



Jennifer Eisenpresser. *From the Fourteenth Floor*. Oil on canvas, 50" × 56".

*Results from biochemotherapy protocols suggest an improvement in response rates for patients with systemic melanoma when compared with single-agent therapy.*

# Metastatic Melanoma: Chemotherapy to Biochemotherapy

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**Background:** *Single-agent or combination chemotherapy regimens have not impacted the short median survival of patients with metastatic melanoma, and complete or durable responses are rare. Biologic response modifiers (interferon and interleukin-2) have produced durable remissions in a small cohort of patients, and phase II trials of biochemotherapy suggest more benefit.*

**Methods:** *The authors retrospectively reviewed the status of the current treatments of metastatic melanoma focusing on biochemotherapy.*

**Results:** *Regimens include both sequential and concurrent approaches for inpatient and outpatient treatment settings. Overall response rates in phase II trials are 40% to 60% with complete responses of 10% to 20% and median survivals in the 11- to 12-month range. Modifications of concurrent biochemotherapy regimens have maintained efficacy and reduced toxicity. Small phase III trials suggest a survival advantage of biochemotherapy ( $P=.05$ ).*

**Conclusions:** *Biochemotherapy remains a promising new treatment for metastatic melanoma. A large Intergroup trial E3695 comparing concurrent biochemotherapy to combination chemotherapy alone is powered to answer important survival questions.*

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## Introduction

The incidence of melanoma has steadily increased over the past 3 decades. In 2001, approximately 50,000 new cases will have been diagnosed and almost 10,000 deaths will have occurred.<sup>1</sup> Importantly, melanoma strikes individuals in the prime of their lives (median age 45 years), almost 2 decades before most solid tumors arise (breast, colon, lung, prostate).

Prompt detection and surgical treatment of early-stage disease can cure most patients. However, the majority of patients with deep primary tumors or tumors that metastasize to regional lymph nodes will succumb to distant metastases. Median survival after the onset of distant metastases is only 6 to 9 months, and the 5-year survival rate is less than 5%.<sup>2,4</sup> Novel treatment approaches are needed.

## Single-Agent Chemotherapy

Single-agent chemotherapy has been ineffective in the treatment of advanced melanoma. Dacarbazine, the only drug approved by the US Food and Drug Administration (FDA) for treatment of melanoma, has a response rate of only 10% to 20%.<sup>5,6</sup> Complete or durable responses are rare, median survival is not improved, and the 5-year survival rate remains less than 2%.<sup>7</sup> Other single-agent chemotherapy agents including platinum compounds, vinca alkaloids, nitrosoureas, and taxanes have similar activity as dacarbazine and have not improved clinical outcome.<sup>4</sup> Temozolomide, an oral formulation of dacarbazine with central nervous system (CNS) penetration, has been recently approved by the FDA for treatment of high-grade gliomas. Studies of temozolomide in advanced melanoma suggest a comparable systemic response rate as that seen with dacarbazine (15% to 20%).<sup>8,9</sup> Current clinical trials are evaluating the role of temozolomide in the prevention and treatment of melanoma CNS metastases, an increasingly common and important clinical challenge.

## Combination Chemotherapy

The disappointing results of single-agent chemotherapy led to the development of combination regimens in the 1980s in efforts to improve outcome in patients with metastatic disease. Initial combinations added either a vinca alkaloid or cisplatin to dacarbazine. Minimal improvement in response rate (20% to 30%) was observed.<sup>4</sup> More aggressive multi-agent combinations followed and resulted in response rates of 30% to 50% in single-institution phase II trials. Two published regimens, the Dartmouth regimen<sup>10</sup> (carmustine, cisplatin, dacarbazine, and tamoxifen) and CVD<sup>11</sup> (cisplatin, vinblastine, and dacarbazine) were commonly used as standard treatment for metastatic disease in the community. Despite encouraging response rates, complete or durable remissions remained rare. A phase III community-based trial sponsored by M.D. Anderson comparing CVD to dacarbazine alone was published in abstract form. Although there was a trend toward improved response rate and survival in the combination chemotherapy arm, these results were not statistically

significant.<sup>12</sup> More recently, a larger phase III trial comparing the Dartmouth regimen to dacarbazine alone was published. There was a trend for improved response rate (18.5 % vs 10.2 %) in the combination chemotherapy arm, but this was not statistically significant. No improvement was seen in median or long-term survival in the combination arm, and toxicity was greater with combination chemotherapy.<sup>13</sup> Since survival has not been shown to be improved by the use of single or combination chemotherapy for metastatic melanoma, treatment decisions remain controversial, and quality of life and toxicity issues from treatment assume greater importance.

## Tamoxifen

Tamoxifen has a long-standing and controversial history in the treatment of advanced melanoma. Proportions of melanoma cells were recognized to express estrogen receptors leading to a series of clinical trials with antiestrogen therapy.

Initial case reports suggested activity of single-agent tamoxifen in metastatic melanoma. However, a large European tamoxifen trial demonstrated a disappointing objective response rate of only 5%.<sup>14</sup> Failing as a single agent, tamoxifen was next tested in combination with chemotherapy. Cocconi et al<sup>15</sup> published a small phase III trial demonstrating an improvement of response (28% vs 12%,  $P=.03$ ) and survival (48 weeks vs 29 weeks,  $P=.02$ ) with the addition of tamoxifen to dacarbazine compared to dacarbazine alone. McClay et al<sup>16,17</sup> reported a significant reduction in the objective response rate when tamoxifen was omitted from the combination chemotherapy Dartmouth regimen in a series of small phase II trials.

Clinical data supporting the value of tamoxifen in combination with chemotherapy were supported by preclinical models. These models suggested that high-dose tamoxifen synergized with cisplatin and reversed multidrug resistance (MDR).<sup>18-23</sup> However, in the last decade, two large randomized trials<sup>24,25</sup> with low- and high-dose tamoxifen in combination with either dacarbazine alone or the Dartmouth regimen failed to demonstrate an advantage to the addition of tamoxifen. Recently, a recent phase II study of high-dose tamoxifen added to concurrent biochemotherapy did not improve response rate or survival.<sup>26</sup>

Despite a rationale for antiestrogen therapy in melanoma, supportive preclinical data, and encouraging early clinical data, larger randomized trials have failed to find a supportive role for tamoxifen in the treatment of metastatic melanoma.

## Biologic Response Modifiers

The relationship between melanoma and the immune system has been recognized for decades. This has led to intensive study of immune-based treatment strategies with biologic response modifiers. Interferon and interleukin-2 (IL-2) have important roles in both adjuvant therapy and treatment of metastatic disease.

Interferon has direct antiproliferative effects on melanoma cells and indirect effects of modulating host immune response.<sup>27</sup> Single-agent interferon alfa has a response rate of 15% and complete remission rates of 3% to 5% in advanced disease.<sup>28</sup> Interferon added to dacarbazine in a small phase II trial by Falkson et al<sup>29</sup> resulted in an encouraging response rate of 53%. However, a follow-up large randomized trial demonstrated no benefit for the addition of interferon to dacarbazine.<sup>24</sup> Recently, high-dose interferon alfa-2b has been approved by the FDA for the adjuvant treatment of stage IIB and III disease based on the results of a large randomized clinical trial demonstrating a survival advantage to interferon compared to observation (E1684).<sup>30</sup>

IL-2 does not have direct cytotoxic effects on melanoma cells, but it indirectly causes tumor cell lysis by proliferating and activating cytotoxic T lymphocytes. Preclinical data of IL-2 support a dose-response relationship favoring high-dose therapy.<sup>27,28</sup> Rosenberg et al<sup>31</sup> treated a series of metastatic melanoma patients in NCI-sponsored phase II trials with a high-dose bolus schedule of IL-2. Objective responses were observed in 15% to 20% of patients. More importantly, 5% to 7% of patients achieved complete, durable remissions of disease and the 7-year survival rate was 10%.<sup>32</sup> This durability of response and survival led to FDA approval of IL-2 for the treatment of metastatic melanoma without randomized trial data. Toxicity resulting from high-dose IL-2 remains a formidable barrier to more widespread use. In younger patients with preserved performance status and absence of comorbid cardiovascular disease, high-dose IL-2 remains an established treatment option. In an effort to improve efficacy, Rosenberg and colleagues at the NCI are conducting a series of trials with high-dose bolus IL-2 with or without a combination of HLA-matched peptide vaccines.

Alternative IL-2 dosing schedules have been tested in a number of clinical trials. Intermediate- and high-dose continuous infusion schedules ( $18 \times 10^6$  IU/day for 5 days) remain common treatments in Europe and result in comparable objective responses (15% to 20%) as high-dose bolus IL-2.<sup>33-35</sup> In addition, durable remissions are observed in a small subset of patients. More recently, the European investigators piloted continuous

infusion IL-2 in a decrescendo-dosing schedule. A small randomized phase III trial comparing continuous infusion IL-2 plus interferon vs continuous infusion decrescendo IL-2 plus interferon demonstrated improved response rates and reduced toxicity with decrescendo dosing.<sup>36</sup> This is now the standard dosing schedule for incorporation of IL-2 in biochemotherapy regimens in Europe.

Subcutaneous outpatient dosing of IL-2 is desirable in efforts to reduce the toxicity and high inpatient costs of treatment. To date, however, objective responses to low-dose subcutaneous IL-2 as a single agent in metastatic melanoma have been inconsistent. This observation differs from the data with low-dose IL-2 in metastatic renal cell carcinoma. A recent randomized phase II study<sup>37</sup> of outpatient biochemotherapy incorporating either subcutaneous or intravenous bolus IL-2 has reported response rates and durable responses that are superior in the intravenous IL-2 arm. Additional ongoing clinical trials in metastatic melanoma are investigating the addition of histamine to low-dose IL-2 on an outpatient basis. Preclinical data suggest that histamine augments the antitumor response of IL-2.<sup>38</sup> A randomized trial that compared outpatient low-dose IL-2 with or without histamine in metastatic melanoma reported that overall survival was not different between the two arms.<sup>39</sup> However, the subgroup of patients with liver metastases demonstrated significant improvement in survival with IL-2/histamine compared with IL-2 alone. A confirmatory phase III trial will open in early 2002 in the United States and Europe comparing outpatient subcutaneous IL-2 with or without histamine in patients with liver metastases.

## Biochemotherapy

### *Sequential Biochemotherapy*

Biochemotherapy, the combination of chemotherapy and biologic response modifiers, was developed in the early 1990s to improve response rates and durable remissions in metastatic melanoma. The initial regimens were given sequentially (chemotherapy followed by biologic response modifiers) because of concern of toxicity if all the drugs were given simultaneously (Table 1).<sup>40-44</sup> Single-institution phase II studies<sup>45-48</sup> consistently demonstrated objective response rates of 50% to 60%, complete remission rates of 10% to 20%, and a median survival of approximately 11-12 months. Paradoxically, these sequential regimens were highly toxic because of the duration of treatment (10 to 14 days) and the combined and non-overlapping toxicities of chemotherapy and biologic response modifiers. Investigators at M.D. Anderson have recently reported the

first single-institution phase III randomized trial of sequential biochemotherapy (CVD-Bio) compared with combination chemotherapy (CVD) alone.<sup>49</sup> This trial demonstrated a significant improvement of response and time to progression favoring the biochemotherapy arm and a 3-month improvement in median survival ( $P=.05$ ). However, the toxicity of sequential biochemotherapy was considerable, resulting in prolonged hospitalization. The toxicity and expense of this regimen have precluded its general use in community-based settings.

### Outpatient Sequential Biochemotherapy

Preclinical and early clinical data suggested high-dose IL-2 was necessary for objective clinical responses that precluded outpatient regimens. However, a clinical dose threshold of IL-2 has never been clearly established. With this in mind, an outpatient sequential biochemotherapy regimen (carmustine, cisplatin, dacarbazine, tamoxifen, IL-2, and interferon with lower-dose subcutaneous IL-2 and interferon) was developed by Thompson et al.<sup>43</sup> A single-institution phase II trial suggested efficacy was preserved and toxicity was reduced compared to inpatient sequential regimens. A large multicenter phase II trial with this outpatient biochemotherapy regimen is complete but not yet

reported. Flaherty et al<sup>44</sup> recently published the results of a randomized phase II trial of outpatient sequential biochemotherapy (dacarbazine, cisplatin, IL-2, and interferon). This trial was designed to determine whether dose and schedule of IL-2 are critical to the efficacy of biochemotherapy. Low-dose subcutaneous IL-2 (5 MU/m<sup>2</sup>) was compared to higher-dose intravenous IL-2 (18 MU/m<sup>2</sup>). The overall response rate (36% vs 17%) and complete remission rate (11% vs 3%) was superior in the intravenous IL-2 arm. If the response activity of this outpatient intravenous IL-2 regimen is confirmed, it will likely be compared with inpatient biochemotherapy regimens in subsequent randomized trials. The dose threshold of IL-2 for durable clinical responses remains an active research question.

### Concurrent Biochemotherapy

The first concurrent inpatient biochemotherapy regimen was developed by Legha et al<sup>40</sup> in an effort to maintain IL-2 dose intensity and reduce toxicity. The “Legha” regimen combined cisplatin, vinblastine, and dacarbazine (CVD) chemotherapy with continuous infusion IL-2 (9 MU/m<sup>2</sup> per day) for 4 days and 5 days of subcutaneous interferon alfa (5 MU/m<sup>2</sup> per day) at 21-day intervals. The results were encouraging with an overall response rate of 64%, a complete response

Table 1. — Phase II Results for Chemotherapy With Interleukin-2 Infusion and Interferon

	Principal Investigator	Regimen/Dose	No. of Patients	Response			Comments
				Complete Response	Partial Response	Total	
<b>IL-2 Infusion and IFN-<math>\alpha</math>2</b>	Legha <sup>40</sup>	Concurrent CVD/IL-2 infusion/IFN- $\alpha$ 2 SC	53	11 (21%)	23 (43%)	64%	Survival for concurrent and sequential therapy equivalent
	McDermott <sup>41</sup>	Modified concurrent CVD/IL-2 infusion/IFN- $\alpha$ 2 SC	40	8 (20%)	11 (28%)	48%	Response rate equivalent in patients with prior IFN; frequent CNS relapse
	O'Day <sup>42</sup>	Concurrent CVD/ tamoxifen “decrecendo” IL-2/IFN- $\alpha$ 2 SC	45	10 (23%)	15 (34%)	57%	14% disease-free from 10-36 mo
	Total		138	29 (21%)	49 (36%)	57%	
<b>IL-2 SC and IFN-<math>\alpha</math> SC</b>	Thompson <sup>43</sup>	CBDT/IL-2 (SC)/IFN- $\alpha$ 2	53	10 (19%)	12 (23%)	42%	2 complete responses ongoing >2 y
	Flaherty <sup>44</sup>	CD/IL-2 (SC)/IFN- $\alpha$ 2 vs CD/IL-2 (IV)/IFN- $\alpha$ 2	38	1 (3%)	6 (16%)	19%	Randomized phase II study; results suggest improved results with IV IL-2
			44	5 (12%)	11 (25%)	37%	
Total		135	16 (12%)	29 (21%)	33%		
B = carmustine C = cisplatin CNS = central nervous system D = dacarbazine IFN = interferon- $\alpha$		IL-2 = interleukin-2 T = tamoxifen V = vinblastine SC = subcutaneous IV = intravenous					
From Lotze M, Dallal R, Kirkwood J, et al. Cutaneous melanoma. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. <i>Cancer: Principles &amp; Practice of Oncology</i> . 6th ed. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2001:2012-2069. Chap 42. Reprinted with permission.							

rate of 21%, median survival of 12 months, and a 2-year survival rate of 10%. Efficacy was comparable to the inpatient sequential regimens, but the regimen was significantly less toxic. Without the routine use of growth factor support, fever/neutropenia occurred in 64% of patients and was the most significant reversible toxicity.

### *Toxicity Concurrent Biochemotherapy*

Despite reduction of toxicity with concurrent biochemotherapy regimens, overall toxicity remains high compared with other neoplastic therapies for cancer. Biochemotherapy patients can be managed on inpatient oncology units without routine intensive monitoring or vasopressor support; however, all patients experience constitutional symptoms including fever, chills, rigors, myalgias, fatigue, anorexia, and headache to varying degrees. Gastrointestinal symptoms of nausea, vomiting, and diarrhea are also prominent. Hematologic toxicity is expected and includes leukopenia, anemia, and thrombocytopenia. Neutropenia and anemia can be well managed with empiric growth factor support. Cumulative thrombocytopenia is managed with dose reductions of chemotherapy. Intermediate-dose IL-2-specific toxicity includes varying degrees of capillary leak syndrome with hypotension, fluid retention, and third-spacing, pulmonary congestion and reversible end-organ dysfunction.

### *Modified Concurrent Biochemotherapy*

The Legha regimen was subsequently modified by McDermott et al<sup>41</sup> to reduce toxicity further so that treatment could be given safely in community-based hospital settings and tested in randomized clinical trials. The modifications included reduction in the vinblastine dose, empiric granulocyte colony-stimulating factor (G-CSF) posttreatment, routine 5-HT3 antagonist anti-emetic therapy, prophylactic antibiotics, frequent changes in central lines, dose reductions for toxicity, and limitation of treatment to a maximum of 4 cycles of therapy. In a phase II trial with these modifications, toxicity was improved and the response rate was 48%, the complete remission rate was 20%, and the median survival was 11 months. Fever/neutropenia was not observed. G-CSF has now become a standard component of concurrent biochemotherapy regimens. An Intergroup E3695 randomized trial comparing this modified Legha CVD-Bio regimen to CVD chemotherapy alone is ongoing.

Further modifications of the Legha regimen have been published<sup>42</sup> with decrescendo dosing of continuous infusion IL-2. The rationale for decrescendo dosing of IL-2 is based on improved clinical response and

reduced cumulative IL-2 toxicity in a small randomized trial.<sup>36</sup> The same total dose of IL-2 (36 MU/m<sup>2</sup> over 4 days) reported by Legha was given but in a front-loading decrescendo schedule (18 MU/m<sup>2</sup> on day 1, 9 MU/m<sup>2</sup> on day 2, and 4.5 MU/m<sup>2</sup> on days 3 and 4).<sup>42</sup> In a phase II trial of poor prognosis stage IV patients, the response rate was 57%, the complete remission rate was 23%, and the median survival was 11 to 12 months. Cumulative cardiovascular and capillary leak toxicity was improved compared to the original Legha concurrent regimen. Clinically significant pulmonary capillary leak was not observed. More than 85% of patients were discharged on the fifth hospital treatment day at the completion of their therapy.

In efforts to build on responses achieved with concurrent biochemotherapy and prevent rapid disease progression, a novel maintenance biotherapy protocol was developed with low-dose IL-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF) followed by inpatient intermittent high-dose decrescendo pulses of IL-2 over 48 hours.<sup>50</sup> In a pilot study, objective complete responses were observed in a small group of patients who achieved a partial response to biochemotherapy.<sup>50</sup> Overall survival appears prolonged compared with matched historical controls not treated with maintenance therapy. A multicenter phase II metastatic melanoma trial is ongoing with induction concurrent biochemotherapy (decrescendo IL-2) followed by maintenance biotherapy with IL-2 and GM-CSF for patients achieving stable disease, partial response, or complete remission.

## **Phase III Clinical Trials**

Currently four sequential biochemotherapy phase III trials have been completed,<sup>35,46,51,52</sup> and one concurrent biochemotherapy trial is ongoing<sup>44</sup> (Table 2). The trials reported to date have been small and generally underpowered to detect small survival differences.

The first was a 138-patient European study by Keilholz et al<sup>35</sup> of interferon and decrescendo IL-2 with or without cisplatin chemotherapy. Response rate was significantly increased from 18% to 33% with cisplatin ( $P=.04$ ). The median survival was similar — 9 months in both arms. However, the study was small and thus was powered to detect a 100% improvement in median survival from 12 to 24 months and a 2-year survival rate from 25% to 50%.

A larger phase III trial has recently been completed by the EORTC<sup>51</sup> comparing cisplatin, dacarbazine, and interferon with or without decrescendo IL-2. In a preliminary analysis of the first 118 patients, response rates

Table 2. — Phase III Trials of Biochemotherapy for Stage IV Melanoma

Trial (Principal Investigator)	Design	Status
European Organization for Research and Treatment of Cancer (Keilholz) <sup>35</sup>	Decrescendo IL-2 + IFN- $\alpha$ 2 + C vs decrescendo IL-2 + IFN- $\alpha$ 2	Higher response rate IL-2/IFN- $\alpha$ 2 + C, without overall survival difference
National Cancer Institute, Surgery Branch (Rosenberg) <sup>52</sup>	CD/tamoxifen vs CD/tamoxifen + high-dose IL-2 + IFN- $\alpha$ 2	No significant difference in response rate or survival between the two groups
European Organization for Research and Treatment of Cancer (Keilholz) <sup>51</sup>	CD/IFN- $\alpha$ 2 vs C/D/IFN- $\alpha$ 2 + IL-2	No significant difference in response rate or survival (preliminary analysis)
M.D. Anderson Cancer Center (Legha) <sup>46</sup>	CVD vs sequential CVD + IL-2/IFN- $\alpha$ 2	Higher response rate, time to progression, improved survival ( $P=.05$ ) favoring biochemotherapy
Eastern Cooperative Oncology Group/Southwest Oncology Group E3695 (Flaherty) <sup>44</sup>	CVD vs concurrent CVC + IL-2/IFN- $\alpha$ 2	Pending

C = cisplatin      IL-2 = interleukin-2  
D = dacarbazine      V = vinblastine  
IFN = interferon

Lotze M, Dallal R, Kirkwood J, et al. Cutaneous melanoma. In: Devita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. 6th ed. Philadelphia, Pa: Lippincott, Williams & Wilkins; 2001:2012-2069. Chap 42. Modified with permission.

were similar in the two arms (22% vs 28%, nonsignificant), and survival was comparable. In the subgroup of good performance status patients (ECOG 0), however, durable remissions were higher in the IL-2 arm (10 vs 2 patients). Conclusions regarding this trial will await final study analysis.

Rosenberg et al<sup>52</sup> at the NCI Surgery Branch performed a 102-patient randomized trial of sequential dacarbazine, cisplatin, tamoxifen, interferon and high-dose bolus IL-2 compared to the chemotherapy alone. No phase II data had been generated with this biochemotherapy regimen prior to phase III testing, and toxicity was considerable. The response rate was almost doubled in the biochemotherapy arm 44% vs 27% ( $P=.07$ ), but survival was not significantly different. In fact, there was a trend toward a survival advantage in the chemotherapy-alone arm (5.8 vs 10.7 months,  $P=.05$ ). The study was powered to detect a difference in response from 30% to 55%. It was not powered for survival analysis. The chemotherapy-alone arm had a projected 5-year survival rate of approximately 25% (suggesting patient selection), and crossover to high-dose bolus IL-2 therapy was allowed for patients treated with chemotherapy alone, which further complicated the survival analysis.

In 2000, Eton et al<sup>49</sup> presented the first US randomized study comparing sequential biochemotherapy to combination chemotherapy alone. This 183-patient study demonstrated a significant improvement in

response rate (25% to 48%) and time to progression (2.4 to 4.9 months) favoring the biochemotherapy arm. There was a 30% improvement in median survival from 9.2 to 11.9 months ( $P=.05$ ).

The current ECOG/Intergroup E3695 trial compares concurrent CVD-Bio to CVD chemotherapy alone. The accrual goal has recently been increased to 482 patients. This will have a 90% power to detect a 33% improvement in median survival from 9 to 12 months. The study should complete accrual in June 2002 and will be critical in determining the role of biochemotherapy in the treatment of advanced melanoma.

## Conclusions

Metastatic melanoma has remained refractory to systemic treatment for decades. Single-agent or combination chemotherapy or biologic response modifiers alone have not resulted in response rates of durable remissions that are high enough to affect median survival. In the past decade, biochemotherapy regimens have been developed that appear to produce systemic response in approximately 50% of patients and durable remissions in 10% to 20%. This may improve the median survival from 6–9 months to 12 months. Modified concurrent biochemotherapy regimens have preserved efficacy and reduced toxicity, thus allowing for larger randomized community-based clinical trials that are

currently ongoing. These trials will determine the role of biochemotherapy as first-line treatment for metastatic disease.

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