulmonary melanoma (diagnosed at thoracotomy) and 1 patient with metastatic melanoma involving the right temporoparietal lobe. None of these patients had any previous history of melanoma or any other area of involvement at the time of surgery. The 2 patients diagnosed at thoracotomy developed metastatic disease at 14 and 15 months, respectively, and both died shortly thereafter. The patient diagnosed at craniotomy developed metastatic disease 6 months later and died shortly thereafter. The median survival for the 34 patients initially treated surgically with removal of all metastatic melanoma (Table 6) was only 18 months (range, 3 to 100+ months), compared with the median survival of 31 months for all 426 patients from diagnosis to death, further suggesting that an earlier primary had escaped diagnosis in the former group. The survival of 31 patients with metastatic melanoma from an unknown primary with disseminated nonresectable disease at the time of diagnosis is shown in Table 7. The median survival for this group was only 7 months.

**Therapeutic Results**

There were 75 objective responses for a response rate of 19%, including 13 complete responders (3%). The median survival from onset of chemotherapy to death was 4.7 months.

The study analyzes the results with several different treatment regimens used in disseminated malignant melanoma (Table 1). Table 8 compares these regimens in a variety of parameters. As can be seen, these groups were comparable as to age and sex. The metastatic involvement was similar in each of the treatment groups. It is too early to evaluate the DIC-BCG group and, therefore, they are not included in Table 8. This study will be separately analyzed when complete. All patients were evaluated for prior therapy, tumor burden, and intervals from diagnosis to metastasis and from metastases to chemotherapy with DIC (alone or in combination). There were no appreciable differences between the DIC, BVD, or DIC-BCG groups, but the DIC-procarbazine group had a higher percentage of

### Table 7

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Involved site of diagnosis</th>
<th>Median interval from start of chemotherapy to death (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Lungs</td>
<td>16+</td>
</tr>
<tr>
<td>5</td>
<td>s.c. + nodes</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>s.c. (multiple)</td>
<td>14+</td>
</tr>
<tr>
<td>4</td>
<td>s.c. + lungs</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Nodes</td>
<td>7+</td>
</tr>
<tr>
<td>2</td>
<td>s.c., nodes, lungs</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>Lungs, liver, bone</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>Liver, bone, s.c.</td>
<td>6+</td>
</tr>
<tr>
<td>1</td>
<td>CNS + lungs</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>Liver + lungs</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>Liver + bone</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>Nodes + bone</td>
<td>2</td>
</tr>
</tbody>
</table>

**Advanced Metastatic Malignant Melanoma**

Table 8 compares these regimens in a variety of parameters. As can be seen, these groups were comparable as to age and sex. The metastatic involvement was similar in each of the treatment groups. It is too early to evaluate the DIC-BCG group and, therefore, they are not included in Table 8. This study will be separately analyzed when complete. All patients were evaluated for prior therapy, tumor burden, and intervals from diagnosis to metastasis and from metastases to chemotherapy with DIC (alone or in combination). There were no appreciable differences between the DIC, BVD, or DIC-BCG groups, but the DIC-procarbazine group had a higher percentage of

### Table 8

<table>
<thead>
<tr>
<th>No. of patients studied</th>
<th>Male/female (%)</th>
<th>Complete remissions/partial remissions (%)</th>
<th>Median duration response (mo.)</th>
<th>Median survival of responders (mo.)</th>
<th>% with no change</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>113</td>
<td>52/58</td>
<td>17 (19/113)°</td>
<td>2/17</td>
<td>8</td>
</tr>
<tr>
<td>BVD</td>
<td>106</td>
<td>62/38</td>
<td>19 (20/106)°</td>
<td>3/17</td>
<td>9.5</td>
</tr>
<tr>
<td>DIC-procarbazine</td>
<td>62</td>
<td>56/44</td>
<td>16 (10/62)°</td>
<td>2/8</td>
<td>6</td>
</tr>
</tbody>
</table>

### Notes

- ° Number responding/number studied.
- ° Range of months.
- ° Number with no change/number studied.
- ° Number with progression/number studied.
- ° Number responding after 2 or more courses/number evaluable.
patients who had prior therapy and a longer interval from development of metastases to initiation of DIC-procarbazine chemotherapy, probably accounting for the slightly inferior results with this regimen.

Chemotherapy

DIC. There were 113 patients treated with DIC alone, with an objective response rate of 17% for all patients and 22% for evaluable patients. The survival curves for all patients and for those patients with progression, no change, and objective response are depicted in Charts 1 and 2. The median survival from detection of metastatic disease was 5 months.

An analysis of the 19 responders is shown in Table 9. Six of the 19 patients had CNS relapses while maintaining stable disease or remissions peripherally. Nine patients had nonvisceral responses and 10 patients had visceral responses with 9 pulmonary and 2 hepatic responses in these 10 patients.

BVD. There were 106 patients treated with the 3-drug combination of BCNU, vincristine, and DIC with an objective response demonstrated in 19% for all patients and 24% for evaluable patients. The corresponding survival curves are shown in Charts 3 and 4. The median survival from detection of metastatic disease was 5.5 months.

The 20 responders are shown in Table 10. Unlike all the other studies, most of these responders had visceral disease,
Advanced Metastatic Malignant Melanoma

especially pulmonary metastases. There were 17 patients who had a visceral response with 14 pulmonary, 5 hepatic, 2 CNS, and 2 bone marrow responses. Only 2 of the relapses were due to CNS disease. Thus, for the patient with disseminated melanoma with visceral involvement, there appeared to be a higher response rate with the addition of BCNU. There was no evidence that these 20 responders had a different pattern of metastatic spread or were treated earlier in their course of metastatic disease than the BVD group as a whole or than the patients treated with DIC alone.

DIC-Procarbazine. There were 62 patients treated with the combination of DIC and procarbazine. There was an

Table 10

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Location of primary</th>
<th>Metastases</th>
<th>Areas of response</th>
<th>Areas of relapse</th>
<th>Duration (mo.)</th>
<th>Survival (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T. W.</td>
<td>34</td>
<td>F</td>
<td>Extremity</td>
<td>s.c., nodes, CNS</td>
<td>Lungs, CNS, s.c.</td>
<td>Lungs</td>
<td>5.75</td>
<td>11.75</td>
</tr>
<tr>
<td>R. W.</td>
<td>64</td>
<td>M</td>
<td>Trunk</td>
<td>s.c., nodes, lungs</td>
<td>s.c., nodes</td>
<td>?</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>B. T.</td>
<td>18</td>
<td>F</td>
<td>Head</td>
<td>s.c., liver, small bowel</td>
<td>s.c., liver</td>
<td>s.c., liver</td>
<td>9</td>
<td>32.5</td>
</tr>
<tr>
<td>W. T.</td>
<td>62</td>
<td>M</td>
<td>Extremity</td>
<td>Lungs + nodes</td>
<td>Nodes</td>
<td>Nodes</td>
<td>3.25</td>
<td>6.5</td>
</tr>
<tr>
<td>R. T.</td>
<td>51</td>
<td>M</td>
<td>Neck</td>
<td>Lungs + nodes</td>
<td>Lungs + nodes</td>
<td>Lungs</td>
<td>9+</td>
<td>9.75+</td>
</tr>
<tr>
<td>O. T.</td>
<td>60</td>
<td>F</td>
<td>Head</td>
<td>Lungs</td>
<td>?</td>
<td>(?) CNS</td>
<td>3.75</td>
<td>4.75</td>
</tr>
<tr>
<td>I. S.*</td>
<td>42</td>
<td>F</td>
<td>Extremity</td>
<td>Lungs</td>
<td>Lungs</td>
<td>None</td>
<td>29+</td>
<td>30+</td>
</tr>
<tr>
<td>L. S.</td>
<td>56</td>
<td>M</td>
<td>Extremity</td>
<td>Lungs + s.c.</td>
<td>Lungs + s.c.</td>
<td>Lungs</td>
<td>3</td>
<td>9.5</td>
</tr>
<tr>
<td>D. S.</td>
<td>76</td>
<td>F</td>
<td>Extremity</td>
<td>Lungs + s.c.</td>
<td>Lungs + s.c.</td>
<td>Lungs + s.c.</td>
<td>4.5</td>
<td>5.75</td>
</tr>
<tr>
<td>R. S.</td>
<td>40</td>
<td>M</td>
<td>Head</td>
<td>s.c.</td>
<td>Lungs, s.c.</td>
<td>Lungs, s.c.</td>
<td>4.5</td>
<td>7.75</td>
</tr>
<tr>
<td>P. P.</td>
<td>37</td>
<td>M</td>
<td>Trunk</td>
<td>Skin, s.c., nodes, liver, bone marrow</td>
<td>Lungs, liver, nodes, bone marrow</td>
<td>Same</td>
<td>3.5</td>
<td>5.5</td>
</tr>
<tr>
<td>A. P.</td>
<td>75</td>
<td>M</td>
<td>Head</td>
<td>Lungs, nasopharynx</td>
<td>Lungs</td>
<td>Nasopharynx</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>A. M.</td>
<td>56</td>
<td>F</td>
<td>Extremity</td>
<td>s.c., CNS, lungs</td>
<td>Lungs, s.c., CNS</td>
<td>?</td>
<td>3</td>
<td>3.75</td>
</tr>
<tr>
<td>T. M.</td>
<td>66</td>
<td>M</td>
<td>Trunk</td>
<td>s.c.</td>
<td>s.c.</td>
<td>s.c.</td>
<td>2</td>
<td>7.5</td>
</tr>
<tr>
<td>G. H.</td>
<td>36</td>
<td>M</td>
<td>Head</td>
<td>Lungs</td>
<td>Small bowel, bone marrow</td>
<td>Lungs, s.c., liver, lungs</td>
<td>8</td>
<td>12.25</td>
</tr>
<tr>
<td>L. H.</td>
<td>71</td>
<td>F</td>
<td>Extremity</td>
<td>s.c., liver, lungs</td>
<td>s.c., liver, lungs</td>
<td>Liver</td>
<td>5</td>
<td>18.5</td>
</tr>
<tr>
<td>I. E.</td>
<td>42</td>
<td>F</td>
<td>Eye</td>
<td>Liver</td>
<td>Liver</td>
<td>Liver</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>R. C.*</td>
<td>60</td>
<td>M</td>
<td>Unknown</td>
<td>Lungs, bone marrow</td>
<td>Lungs, bone marrow</td>
<td>Lungs, s.c.</td>
<td>46+</td>
<td>46+</td>
</tr>
<tr>
<td>V. D. C.</td>
<td>69</td>
<td>F</td>
<td>Extremity</td>
<td>s.c., lungs, bones</td>
<td>Lungs, s.c.</td>
<td>s.c., bones</td>
<td>1.75</td>
<td>9.5</td>
</tr>
<tr>
<td>M. A.</td>
<td>50</td>
<td>M</td>
<td>Trunk</td>
<td>Skin, s.c., nodes, liver</td>
<td>s.c., skin, nodes, liver</td>
<td>CNS</td>
<td>9.25</td>
<td>11.25</td>
</tr>
</tbody>
</table>

* Complete remission.
objective response rate of 16% for all patients and 22% for evaluable patients. Although the median survival was only 3 months, the median survival from detection of metastatic disease was 5.75 months.

DIC-BCG. The present protocol at this institution for disseminated malignant melanoma employs a combination of chemotherapy (DIC) and immunotherapy (BCG) by scarification on Days 7, 12, and 17 of each treatment course. It is too early at this time to evaluate these patients, and they will be analyzed more completely at a later date.

CNS Disease. Twenty-six of 47 patients, in whom CNS metastases were demonstrated during prechemotherapy evaluation, received whole brain radiotherapy, and 8 of these patients showed an objective response as signified by an improvement in their brain scan or EEG, plus objective improvement. Many of the other patients had an improved neurological status, but it was difficult to attribute this to the radiotherapy, as most of these patients were concomitantly treated with dexamethasone. The median survival for these 8 responders was 5 months.

DIC probably does not penetrate the blood-brain barrier; therefore, it is of minimal value if any in the treatment of CNS melanoma (8). There were numerous patients who responded to DIC chemotherapy only to later develop CNS metastases while still maintaining peripheral control of their disease. Because of the poor results with chemotherapy of CNS melanoma, whole-brain radiotherapy was often utilized. It has been traditionally taught that melanoma is radioresistant. However, it was our impression that melanoma was not radioresistant but was "radiorecurrent;" that is, there was a significant response rate to radiotherapy, but the responses were usually of short duration (6).

Nonvisceral Disease. It is noteworthy that the response of DIC for nonvisceral disease was 28% (25 of 90). In contrast, the response rate for DIC (when used alone or in combination) for patients with visceral disease was only 13% (45 of 336). In the BVD study, the response for visceral involvement was 20% (17 of 84); excluding this study, the response for visceral metastases was only 11% (28 of 252).

Pulmonary Metastases. There was a striking difference in the response rate and survival for patients who had pulmo-

Table 11
Response rate by sex

<table>
<thead>
<tr>
<th>Study</th>
<th>Male response rate (%)</th>
<th>Female response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>BVD</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>DIC-procarbazine</td>
<td>15</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 12
Dosage/response relationship (DIC)

<table>
<thead>
<tr>
<th>Starting dosage (mg/sq m)</th>
<th>No. responding/no. treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>0/3</td>
</tr>
<tr>
<td>100</td>
<td>0/5</td>
</tr>
<tr>
<td>125</td>
<td>0/2</td>
</tr>
<tr>
<td>150</td>
<td>2/12 (17)*</td>
</tr>
<tr>
<td>200</td>
<td>2/16 (12)</td>
</tr>
<tr>
<td>250</td>
<td>14/70 (20)</td>
</tr>
<tr>
<td>400</td>
<td>2/6 (33%)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, percentage of patients responding.

Sex. Initial studies with DIC showed a higher response rate in females (9). As can be seen from Table 11, there was also a higher response rate for females in the BVD and DIC-procarbazine study, although not as pronounced.

Dose-Response Relationship. In the early DIC study, a variety of initial dosages were used, as this was a Phase 1 study investigating dosage tolerance (Table 12). The usual starting i.v. dosage was 250 mg/sq m for 5 consecutive days, but varied from 75 to 400 mg/sq m. No responses were noted below a dosage of 150 mg/sq m.

Myelosuppression. Myelosuppression was relatively mild in the 2 studies in which DIC was the only chemotherapeutic agent used (DIC and DIC-BCG). In the DIC study, 68 of 107 (63%) of the evaluable patients had no myelosuppression (white blood count greater than 4,000 and platelet count greater than 150,000) with the 1st course; with DIC-BCG, 69 of 103 (67%) of the evaluable patients likewise had no myelosuppression. Only 23 of 210 (11%) had moderate or severe myelosuppression (white blood count less than 2,000 or platelet count less than 75,000). The response rate for these 23 patients was 35% (8 of 23 objective responses).

Eosinophilia. DIC is one of the few chemotherapeutic agents associated with the production of eosinophilia. Transient eosinophilia (as high as 50%) occurred with no other known cause to account for the increase. The eosinophilia would usually first appear at the end of a 5-day course of DIC and would disappear by the time the next course would start 3 weeks later. In 219 patients in which DIC was the sole chemotherapeutic agent used, 18 (8%) exhibited eosinophilia greater than 10%. These 18 patients were analyzed for a difference in response rate, toxicity, or survival, but no significant relationship was noted.

Results of Continuing Therapy with Progressive Disease. There were 96 patients with progressive disease (greater than 50% increase or development of new lesions) who received another course of the same type of chemotherapy at that time, often in a higher dosage. Most of these courses...
involved the 1st or 2nd course of treatment. Ninety-five of
the 96 patients then progressed on the subsequent course
of the same type of chemotherapy, and 1 patient had stable
disease for 2 more courses before progression. Although
many chemotherapists tend to give at least 2 courses of any
form of intermittent chemotherapy before proclaiming it a
failure on an individual patient, it can be clearly seen that
once a patient with malignant melanoma exhibits progressive
disease on DIC, alone or in combination, there is no value in continuing this form of therapy.

**Autopsy Data.** Ninety-six autopsies were performed on
this series of patients. All 96 patients had disseminated
melanoma at autopsy, and this was directly or indirectly the
cause of death in all patients. Eleven patients had the
following complications: pneumonia, 6 patients; pulmonary
embolism, 4 patients; peritonitis, 3 patients; pulmonary
edema, 3 patients; and disseminated intravascular coagula
tion, 2 patients.

The areas involved in autopsy are shown in Table 13. These studies reveal the widespread disseminated nature of
malignant melanoma. Despite the high incidence of cardiac
and adrenal involvement at autopsy, there were very few
incidents of clinical involvement of these organ systems.

**DISCUSSION**

Malignant melanoma remains one of the most challeng-
ing cancers to treat successfully. Because of its propensity
for widespread metastases, it is important to be aware of the
extent of disease and possible metastatic spread before
planning any radical surgical procedure or before beginning
any chemotherapeutic regimen. A careful history and
physical and chest X-ray are quite routine in evaluating any
patient with melanoma. A liver scan is not needed as part of
the routine evaluation unless there is clinical suspicion of
hepatic metastases or abnormalities in liver function tests,
especially noting the LDH level, as only 3 of 134 patients
(2%) with normal LDH levels had liver metastases. A brain
scan and EEG should be included for all patients with
disseminated melanoma or for any melanoma patient with
signs or symptoms of CNS disease. It is noteworthy that 13
of the 47 patients (27%) who had CNS metastases in this
series of 426 patients had no signs or symptoms of CNS
disease during their prechemotherapy evaluation. Perhaps
all patients with primary trunk or head and neck melanoma
being evaluated for surgery should also have a brain scan
and EEG due to the higher incidence of CNS metastases
from these primary sites (Table 5).

Persistent abdominal pain or gastrointestinal blood loss
in any patient with melanoma should alert the clinician to
the possibility of small bowel involvement with metastatic
melanoma. Bone pain or tenderness would be an indication
for a bone X-ray and bone marrow examination.

Disseminated melanoma remains one of the most che-
omoresistant cancers, as the response rate for all patients was
only 18% (23% response rate for evaluable patients), and the
median survival from onset of chemotherapy to death was
only 4.7 months. Certainly, the presently available che-
mothereapeutics agents are probably not capable of affecting a
major improvement in these disappointing survival data. It

<table>
<thead>
<tr>
<th>Table 13</th>
<th>Areas of involvement in 96 autopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. involved</td>
</tr>
<tr>
<td>Lungs</td>
<td>84</td>
</tr>
<tr>
<td>Liver</td>
<td>73</td>
</tr>
<tr>
<td>Nodes</td>
<td>71</td>
</tr>
<tr>
<td>Kidneys</td>
<td>56</td>
</tr>
<tr>
<td>Heart</td>
<td>53</td>
</tr>
<tr>
<td>Adrenals</td>
<td>52</td>
</tr>
<tr>
<td>Skin</td>
<td>52</td>
</tr>
<tr>
<td>s.c.</td>
<td>48</td>
</tr>
<tr>
<td>CNS</td>
<td>46</td>
</tr>
<tr>
<td>Spleen</td>
<td>41</td>
</tr>
<tr>
<td>Pancreas</td>
<td>36</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>26</td>
</tr>
<tr>
<td>Small bowel</td>
<td>25</td>
</tr>
<tr>
<td>Bone</td>
<td>22</td>
</tr>
<tr>
<td>Thyroid</td>
<td>20</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>15</td>
</tr>
<tr>
<td>Pleura</td>
<td>14</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>14</td>
</tr>
<tr>
<td>Large bowel</td>
<td>13</td>
</tr>
<tr>
<td>Bladder</td>
<td>13</td>
</tr>
<tr>
<td>Pericardium</td>
<td>11</td>
</tr>
<tr>
<td>Stomach</td>
<td>7</td>
</tr>
<tr>
<td>Testes</td>
<td>7</td>
</tr>
<tr>
<td>Ovaries</td>
<td>7</td>
</tr>
<tr>
<td>Prostate</td>
<td>5</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>4</td>
</tr>
<tr>
<td>Uterus</td>
<td>4</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3</td>
</tr>
<tr>
<td>Ureters</td>
<td>2</td>
</tr>
<tr>
<td>Larynx</td>
<td>2</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
</tr>
<tr>
<td>Vagina</td>
<td>2</td>
</tr>
</tbody>
</table>

* Eleven autopsies excluded CNS examination.

is hoped that a combination chemotherapy plus immuno-
therapy approach (such as DIC-BCG) will lead to improved
survival in patients with metastatic melanoma.

**REFERENCES**

1. Ackerman, L. V., and del Regato, J. A. Cancer: Diagnosis, Treatment
2. Beresford, H. R. Melanoma in the Nervous System. Treatment of
4. Einhorn, L. H., Burgess, M. A., and Gottlieb, J. A. Metastatic
   Patterns in Choroidal Melanoma. Cancer, in press.
   Management of Patients with Cerebral Metastases from Malignant
   Studies with the Antitumor Agent 5-(3,3-Dimethyl-1-Triazeno) Imida-
9. Luce, J. K. Chemotherapy of Malignant Melanoma. Cancer, 30:
10. Luce, J. K., Thurman, W. G., Isaacs, B. L., and Talley, R. W. Clinical
    Trials with the Antitumor Agent 5-(3,3-Dimethyl-1-Triazeno) Imida-
L. H. Einhorn et al.


Prognostic Correlations and Response to Treatment in Advanced Metastatic Malignant Melanoma

Lawrence H. Einhorn, M. Andrew Burgess, Carlos Vallejos, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/34/8/1995

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.