Treatment of metastatic melanoma with combined chemotherapy containing cisplatin, vinblastine and dacarbazine (CVD) and biotherapy using interleukin-2 and interferon-a

S. S. Legha, S. Ring, A. Bedikian, C. Plager, O. Eton, A. C. Buzaid & N. Papadopoulos

Metastatic melanoma is commonly treated with chemotherapy and/or biological agents used separately. In this study we have investigated the efficacy of combined chemotherapy using cisplatin, vinblastine, DTIC (CVD) and biological therapy using interleukin-2 (IL-2) and interferon-a (IFN-a) in patients with metastatic melanoma.

Patients and methods: All patients had advanced, inoperable melanoma without prior treatment with chemotherapy or biotherapy, a performance status of ECOG 0-2 and no evidence of symptomatic brain metastases. The CVD regimen consisted of cisplatin 20 mg/m²/d × 4, vinblastine 1.6 mg/m²/d × 5 and DTIC 800 mg/m² × 1, repeated at 21-day intervals. The biotherapy regimen included IL-2, 9 × 10^6 IU/m²/d × 4 days and IFN-α, 5 × 10^6 U/m²/d SC × 5 days. The CVD and biotherapy regimens were integrated initially, in an alternating manner at 6-week intervals and subsequently, in a sequential fashion where patients were randomized to receive either CVD immediately followed by biotherapy (CVD/Bio) or the reverse sequence (Bio/CVD). Patients were admitted to the hospital for IL-2 administration and for monitoring and treatment of IL-2 induced side effects. The phase II results of the integrated therapy (biochemotherapy) studies were retrospectively compared to our previously reported results with the CVD regimen used alone.

Results: The alternating biochemotherapy program was used in 40 patients and the sequential biochemotherapy was used in 62 patients. The alternating regimen produced 2 CRs and 11 PRs for an overall response rate of 33% among 39 evaluable patients. The sequential biochemotherapy produced 14 CRs and 23 PRs for an overall response rate of 60% (95% CI, 47% to 72%). The sequence of CVD/Bio resulted in a higher response rate (11 CRs + 11 PRs (69%)) compared to the Bio/CVD sequence (3 CRs + 12 PRs (50%)). Although the duration of PRs was short (median, 8 months), the median duration of CRs was 3+ years and 10 of 16 CRs are currently disease free for periods of 3+ to 6+ years. The median survival of patients receiving sequential biochemotherapy was 13 months compared to 9 months for the CVD treated group (P = 0.04). Treatment with biochemotherapy was associated with severe toxicity including intense myelosuppression, infections, IL-2 induced constitutional toxicity and hypotension. However, the IL-2 induced toxicities were generally manageable on a regular ward, except for 15% of the patients who required transfer to an intensive care unit for treatment of complications associated with the treatment.

Conclusions: The sequential combination of CVD with IL-2 + IFN-a appears to have produced an increase in the number of durable responses in patients with metastatic melanoma. The toxicity of this program, although severe, was manageable. The biochemotherapy regimen produced an apparent increase in the median survival compared to that observed with the CVD regimen. However, a prospective comparison of these two regimens will be required to confirm these observations.

Key words: biochemotherapy, biotherapy, chemotherapy, interferon-α, interleukin-2, melanoma

Introduction

Systemic therapy for metastatic melanoma in the past has predominantly consisted of chemotherapy. Although several cytotoxic agents have shown a low level of activity, dacarbazine (DTIC) is considered the most active single agent and is often used as the standard chemotherapy. When used as a single agent, DTIC has produced objective response in 15% to 20% of patients with a complete response (CR) rate of less than 5%. Combinations of dacarbazine plus cisplatin with vinblastine (CVD) or with a nitrosourea (Dartmouth regimen) have produced higher response rates ranging from 25% to 40% [1, 2] but these regimens have not been prospectively tested and not yet proven to be superior to dacarbazine alone [1, 2]. At the M. D. Anderson Cancer Center we have developed and used the CVD regimen, which has produced a response rate of 40% with a response duration of 9 months, as our standard chemotherapy [1]. However, the CR rate with CVD has been low, approximately 5%, and the long-term control of disease with this regimen as well as other chemotherapy regimens has been observed in less than 2% of the patients with metastatic disease [3].

During the past 10 years, interferon-α (IFN-α) has been widely tested against metastatic melanoma and
has yielded response rates of 10% to 20% in different trials, with an average response rate of 15% [4]. In our experience with IFN-α, responses were observed both in untreated as well as in patients resistant to chemotherapy, indicating lack of cross resistance between IFN-α and cytotoxic agents [5]. More recently interleukin-2 (IL-2) has been evaluated in phase II trials and also found to have significant activity against advanced melanoma, with response rates ranging from 15% to 20% [6, 7]. Furthermore, complete responses have been observed in 5% of the patients treated with IL-2 and most of the CRs have been durable for 5+ years [8]. Based on the laboratory evidence of additive antitumor activity, combinations of IL-2 + IFN-α have been tested in patients with metastatic melanoma and have produced response rates ranging from 10% to 30% [9–11]. Although the combination of two biological agents has not been clearly established to be superior to single agent IL-2, an apparently higher level of activity was achievable using IL-2 dose levels lower than those used in the single-agent IL-2 studies and therefore resulted in less severe toxicity. The independent antitumor activity of both IL-2 and IFN-α against melanoma and their lack of cross resistance with cytotoxic chemotherapy has raised the prospect of combining biotherapy with chemotherapy in patients with metastatic melanoma. Based on their potential opposing effects on the immune system, there was initially a theoretical concern of antagonism between chemotherapy and biotherapy (IFN-α + IL-2). Moreover the overlapping toxicities common to both types of therapy such as anorexia, nausea, vomiting, renal toxicity and myelosuppression were of additional concern. The major concern in combining chemotherapy and IL-2 in close proximity has been the potential for chemotherapy-induced depletion of host immune effector cells required for the antitumor activity of IL-2. In order to explore the combined use of biotherapy and chemotherapy, hereafter called biochemotherapy, we initially tested an alternating schedule of biotherapy and chemotherapy administration with an interval of 6 weeks between the 2 regimens in order to allow recovery from toxicity and an assessment of response to each component of therapy. Subsequently, we tested the sequential use of biotherapy and chemotherapy without any gap between them, using an immediate sequence of chemotherapy followed by biotherapy and vice versa. The results of alternating biochemotherapy and that of sequential biochemotherapy, both in the sequence of chemotherapy followed by biotherapy (CVD/Bio) and biotherapy followed by chemotherapy (Bio/CVD), are presented in this report. The results of biochemotherapy programs are also compared to our historical data obtained with the CVD regimen used alone.

Patients and methods

Patient eligibility

All patients participating in these studies had histologically documented diagnosis of metastatic melanoma which was not surgically resectable. Patients were required to be older than 16, but less than 70 years of age and to have an expected survival of 8 weeks or longer. They were required to have a Karnofsky performance status of 50% or better (ECOG, PS 0–2) and to have measurable or evaluable sites of metastases in order to assess response to treatment. Patients had to have adequate organ functions as defined by normal serum bilirubin (< 1.2 mg/dl), serum creatinine level < 1.6 mg/dl and to have a normal blood counts with WBC count of > 3500/mm³ and a platelet count of > 100,000/mm³. Patients with symptomatic brain metastases, medical conditions requiring steroids and those with significant intercurrent illnesses such as serious infection, significant psychiatric illness or hypercalcemia were excluded. However, patients with brain metastases were not excluded if the lesions could be resected and patient rendered disease-free or if patient had small lesions, without surrounding edema, and were well controlled with radiotherapy, and not requiring steroids. Furthermore, patients were required to have near normal cardiac and pulmonary functions. Patients older than 70 years of age or those with any significant cardiac illness such as symptomatic coronary artery disease or previous history of myocardial infarction, impaired left ventricle function (EF < 50%) on account of organic heart disease or serious cardiac arrhythmias requiring therapy, were excluded. Patients with a history of pulmonary dysfunction were not eligible unless they had a vital capacity and FEV-1 of > 75% of the predicted normal value. Patients with symptomatic malignant effusions due to pleural, pericardial or peritoneal metastases of melanoma were excluded. Patients with prior exposure to chemotherapy or biotherapy were not eligible for these studies.

Pretreatment evaluation

Baseline studies included a complete history and physical examination with a recording of measurable metastatic lesions. A complete laboratory evaluation including CBC, differential, platelet count, chemistry profile including liver and renal functions, serum electrolytes, serum magnesium level and coagulation studies were carried out within 1 week of entry to protocol. A complete staging work up including chest X-ray and, if necessary, CT scan of chest, CT scan of the abdomen and a CT scan or MRI of the brain was done prior to protocol entry. A bone scan or bone X-rays were only done in patients who were suspected of having bone metastases by virtue of presence of significant bone pain. All patients had baseline EKG and measurement of the cardiac ejection fraction with nuclear cardiac scan or echocardiography. Patients with a history suggestive of ischemic heart disease underwent a stress EKG and those with a history of chronic bronchitis or emphysema underwent complete pulmonary function studies including vital capacity, FEV-1 and DLCO to assess the degree of lung dysfunction. A central venous catheter was inserted for administration of chemotherapy and IL-2.

The treatment protocols were approved by the M. D. Anderson Cancer Center Human Investigations Review Board (IRB). A written Informed Consent indicating the investigational nature of this therapy was obtained from each participant patient.

Treatment plan

All eligible patients treated with biochemotherapy received the chemotherapy regimen consisting of cisplatin + vinblastine + DTIC (CVD) and the biotherapy regimen (Bio) consisting of IL-2 + IFN-α. The doses and the schedule of administration of both regimens are shown in Table 1. Whereas the CVD regimen was generally administered in the outpatient clinic, the biotherapy regimen required hospitalization on account of the need for monitoring and treatment.
Chemotherapy regimen (CVD)

Cisplatin was administered in a dose of 20 mg/m² i.v. daily for 4 days (d 2–5). It was mixed in 250 ml of normal saline and infused over 30 minutes. All patients received prehydration with 1000 ml of 5% dextrose in 0.45% saline given over 2 hours preceding each dose of cisplatin. Vinblastine was used in a dose of 1.6 mg/m² daily for 5 days as a short infusion over 15–30 minutes. DTIC was used in a dose of 800 mg/m² mixed in 500 ml 5% dextrose in water and administered over 1–2 hours on day 1. The courses of CVD were repeated at 21-day intervals provided the blood counts had recovered to adequate levels. All patients received premedication with antihistamines and a routine supplement of magnesium sulfate in a dose of 8–12 meq/L i.v. daily in the prehydration fluid. Because of their potent and overlapping emetic effects, DTIC was given on day 1 and cisplatin was administered on days 2 to 5 during the early part of the IL-2 induction. The availability of better antiepileptics has allowed administration of both DTIC and cisplatin on day 1 and the CVD regimen has been shortened to 4 days of therapy. The doses of chemotherapy were reduced by 20% in patients who developed infection during neutropenia.

Biotherapy regimen (IL-2 + IFN-α)

Patients were hospitalized for administration of the biotherapy component of treatment which was delivered in a general ward setting. IL-2 (Hoffmann-La Roche, Inc., Nutley, NJ), with a specific activity of 6 × 10⁶ U/mg protein was given in a dose of 3 × 10⁶ U/m² (equivalent to 9 × 10⁶ international units (IU)/m²) daily for 4 days as a continuous infusion over 96 hours. The daily dose of IL-2 was mixed in 250 ml of normal saline and delivered as a continuous infusion over 24 hours with the aid of a mechanical pump. Interferon-α 2a in a dose of 5 × 10⁶ U/m² was given SC daily for 3 days along with IL-2. The choice of these dose levels of biotherapy was based on our previous experience with this regimen producing tolerable toxicity and showing significant activity in patients with metastatic melanoma [12]. During IL-2 administration, all patients received intravenous fluids through a central venous catheter, at a rate of 75 ml/hour which was increased to 100 ml/hour in patients with excessive fluid losses from the GI tract. Blood pressure was monitored routinely at 4-hour intervals and the hypotension was managed initially with normal saline boluses of 500 ml × 1–2 in order to maintain euvolemic and the systolic blood pressure at >90 mm Hg. Excessive fluid administration was avoided and dopamine was instituted instead, starting at a dose of 5 mcg/kg/min in order to maintain renal perfusion and as an aid to sustain the blood pressure. The dose of dopamine was titrated and could be increased to a maximum of 10 mcg/kg/min, beyond which the IL-2 infusion was interrupted if the blood pressure could not be maintained at >90 mm Hg. Acetaminophen 650 mg was used q 4 hours around the clock to control fever and naproxen 375 mg, was used q 12 hours PRN for temperatures of >39.5°C. All patients were premediated with antiepileptics consisting of ondansetron 20–32 mg i.v. once daily, supplemented as needed, with lorazepam 1 mg i.v. q 8 hours around the clock. Refractory nausea was treated with prochlorperazine 10–20 mg i.v. q 6 hours. Anti-diarrheal agents such as lomotil and/or loperamide were used PRN. Pruritus was managed with routine lubrication of skin and diphenhydramine or hydroxyzine as needed. Chills and rigors were controlled with meperidine 50 mg i.v. as needed. Patients were weighed once daily and a careful record of intake and output was kept. Hepatic and renal function along with complete blood counts and electrolytes were monitored at 2–3 day intervals during IL-2 administration and 1–2 x/week thereafter.

IL-2 therapy was interrupted if patient developed refractory hypotension or respiratory distress due to pulmonary edema. Development of acute left ventricle failure or increase in serum creatinine to a level of >3 mg/dl were also used as indications to stop IL-2 administration. IL-2 therapy could be restarted after recovery from acute toxicity which generally resolved within 12 to 24 hours. The subsequent dose of IL-2 in such cases was reduced to 2 × 10⁶ U/m² (6 × 10⁶ IU/m²) per day. Biotherapy was also withheld if platelet counts fell to <20,000/mm² during the period of drug administration.

Study design

The integration of biotherapy into chemotherapy was carried out as per the schema shown in Figure 1 and tested 2 different schedules of administering biochemotherapy. In the first program, designated alternating biochemotherapy, chemotherapy and biotherapy were used in an alternating schedule at 6-week intervals. When the preliminary results of this treatment regimen failed to show any evidence of additive antitumor activity, a sequential biochemotherapy program was designed where one component of therapy was followed by the other in an immediate sequence. In both programs, patients were randomly assigned, using a balanced block design, to begin either with chemotherapy followed by biotherapy (CVD/Bio) or biotherapy followed by chemotherapy (Bio/CVD). In order to attain comparability in the distribution of various patient characteristics, all patients were stratified by sex, performance status (PS 0 versus PS 1–2) and tumor characteristics defined as favorable (small volume soft tissue or lung metastases) versus unfavorable (bulky tumor with a diameter of >8 cm. in soft tissues or aggregate of lung metastases and/or any visceral metastases in organs such as liver, brain or bone).

Table 1. Dose and schedule of biochemotherapy.

<table>
<thead>
<tr>
<th>Biotherapy regimen (IL-2 + IFN-α)</th>
<th>Chemotherapy regimen (CVD)</th>
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</thead>
<tbody>
<tr>
<td>Interferon-α 2a: 5 × 10⁶ U/m²/d × 5 days SC</td>
<td>Cisplatin 20 mg/m²/d × 4 days</td>
</tr>
<tr>
<td>Interleukin-2: 9 × 10⁶ IU/m²/d × 4 days i.v. CI</td>
<td>Vinblastine 1.6 mg/m²/d × 5 days</td>
</tr>
<tr>
<td>DTIC 800 mg/m²/d × 1 day</td>
<td>DTIC 800 mg/m²/d × 1 day</td>
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</table>

The CVD regimen was repeated q 21 days and biotherapy was administered before or after CVD.

of the IL-2 induced hypotension and for symptomatic control of constitutional toxicities due to biotherapy.

Study design

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**Alternating biochemotherapy**

In order to avoid overlapping toxicities of chemotherapy and biotherapy, the alternating program was explored initially in a group of 40 patients. Patients randomized to chemotherapy received 2 cycles of CVD during the first 6 weeks of treatment and then went on to receive biotherapy. Patients showing response to initial CVD (CR, PR, MR) subsequently received alternating cycles of biotherapy and chemotherapy at 6-week intervals for a total of 6 cycles of CVD and 3 courses of biotherapy. Patients who progressed during initial CVD were treated subsequently with biotherapy alone. Patients who were initially randomized to biotherapy received IL-2 + interferon daily ×5/week for 3 weeks and were off therapy for the subsequent 3 weeks at which time their response to biotherapy was assessed. Those patients showing any evidence of objective response to the first 3-week course of biotherapy received a second course of biotherapy starting 6 weeks from the beginning of treatment. After the first 2 courses of biotherapy, patients went on to receive 2 courses of CVD and subsequently received 6-week alternating courses of biotherapy and CVD for those responding to biotherapy whereas the biotherapy failures received CVD alone. Overall, the responding patients received a maximum of 6 cycles of CVD and 3–4 courses of biotherapy.

**Sequential biochemotherapy**

In the sequential biochemotherapy program, patients were randomized to receive either CVD followed by biotherapy beginning the next day after completion of chemotherapy (CVD/Bio sequence) or begin with biotherapy over 5 days followed by CVD beginning on day 6 (Bio/CVD sequence). In both sequential programs, the next course of biotherapy was started on or about day 16 of the CVD cycle or as soon as patient started to show some recovery from myelosuppression (ANC >500/mm³, platelets >50,000/mm³) caused by the preceding course of CVD. In the Bio/ CVD sequence, patients received biotherapy both prior to and immediately after CVD during the periods of time when patients had not yet developed significant myelosuppression (Figure 1). The response to sequential biochemotherapy was assessed after 6 weeks (2 cycles of CVD) of therapy. Patients who achieved an objective response (CR or PR) continued on treatment for another 6 weeks, whereas those who had no objective regression of tumor were taken off study. After completing 4 cycles of biochemotherapy over a period of 12 weeks, the responding patients continued on CVD alone for 2 additional courses, for a total of 6 cycles of CVD for the entire treatment program delivered over 18 weeks. No subsequent maintenance therapy was prescribed and the patients were monitored at 2–3-month intervals, off all therapy. Retreatment was offered to those patients who had either a prior complete response or a good quality PR such that the tumor relapsed >6 months after the last cycle of chemotherapy.

**Response criteria**

Response was measured after 6 weeks of initial therapy. Complete response (CR) was defined as a complete resolution of all clinical and radiological evidence of disease, lasting for a minimum of 4 weeks. Patients with minimal residual disease on CT examination were also considered in CR if the residual changes were so minuscule as to be compatible with scar tissue as well as by the stability of the residue for a period of more than 12 months and by subsequent lack of relapse at the original site of metastasis. A partial response (PR) was defined as a reduction of 50% or greater in measurable metastases calculated by the sum of products of the greatest perpendicular diameters, without appearance of any new metastases. A <50% regression of tumor was considered a minor response (MR). Progressive disease (PD) was defined as >25% increase over baseline tumor measurements or appearance of any new lesions. No change (NC) or stable disease category was used for patients whose tumor showed no progression or regression after a period of 6 weeks of therapy. Response duration was measured from the onset of treatment to the time of first evidence of progressive disease, and hence equated with time to progression (TTP).

**Statistical methods**

The results of alternating and sequential biochemotherapy programs were compared to our historical results with the CVD regimen which was used in 50 consecutive patients and reported previously [1]. Survival curves were plotted using the product limit method of Kaplan and Meier. Although patients were not prospectively randomized among the 3 different treatment regimens, the differences in TTP and in survival curves were tested using the log rank test in order to obtain an estimate of the impact of this therapy on survival. The differences in the proportions were tested by the Chi-square method or Fisher's exact test.

**Results**

**Alternating biochemotherapy**

From May 1989 to October 1990, 40 patients with advanced metastatic melanoma were entered on the alternating biochemotherapy protocol (Table 2). Twenty-one patients were randomized initially to biotherapy and 19 to the CVD regimen. One patient died due to myocardial infarction on day 10 following the first cycle of CVD and is not included in further analyses. Of the 21 patients randomized to initial biotherapy, 5 attained PR (24%), 1 MR and 15 progressed after 6 weeks of therapy (Table 3). The PRs were observed in visceral metastases (3), lung (1) and soft tissue lesions (1). Among the 18 evaluable patients who received initial chemotherapy, there were 2 PRs (11%), 4 MRs and 12 PD after 6 weeks of therapy. The final therapeutic result of both treatment regimens taken together yield-

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<table>
<thead>
<tr>
<th>Table 2. Patient characteristics.</th>
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<tbody>
<tr>
<td>CVD regimen</td>
</tr>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Males/females</td>
</tr>
<tr>
<td>Median Age</td>
</tr>
<tr>
<td>(Range)</td>
</tr>
<tr>
<td>Performance status (%)</td>
</tr>
<tr>
<td>0–1</td>
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<tr>
<td>2, 3</td>
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<tr>
<td>Number of disease sites (%)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3 or more</td>
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<tr>
<td>Sites of metastasis (%)</td>
</tr>
<tr>
<td>Soft tissue</td>
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<tr>
<td>Lung ± soft tissue</td>
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<tr>
<td>Visceral</td>
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<tr>
<td>Liver</td>
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<tr>
<td>Bone</td>
</tr>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>Other viscera</td>
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</table>
ed 2 CRs and 11 PRs for an overall response rate of 33% (95% CI, 19%-50%) among 39 evaluable patients. There were 10 patients who had a minor response and 16 failed to have any response. Despite the poor overall results with alternating biochemotherapy, the 2 patients who attained CR have continued to be free of disease for 72+ months and 75+ months. Both patients received initial biotherapy, one achieved a CR in liver and skin metastases and subsequently achieved a CR on CVD alternating with biotherapy and the second patient, with a large soft tissue mass, progressed on biotherapy but achieved a CR on CVD used subsequently. Besides these 2 patients, a third patient is alive for 72+ months. She initially progressed on CVD, then achieved a short PR on biotherapy and subsequently was rendered disease free with surgical resection of the residual tumor in the skin. All the remaining patients have expired. The median survival of the entire group of patients on alternating biochemotherapy was 11 months.

**Sequential biochemotherapy**

Between October 1990 to October 1992, 62 patients with advanced metastatic melanoma were registered on the Sequential Biochemotherapy study (Table 2). Among them, there were 43 males and 19 females with a median age of 42 (range, 20–63 years). All except 6 patients had a PS of 0 or 1. No prior systemic therapy had been used in any patient although prior surgical resection and/or whole brain radiotherapy had been carried out in 7 patients who had brain metastasis from melanoma. The general characteristics of patients included in the two biochemotherapy trials were not significantly different when compared to patients treated with the CVD regimen, which preceded the biochemotherapy studies and are shown in Table 2.

Response to treatment was assessed after 6 weeks of therapy during which all patients received 2 cycles of CVD and three 5-day cycles of biotherapy given as per Figure 1. Two patients died due to toxicity prior to assessment of response, leaving 60 patients evaluable for response. Fourteen patients achieved complete response for a CR rate of 23%. In addition, 23 patients attained PR, 11 had MR, 5 had stable disease and 7 patients had progressive disease (Table 3). Thus the overall CR + PR rate among the 62 registered patients was 60% (95% CI, 47%-72%). The response to biochemotherapy was rapid in onset and was often noted within 2 to 3 weeks from the beginning of the first course of treatment. Nearly all the responders achieved a PR by the time of their first assessment of response after 6 weeks of therapy. Interestingly, the response rate was influenced by the sequence of administration of chemotherapy and biotherapy (Table 3). Among the 32 patients treated with CVD followed by biotherapy (CVD/Bio), there were 11 CRs (34%) and 11 PRs for an overall response rate of 69%. In contrast, among the 30 patients treated with biotherapy followed by CVD (Bio/CVD), there were 3 CRs (10%) and 12 PRs for a response rate of 50%. Although the overall response rates are not significantly different ($P = 0.21$), the difference in the CR rate between the 2 sequences is statistically significant ($P = 0.03$).

The overall median survival of 60 patients on sequential biochemotherapy was 13 months. At a median follow up of 45 months (range 33–57 months) 15 of 62 patients (24%) were alive at the time of last analysis in July 1995; 11 were disease free and 4 were alive with disease. Nine patients (8 CR + 1 PR) have stayed progression-free following completion of their biochemotherapy, whereas 2 patients (1 PR and 1 CR) had resection of residual or recurrent disease and were surgically rendered free of disease (SCR). Among the 14 CRs induced with biochemotherapy, 8 patients have no evidence of residual disease and have been progression-free for periods of 40+ months to 52+ months. The characteristics of these 8 patients with durable CRs are shown in Table 4. The median duration of 23 PRs was 8 months and all except 2 patients have relapsed and subsequently died. One of the PRs has slowly regressing perinephric disease and still has some residual density on CT scan of the abdomen. She also has had resection of a metastatic brain lesion and is currently alive and well, 60+ months from the beginning of her therapy. The second patient, after attaining PR, had surgical resection of the residual tumor in her breast and is categorized as a surgical CR (SCR).
Table 4. Characteristics of patients with durable CRs induced by sequential biochemotherapy.a

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Metastatic sites</th>
<th>Dates of treatment</th>
<th>Duration of responseb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. J.C.</td>
<td>36</td>
<td>M</td>
<td>Lymph nodes</td>
<td>3/91 8/91</td>
<td>52+ Mo</td>
</tr>
<tr>
<td>2. H.S.</td>
<td>21</td>
<td>M</td>
<td>Abdominal mass</td>
<td>3/91 9/91</td>
<td>52+ Mo</td>
</tr>
<tr>
<td>3. P.B.</td>
<td>46</td>
<td>M</td>
<td>Lung</td>
<td>11/91 4/92</td>
<td>48+ Mo</td>
</tr>
<tr>
<td>4. R.H.</td>
<td>41</td>
<td>M</td>
<td>Liverc</td>
<td>12/91 7/92</td>
<td>48+ Mo</td>
</tr>
<tr>
<td>5. G.B.</td>
<td>30</td>
<td>M</td>
<td>Mediastinum, neck nodes</td>
<td>5/92 10/92</td>
<td>42+ Mo</td>
</tr>
<tr>
<td>6. D.F.</td>
<td>35</td>
<td>M</td>
<td>Lung, pleura</td>
<td>5/92 12/92</td>
<td>41+ Mo</td>
</tr>
<tr>
<td>7. J.M.</td>
<td>44</td>
<td>F</td>
<td>Liver, lung, lymph nodes</td>
<td>6/92 11/92</td>
<td>40+ Mo</td>
</tr>
<tr>
<td>8. JJ.</td>
<td>45</td>
<td>M</td>
<td>Lung, Liver, spleen</td>
<td>8/92 1/93</td>
<td>40+ Mo</td>
</tr>
</tbody>
</table>

a All durable CRs received their treatment on the CVD/Bio sequence; none of the CRs on the Bio/CVD sequence were durable.
b Duration of response is defined as progression-free period in months.
c Not biopsy proven (? Hemangiomas).

In Figure 2, the time to progression (TTP) of disease in patients treated with the alternating and the sequential biochemotherapy programs is compared to that of patients treated with the CVD regimen. The median values for TTP were 4 months for CVD, 5.8 months for alternating and 7.5 months for sequential biochemotherapy. There is a definite trend for a longer TTP between sequential biochemotherapy versus CVD (P = 0.06). The survival of patients treated with the three treatment programs are compared in Figure 3. The median survival for the CVD regimen was 9 months in comparison to 11 months for the alternating and 13 months for sequential biochemotherapy. The survival difference between sequential biochemotherapy and the CVD regimen was significant (P = 0.04).

There is also a trend for a longer survival with the sequential program in comparison to the alternating biochemotherapy (P = 0.06). The TTP between the CVD/Bio versus the Bio/CVD sequence of sequential biochemotherapy are compared to TTP of the CVD regimen in Figure 4. The median duration for the CVD/Bio sequence was 7.9 months versus 7.4 months for the Bio/CVD sequence (P = 0.02). The differences between the CVD regimen and the CVD/Bio sequence...
were significant \( (P = 0.02) \) but not so between the Bio/CVD sequence versus CVD \( (P = 0.45) \). The survival curves of the 2 sequential programs in comparison to that of the CVD regimen are shown in Figure 5. The median survival of CVD/Bio sequence (11.7 months) was significantly longer in comparison to the survival of the CVD regimen (9 months) \( (P = 0.02) \). The difference between Bio/CVD sequence versus CVD alone was not significant and neither was the difference in the survival between the 2 different sequences of the Sequential Biochemotherapy program \( (P = 0.10) \).

Toxicity

The predominant toxicity of alternating biochemotherapy was that related to the biotherapy component. Among the 36 patients who received biotherapy, all experienced the constitutional symptoms of chills, fever, myalgias and fatigue. Anorexia, nausea and vomiting of grade I–II were observed in all patients despite the use of antiemetics. Nearly all patients experienced grade I–II diarrhea. The most significant toxicity was liver dysfunction of grade III to IV in 34 patients. However it was mostly in the form of increase in the liver enzymes particularly alkaline phosphatase with only 4 patients showing significant increase (> 3 mg/dl) in bilirubin. Serum creatinine elevations of grade I or II were observed in a majority of patients. Both hepatic and renal function abnormalities were rapidly reversible over several days. Hypotension was observed in 28 patients (78%) but was grade III–IV only in 18 patients (50%) requiring either extra i.v. fluids or the additional use of dopamine to sustain the systolic blood pressure above 90 mm Hg. Six patients had grade IV hypotension (17%) requiring temporary interruption of IL-2 infusion usually on the last day of therapy. The hematologic toxicity of this program was predominantly due to CVD which produced a median nadir WBC count of 1300/mm\(^3\) (ANC = 0) and a median nadir platelet count of 46,000/mm\(^3\). During the period of neutropenia 13 of 39 (33%) patients developed fever requiring antibiotics. Patients also experienced neutropenia during the biotherapy cycles which was milder, with a median nadir neutrophil count of 1100/mm\(^3\) and a median nadir platelet count of 111,000/mm\(^3\) (range 15–175,000/mm\(^3\)). Anemia was also common during both components of therapy and frequently required RBC transfusions.

The toxicity of sequential biochemotherapy was more severe, especially the hematologic effects. Nearly all patients had grade IV neutropenia resulting in a nadir neutrophil count of 100/mm\(^3\) during the first 2 cycles of biochemotherapy, which dropped to zero when the median for all cycles was calculated. Grade IV thrombocytopenia was experienced by 38 patients (61%). Both neutropenia and thrombocytopenia were more severe with the CVD/Bio sequence compared to the Bio/CVD sequence. The neutropenia was complicated by fever requiring antibiotics in 44 patients (71%) during the complete course of their treatment. Among these patients, 14 had neutropenic fever without documented infection whereas 30 patients had positive blood cultures, predominantly with gram-positive organisms, the most frequent being coagulase-negative staphylococci in 14 patients. Two or more episodes of infection occurred in 20 patients. Two patients died of septic shock, both occurring in the CVD/Bio sequence, on the last day of biotherapy in the presence of severe neutropenia and fever induced by IL-2. The non-hematologic toxicity of sequential biochemotherapy using the NCI common toxicity criteria is shown in Table 5. Nine (15%) patients developed life-threatening toxicities requiring transfer to the intensive care unit. These included pulmonary edema (4), congestive heart failure (2), septic shock (2) and GI bleeding (1).

A majority of patients were bed-fast during the 5 days of therapy and did not get outside their hospital room due to extreme fatigue. Oral intake was limited due to the anorexia and frequent nausea, resulting in weight loss in nearly all patients. The median weight loss was 10 kg, range 0–25 kg. All side effects worsened during each successive day of therapy, such that the last 24–48 hours of each 5-day cycle were more distressing. Both myelosuppression and hypotension were cumulative with each successive cycle of therapy, often requiring dose reductions in chemotherapy and sometimes in IL-2. The dose of interferon was kept constant except in a few patients who developed grade IV thrombocytopenia during the biotherapy cycles and required withholding of 5th dose of therapy.
even involving visceral sites, will be cured with the biochemotherapy regimens reported here. Similar reports of occasional durable CRs have been reported both with interferon-alpha [23] and interleukin-2 [8] therapy in advanced melanoma, but the proportion of CRs with biochemotherapy appears to be substantially increased.

The overall survival impact of biochemotherapy is more modest in comparison to the survival of CVD-treated patients, probably due to a predominance of PRs which were similar in duration to the PRs induced by chemotherapy alone. Moreover our study has the caveat of a non-randomized study design which limits our ability to draw firm conclusions. A prospective comparison of biochemotherapy with the standard therapy using chemotherapy alone would be required in order to provide conclusive evidence of the superiority of biochemotherapy over chemotherapy. Such a study has been initiated at our institution where the CVD/Bio regimen is being prospectively compared to the CVD regimen, using a randomized study design.

Although we are encouraged by the improvement in results of treatment using sequential biochemotherapy, the toxicity of this regimen is quite severe and not likely to be tolerable in patients who are elderly (>70 years) and by those in compromised physical condition due to impaired cardiovascular function or due to the existence of multiple brain metastases. However a majority of the patients with metastatic melanoma are under the age of 60 years, such that they can tolerate intense treatment regimens despite their substantial toxicity. Furthermore, the recent availability of hematopoietic growth factors makes it possible to reduce the severity of myelosuppression and the associated risk of infections. In order to further reduce the risk of infections due to biochemotherapy, we have recently modified our CVD regimen by a 25% reduction in the dose of vinblastine to 1.5 mg/m^2/d x 4, keeping the dose of DTIC and cisplatin unchanged. This has significantly elevated the nadir neutrophil counts.

The biochemotherapy program as used in our study also required hospitalization which adds substantially to the cost of this therapy. Delivery of such a treatment regimen on an out-patient basis may be possible in the future but may require reduction in the dose of IL-2 to a level below 9 × 10^6 IU/m^2 which is probably below the threshold of dose which is active against metastatic melanoma [24]. However the experience with lower doses of IL-2 in melanoma is quite limited and needs further study using a dose range of 6–9 × 10^6 IU/m^2 S.C. which is clearly active in patients with metastatic renal carcinoma where IL-2 therapy is increasingly used on an outpatient basis without compromising its anti-tumor activity. Such trials have recently been initiated in patients with metastatic melanoma and will yield useful results in the near future. Because the sequential use of chemotherapy and biotherapy is quite lengthy, we have also conducted a recent study where the chemotherapy and biotherapy components of this treatment were delivered concurrently, compressing the
duration of treatment from 10 days to 5 days, q 21 days. This program of concurrent biochemotherapy has also yielded preliminary results with a high response rate as well as a CR rate of nearly 20% [22]. Whether the overall efficacy of concurrent biochemotherapy, especially the durable CRs, will prove to be equivalent to that of sequential biochemotherapy is not yet clear and will require longer follow up of patients treated on this program.

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Correspondence to:
Sewa S. Legha, MD
Section of Melanoma Medical Oncology
M.D. Anderson Cancer Center
1515 Holcombe Boulevard, Box 77
Houston, TX 77030, USA