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MELANOMA CARE
OPTIONS

ISSUE NO. 3 MARCH 2005

FOSTERING AN INTERDISCIPLINARY APPROACH TO MELANOMA CARE

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Before breaking the seal, see how your melanoma management style compares to the styles of experts in the field by following these simple instructions:

- Read the case presentation below
- Circle your answers to the multiple-choice questions on the back cover
- Detach the perforated back page and fax your answers to 973-682-9077

Or, if you prefer, you can answer the questions and read the article on our Web site at www.MelanomaCare.org, where you can also complete CME materials and register for electronic delivery of *Melanoma Care Options.*

A Patient with Metastatic Melanoma

Lawrence E Flaherty, MD; Thomas E Olencki, DO; Laura Stover, RN, BSN

A 49-year-old white male presented with a primary melanoma on his left posterior calf. Biopsy found the lesion to be 4.89-mm thick with no ulceration. A wide local excision with 2-cm margins was performed along with a sentinel lymph node biopsy (SLNB). The SLNB was microscopically positive in one lymph node, and a completion lymph node dissection (CLND) found 3 additional positive nodes of the 10 dissected. The patient received 1 year of adjuvant high-dose interferon alfa-2b (IFN) therapy. Two years after completion of interferon therapy, a chest x-ray identified bilateral pulmonary nodules, which were confirmed by computerized tomography (CT) scans. Computerized tomography identified no metastases in other sites. The patient's physical examination was unremarkable, and his Karnofsky performance status (KPS) was 100%.

Before continuing, please answer the questions on the back cover and fax to 973-682-9077.

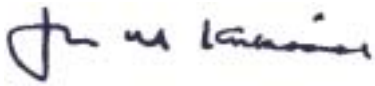
Chairman's Introduction

Dear Reader,

Welcome to ***Melanoma Care Options,*** an interactive newsletter that will put you in the driver's seat. In this newsletter, we describe a case presentation and you will tell us how you would handle it, using the fax-back form on the back of the newsletter. Then read the newsletter to see what the experts from the **Melanoma Care Consortium** had to say. In the next issue we'll present an analysis of what physicians like you decided and how your answers compared to the opinions of our faculty. The cases will come every month for 8 months, so you will have ample opportunity to cast your vote on melanoma cases across the disease spectrum.

Thank you for taking part in this vital and innovative program. We look forward to your input regarding this and the cases to come.

Sincerely,

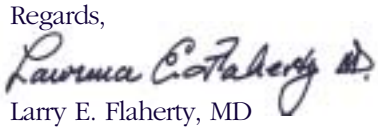


John M. Kirkwood, MD
Chairman, **Melanoma Care Consortium** Steering Committee

Editorial

In this issue, we describe the course of a patient with pulmonary metastases from a primary melanoma on the calf. In this case, we discuss prognosis, staging, recommendations for therapy, and the roles of palliative care and hospice. We discuss the profile of available chemotherapy, biochemotherapy, and investigational therapies. In addition, we explore special considerations in surgical and radiologic management of brain metastases. Throughout this case, we discuss the importance of assessing patient goals and characteristics in counseling and recommending therapies for the patient. Finally, we include an important assessment of the timing of palliative care and hospice discussions, which requires a coordinated effort on the part of the healthcare team and the palliative care team. We hope that you find this case stimulating and that it helps guide you in caring for your patients with the difficult challenge of metastatic melanoma.

Regards,



Larry E. Flaherty, MD

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Continuing Medical Education Information

Instructions for Participation

To receive up to 1.5 AMA PRA category 1 credits for this activity:

- Read the case summary on the front of the newsletter
- Answer and fax back the questions on the back cover
- Read the remainder of the case study inside the newsletter
- Complete the CME posttest answer and evaluation form at the end of the newsletter, and fax or mail these back to the address listed by March 15, 2006
- Within 4 weeks of successful completion, you may access your credit transcript at http://ccehs.upmc.edu/
- 70% of your posttest answers must be correct for you to receive a certificate of credit

Target Audience:

Dermatologists, dermatologic surgeons, surgical and medical oncologists, oncology nurses, primary care physicians, and other health care professionals who treat or screen for melanoma.

Learning Objectives:

After completing this exercise, the participant should be better able to:

- List survival rates for metastatic melanoma based on site of metastasis
- Compare and contrast treatment options for metastatic melanoma
- Propose a role for whole brain radiation therapy (WBRT) for melanoma patients with brain metastases
- Define the role of palliative care and hospice care in the care of patients with metastatic melanoma

Accreditation and Credit Designation:

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**Other healthcare professionals are awarded 0.15 continuing education units (CEUs), which are equal to 1.5 contact hours.*

We gratefully acknowledge an educational grant from Schering-Plough in support of this program.

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Faculty for this activity have been required to disclose all financial or other relationships with pharmaceutical companies, biomedical device manufacturers, and other healthcare-related for-profit entities.

The faculty acknowledges the discussion of off-label use of pharmaceuticals, specifically regarding high-dose interferon alfa-2B.

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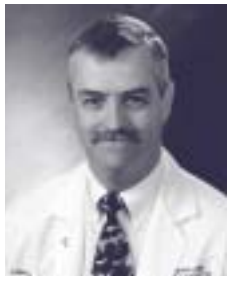
A Patient with Metastatic Melanoma



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CASE PRESENTATION

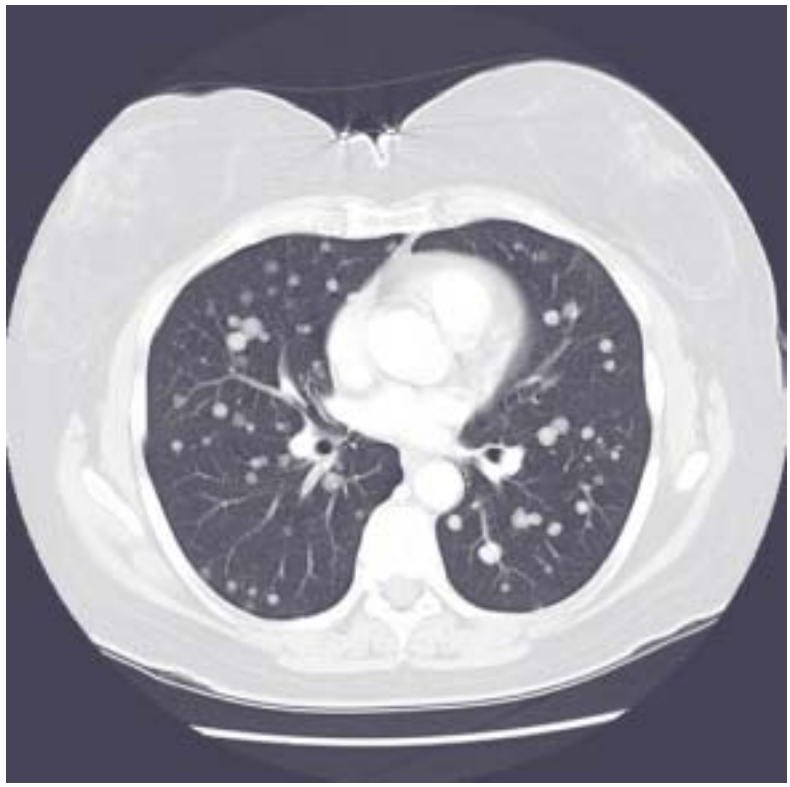
As discussed on the front cover, a 49-year-old white male presented with a primary melanoma on his left posterior calf. Biopsy showed a 4.89-mm thick lesion with no ulceration. A wide local excision with 2-cm margins was performed, along with an SLNB. The SLNB was positive, and a CLND found that 3 additional nodes of the 10 nodes dissected were positive. The patient was staged at T4aN3M0, stage IIIC.

The patient was offered and received 1 year of adjuvant high-dose interferon alfa-2b (IFN). During and after IFN therapy, the patient was followed every 3 months by routine physical examination, chest x-ray, and laboratory testing. Two years after completion of IFN therapy, a chest x-ray identified bilateral pulmonary nodules. Staging was completed by CT scans of the head, chest, abdomen, and pelvis, which confirmed the presence of pulmonary nodules (Figure 1) but which were negative in the other regions. The patient's Karnofsky performance status (KPS) was 100%. A physical examination found that the patient had no palpable lymph nodes, clear lungs, a regular heart beat with no murmurs, and a soft abdomen with no masses. A review of the patient's systems and medications revealed no additional findings for concern.

Decision-making in Metastatic Melanoma

When a possible metastasis is identified, a decision must be made whether a biopsy is needed. When polled, 80% of the faculty stated that they would recommend a biopsy of this patient's lung nodules. Dr Olencki explained that a diagnosis of metastatic melanoma, like any other diagnosis that classifies a patient's disease as incurable, must be treated with caution and respect. A biopsy will make the diagnosis definitive, clarify later decision-making, and may occasionally identify the disorder as curable or non-malignant.

Figure 1



CT scan showing bilateral pulmonary nodules.

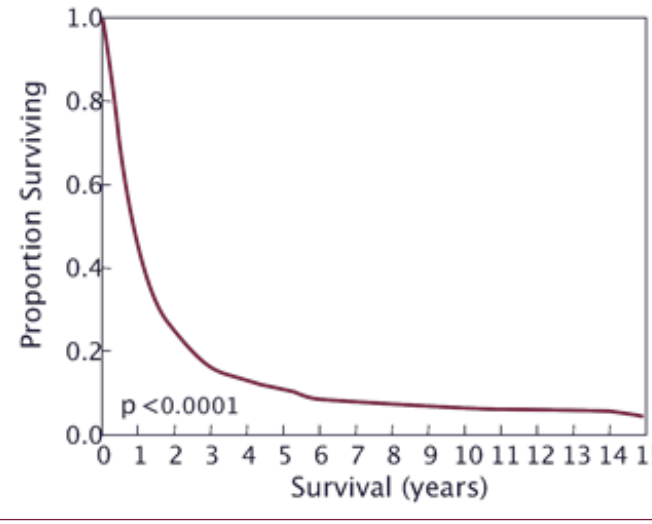
Effective decision-making for patients with metastatic melanoma requires understanding in several key areas, according to Dr Flaherty. These include the natural history of this stage of melanoma; the goals of therapy; comorbidities, toxicities, and other challenges presented by therapy; and the benefits of different therapeutic approaches. The goals of therapy must be based on the patient's preferences, as discussed in Sidebar 1.

Natural History. A median survival duration of typically 6 to 9 months for patients with melanoma has been reported (Figure 2).[1,2] Survival varies depending on the metastasis site. Among patients with skin, subcutaneous tissues, and lymph node metastases (stage M1a) or lung metastases (stage M1b), 1-year survival rates are 59% and 57%, respectively, compared to 41% for patients with metastases to other sites (stage M1c) (P<.0001).[2] The long tail of the survival curve shows that a small fraction of patients may have extended survival times and represents a small but tangible chance for durable benefits from therapy. Although there is a chance for extended survival for all metastatic sites, it is most likely in patients at stage M1a (skin, subcutaneous tissue, or lymph node) with relatively small metastases.

Goals of Therapy. Treatment for patients with malignant melanoma has several goals, particularly maintenance of quality of life, palliation, prolongation of survival, and, for a few patients, long-term survival. Because the relative importance of these goals varies depending on the disease state and the patient's situation and preferences, the treatment plan should be tailored to the individual patient.

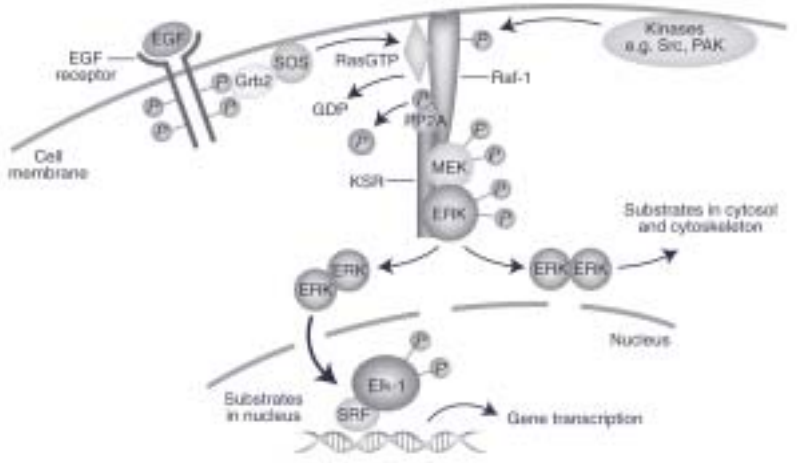
Comorbidities, Toxicities, and Challenges. Challenges related to both the patient and the treatment inevitably arise in treating patients with malignant melanoma. Patient-related issues include the patient's physical and emotional health; the presence, nature, and severity of symptoms; the presence of comorbidities; the progression-free interval; and the pace of disease progression. Treatment-related issues include treatment morbidity, prior systemic therapies, clinical trial accessibility, personal and family

Figure 2



Fifteen-year survival curve of patients with metastatic melanoma.[2] Adapted from Balch CM et al. *J Clin Oncol.* 2001. Reprinted with permission from the American Society of Clinical Oncology.

Figure 3



The organization and function of the Ras-Raf-MEK-ERK pathway.[13] Kolch W, et al. Expert Reviews in Molecular Medicine. 2002. Reprinted with permission from Cambridge University Press.

support systems, and the patient's education and interest in melanoma therapy.

Treatment Options for Metastatic Melanoma

When asked what treatment option they would recommend for this patient, a large majority (74%) of the faculty recommended high-dose interleukin-2 (IL-2). The other options recommended by faculty members were dacarbazine (DTIC)-based single- or multiple-agent chemotherapy (8%), biochemotherapy (BCT) using cisplatin/vinblastine/DTIC (CVD) plus IL-2 or IFN (14%), and a phase I clinical trial (4%). No participants recommended observation or hospice.

Drs Flaherty and Olencki would recommend high-dose IL-2 for this patient, although they mentioned that other choices were also valid: specifically, chemotherapy, if IL-2 was not available, or BCT, as part of a trial. Despite the generally low response rate of systemic melanoma therapies, this patient may have had a relatively good chance of a response because of his good performance status and low tumor volume.[3]

Interleukin-2 Therapy for Melanoma

Interleukin-2 is a standard therapy for stage IV and recurrent melanoma and has received the Food and Drug Administration's (FDA) approval for this indication.[3,4] A course of IL-2 therapy for metastatic melanoma commonly used in clinical practice consists of two treatment cycles separated by a 7- to 10-day rest period. Sidebar 2 gives the detailed regimen recommended in the prescribing information for IL-2. In practice, each treatment cycle is typically given in a hospital setting and consists of up to 14 to 15 doses of IV IL-2 600,000 to 720,000 IU/kg delivered in a 15-minute infusion every 8 hours as tolerated.[3] If the patient responds, therapy can be repeated until a complete response occurs or until no further response is obtained, to a maximum of 2 to 5 courses of therapy. Courses of therapy should be separated by 8 to 12 week rest periods. Sidebar 3 discusses alternate routes of administration for IL-2, which are much less effective and are not recommended.

The high-dose IL-2 regimen was tested in a phase III trial involving 270 patients. The median survival was 12 months, and 11% of the patients survived for at least 5 years.[5] Sixteen percent of the patients experienced a partial or complete response to the therapy, with a median response duration of 9 months.[3] After a median follow-up of 7 years, 44% of the responders were disease or progression free.[5] Approximately 6% of the patients, one-third of the responders, enjoyed a complete response, most of which (58%)

Sidebar 1

Involving the Patient in Decision-Making and Treatment Selection

Because metastatic melanoma is typically a rapidly progressing, debilitating illness with a high mortality, patients and their caregivers need to be actively involved with decision-making regarding therapy choices, palliative care, and hospice care. To allow the patient to make an informed choice from the available therapeutic options, the patient needs to be aware of the advantages and disadvantages of the spectrum of therapies, including reduced quality of life and the possibility of decreased survival associated with aggressive care and the decreased chance of a cure associated with less aggressive approaches.

- The patient needs to be involved in selecting therapies to tailor the trade-offs among therapies to meet personal preferences
- Clinicians should discuss treatment options and the data supporting them with patients before making a recommendation
- Palliative and hospice care should be discussed with the patient and caregivers well before they are needed in order to prepare for the transition to palliative care or hospice.

were durable. Late death from disease was rare, and no relapses occurred in patients whose response continued for at least 30 months.[6] In patients with partial response, local salvage therapy may produce durable disease-free survival.[6] Toxicity was severe but generally reversible when therapy was withdrawn. Before the introduction of routine antibiotic prophylaxis with IL-2 therapy, 6 patients (2.2%) died due to treatment-related sepsis.[6]

In summary, high-dose bolus IL-2 therapy produces an objective response in approximately 16% of patients with metastatic melanoma and a durable response in approximately 6% of patients.[3] Dacarbazine (DTIC), by contrast, was previously reported to produce a response rate of approximately 20%, with durable responses in only 2% of patients.[1] More recently, the response rate for DTIC was found to be a more moderate 10.2%.[7]

Candidates for IL-2 Treatment in Metastatic Melanoma

Patients should be selected carefully for high-dose IL-2 therapy because of its toxicities. Patients should have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and be free of brain metastases. Patients who have a history of heart disease should undergo a cardiac stress test to insure that they are negative for cardiac ischemia. Similarly, patients with a history of lung disease should undergo a pulmonary function test to insure that their forced expiration volume (FEV1) is greater than 2.0 L or 75% of the predicted volume.[3] Based on clinical experience, these restrictions are most relevant in patients more than 40 years of age.

Sidebar 2

FDA-approved IL-2 Regimen[3]

The recommended IL-2 (aldesleukin) for injection treatment regimen is administered by a 15-minute IV infusion every 8 hours. Each course of treatment consists of two 5-day treatment cycles separated by a rest period.

Use a 600,000 IU/kg (0.037 mg/kg) dose administered every 8 hours by a 15-minute IV infusion for a maximum of 14 doses. Following 9 days of rest, the schedule should be repeated for another 14 doses, for a maximum of 28 doses per course, as tolerated. During clinical trials, doses were frequently withheld for toxicity. Metastatic melanoma patients received a median of 18 doses during the first course of therapy.

Patients should be evaluated for response approximately 4 weeks after completion of a course of therapy and again immediately prior to the scheduled start of the next treatment course. Additional courses of treatment should be given to patients only if there is some tumor shrinkage following the last course and retreatment is not contraindicated. Each treatment course should be separated by a rest period of at least 7 weeks from the date of hospital discharge.

Case Presentation Revisited

The patient was treated with one full cycle of high-dose IV IL-2, resulting in a partial response. A second cycle produced no further disease improvement and IL-2 treatment was discontinued. Dr Flaherty noted that, because of the high toxicity of IL-2 therapy, the healthcare provider needs to stop therapy when it provides no further benefits. The patient did well for 8 months, at which point a chest x-ray identified new pulmonary nodules. The patient was restaged by CT scan, which confirmed the pulmonary nodules and identified a new 4 x 4-cm liver metastasis but was negative for brain metastasis.

Treatment for Recurrent Metastatic Melanoma

The faculty was polled about which treatment option they would now recommend for this patient (after progression on high-dose IL-2). The faculty recommended, in decreasing order, biochemotherapy (BCT with CVD plus IL-2/IFN), phase I clinical trial, single-or multi-agent chemotherapy, or observation until symptoms. Drs Olencki and Flaherty both favored chemotherapy in this situation, although they agreed that BCT

Table 1

Summary of results of a phase III trial comparing the 4-agent Dartmouth regimen versus DTIC alone in patients with malignant melanoma.[7]

	Arm A (Dartmouth regimen)	Arm B (Single-agent DTIC)	*P* value
Number of patients	119	121	
Response rate*	18.5%	10.2%	.09
Median survival (months)	7.7	6.3	.52
Terminations owing to grade III/IV toxicity	21%	2%	<.01

*All partial responses.

Table 2

Summary of selected single-institution phase II trials of BCT regimens for metastatic melanoma

Study	Regimen	Route of administration	Number of evaluable patients	Overall response N (%)	Complete response N (%)
McDermott, et al, 2000[32]	CVD/IL-2/IFN	CIV	40	19 (48%)	8 (20%)
Antoine et al, 1997[33]	C/IL-2/IFN (plus or minus T)	CIV	127	62 (49%)	13 (10%)
Richards, et al, 1992[34]	DCBT/IL-2/IFN	IVPB	34	20 (59%)	8 (24%)
Legha, 1997[35]	CVD/IL-2/IFN	CIV	114	69 (60%)	24 (21%)
Keilholz, 1997[36]	C/IL-2/IFN	CIV	60	20 (33%)	3 (5%)
Atkins, et al, 1994[37]	CDT/IL-2	IVPB	38	16 (42%)	3 (8%)
O'Day, et al, 1999[38]	CVDT/IL-2/IFN/G-CSF	CIV	44	25 (57%)	10 (23%)
Overall			457	235 (50%)	71 (15%)

C indicates cisplatin; D, DTIC (dacarbazine); V, vinblastine; T, tamoxifen; B, carmustine; IL-2, interleukin-2; IFN, interferon alfa; G-CSF, granulocyte colony-stimulating factor; CIV, continuous infusion intravenous; IVPB, intravenous piggyback.

or a phase I clinical trial were also reasonable options.

Chemotherapy for Malignant Melanoma

A variety of single-agent and combination chemotherapy treatments have been investigated for malignant melanoma. The single agents provide overall response rates ranging from 12% to 24%.[1] Because of the low response rates associated with single-agent chemotherapy, many combinations of chemotherapeutic agents have been investigated. Early phase II trials of several combination therapies showed promising results, with maximum response rates in the range of 52% to 55%.[8,9] However, multi-center phase III trials contradicted these early trials, finding no significant improvements in efficacy for multi-agent chemotherapy over single-agent DTIC chemotherapy.

One key multicenter trial compared the Dartmouth regimen to DTIC alone in a group of 240 patients randomized into two treatment arms. Arm A (n = 119) was treated with the Dartmouth regimen, consisting of DTIC, cisplatin, carmustine, and tamoxifen, while Arm B (n = 121), was treated with DTIC alone. As shown in Table 1, patients treated with the Dartmouth regimen had a trend toward a higher response rate, but there was no difference in survival between the 2 arms and significantly higher toxicity was apparent in the Dartmouth regimen.[7] The survival curves for the 2 arms were overlapping and not significantly different.

Another important trial of combination therapies was the ECOG trial E3690, which used a 2 x 2 factorial design to evaluate the effects of IFN and tamoxifen in combination with DTIC in 271 patients with stage IV melanoma. The four arms of the trial were DTIC alone, DTIC plus IFN, DTIC plus tamoxifen, and DTIC plus IFN plus tamoxifen.[10] There were no significant differences in response, time to treatment failure, or survival between any of the 4 arms, and the survival curves for treatment with and without tamoxifen and with and without IFN were overlapping and not significantly different.[10]

Dr John Kirkwood asked whether the treatment recommendations would be different for a symptomatic patient. Drs Olencki and Flaherty both said that they would not change their recommendation. Dr Flaherty mentioned that he has used combination chemotherapy for some patients who were rapidly becoming symptomatic, because combination chemotherapy might offer a better chance of controlling the disease until a new therapy such as IL-2 or an investigational drug could be started. Dr Kirkwood said that he tends to consider clinical trials for asymptomatic patients with measurable disease while they are still eligible.

Biochemotherapy

As with combination chemotherapy regimens, early single-institution phase II trials of BCT reported

Sidebar 3

Other IL-2 Regimens

Several IL-2 regimens involving lower doses and subcutaneous administration have been evaluated, with response rates ranging from 0% to 11%.[25-28]

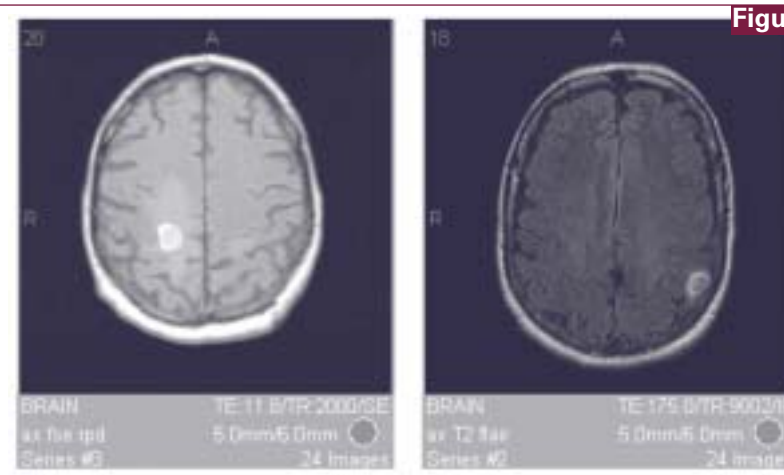
- The combined overall response rate for these 4 trials was much lower than the rate for IV IL-2, at 4%.
- Because of this low response rate, low-dose subcutaneous IL-2 is not recommended despite its favorable adverse event profile.

results for hundreds of patients. Overall and complete response rates were relatively high, ranging from 33% to 60% and 5% to 24%, respectively, with responses at all metastasis sites (Table 2). Complete remissions, mostly durable, occurred in 10% to 20% of patients. According to the faculty, despite the relatively good response rates, central nervous system (CNS) relapses remained a significant problem with BCT therapy.

These trials were followed by several small, randomized phase III trials. The most positive results were from a single-institution trial involving 190 patients with unresectable stage III melanoma (11%) or stage IV melanoma (89%), of which 14% had brain metastases. Patients were randomized to either cisplatin/vinblastine/DTIC (CVD) chemotherapy or to BCT using CVD, IL-2, and IFN. The response rate was significantly better for patients treated with BCT than for those treated with CVD alone (48% versus 25%, $P = .001$).[11]

This high response rate led to a large, multi-institution phase III trial, ECOG E3695, which compared chemotherapy using CVD with BCT using CVD, IL-2, IFN, and granulocyte-colony stimulating factor (G-CSF) in 405 patients with surgically incurable malignant melanoma. Although BCT therapy provided small improvements in the partial response rate and progression-free survival duration, the complete response rate and response duration were numerically worse, there were no differences in overall survival, and none of the differences were statistically significant (Table 3). Thus, this regimen was not effective in this setting.[12] Because of these results, Dr Flaherty no longer offers BCT to patients routinely, except as part of a clinical trial.

Figure 4



MRI images showing 2 brain metastases. Photo courtesy of Laura L. Stover, RN, BSN.

Sidebar 4

Selected Investigational Agents

Many investigational therapies for metastatic melanoma are currently in clinical trials. As of this writing, approximately 114 trials of chemotherapy, BCT, vaccines, or other pharmaceutical therapies are underway or recruiting patients.[24] Further information is available online at www.clinicaltrials.gov. Below is a brief discussion of several promising therapies.

Agent	Description	Status
BAY 43-9006	Raf kinase inhibitor	Response is poor as a single agent but good in combination with carboplatin and paclitaxel, as discussed in the text.[14,15] Currently entering phase III trials (ECOG E2603).
18- peptide vaccine[24]	Aims to immunize the patient against melanoma with a vaccine containing 12 melanoma peptides (12MP) and 6 helper peptides (6HP)	A 4-arm phase II trial (ECOG E1602) is currently recruiting patients. Treatment arms are: • 12MP alone • 12MP + 1 tetanus helper peptide • 12MP + 6HP • 6HP alone
Temozolomide[29,30]	Oral ankylating chemotherapy agent structurally and functionally related to DTIC	A phase III trial found temozolomide to be as efficacious as DTIC with a similar adverse event profile and easier administration. Several trials of combination therapy are currently underway.

Case Presentation Revisited

The patient elected to receive DTIC single-agent chemotherapy. He tolerated treatment well and sustained a response for 4 months. A follow-up CT scan later found slight progression in the liver disease. The patient's ECOG performance status was 1, and he expressed an interest in receiving additional therapy.

Investigational Therapies for Metastatic Melanoma

The faculty members were asked what therapy they would recom-

Table 3

Preliminary results of ECOG3695 comparing chemotherapy to BCT in malignant melanoma.[12]

	Response Rates (%)			Response and Survival Duration (months)		
Regimen	CR	PR	RR	Response Duration	Progression-Free Survival	Overall Survival
CVD (Arm A) n = 201	3	8.4	11.4	9.4	3.6	8.7
BCT (Arm B) n = 204	1.4	15.7	17.1	5.7	5.3	8.4

There were no statistically significant differences between treatment arms.
CR indicates complete response; PR, partial response; RR, response rate.

mend after progression on chemotherapy. A phase I or II clinical trial was the most common recommendation, chosen by 80% of the faculty. Dr Olencki would recommend a clinical trial using an investigational targeted agent, as he feels there is a real chance that this would benefit the patient. Dr Flaherty would also recommend a clinical trial, possibly earlier, after IL-2 therapy failed. Also, both panelists agreed that observation and hospice are also reasonable options for this patient.

A wide variety of investigational agents are currently in clinical trials; Sidebar 4 presents details on a few representative examples of these agents. Research efforts on the molecular mechanisms of melanoma proliferation and metastases are growing, particularly as they relate to growth factor signal transduction mechanisms. Investigators have recently uncovered therapeutic targets such as the Ras-Raf-MEK-ERK pathway shown in Figure 3. This pathway is targeted by BAY 43-9006, which is discussed next.

BAY 43-9006

Cellular proliferation is elevated in approximately 70% of melanomas by a mutation in the B-Raf gene that elevates Raf kinase activity. BAY 43-9006 inhibits Raf kinase and retards growth of human melanoma xenografts. Two phase I trials have investigated the efficacy of BAY 43-9006 in treating metastatic melanoma. In a phase I single-agent trial, it was well tolerated but produced a partial response in only 1 out of 20 patients.[14]

A phase I/II trial investigated BAY 43-9006 in a multi-agent regimen consisting of a 21-day cycle. BAY 43-9006 was administered from day 2 to 19 in three dose levels (100, 200, or 400 mg bid); carboplatin and paclitaxel were each administered on day 1. As shown in Table 4, this regimen provided relatively good response rates and duration of response even in patients who had already progressed after receiving other systemic therapy.[15] Based on these results, a phase III trial, ECOG E2603, will randomize patients with unresectable stage III melanoma or stage IV melanoma to cisplatin plus paclitaxel with or without 400 mg BAY 43-9006 bid.

MANAGEMENT OF BRAIN METASTASES IN MELANOMA

Case Presentation Revisited

This patient chose an available phase I clinical trial. After 2 months of treatment, a re-evaluation found stable disease in the liver. One week later, the patient complained of headaches and a brain MRI revealed 2 brain metastases, shown in Figure 4: a 1.2-cm tumor in the right temporal/parietal area, and a 1.8-cm tumor in the left occipital region.

Table 4

Summary of response rates for therapy with BAY 43-9006, carboplatin, and paclitaxel.[15]

Result		Number (%) of Patients
Overall Response Rate		54 (37%)
Response by number of prior systemic therapies	0	23 (48%)
	1	19 (33%)
	2-4	12 (20%)
Response by disease stage	M1a	7 (71%)
	M1b	10 (30%)
	M1c	37 (32%)
Progression-free survival (months)	> 6	54 (63%)
	> 9	50 (40%)
	>12	41 (22%)

Management of brain metastases in melanoma is a difficult area with no clearly effective therapies. When asked to choose among several options for managing this patient's brain metastases, the faculty divided their recommendations fairly evenly among all of the options as follows: resection followed by whole brain radiotherapy (WBRT) (25%); stereotactic radiosurgery (SRS) alone (25%); WBRT alone (14%); resection followed by SRS (11%); WBRT followed by SRS (11%); resection of both lesions followed by observation (7%); and palliation, steroids, and hospice referral (7%). Dr Flaherty commented that because of this patient's extracranial metastasis, he would recommend SRS or WBRT rather than surgical resection. The lack of a consensus reflects the uncertainties involved in managing this stage of the disease, particularly when concomitant and progressive non-CNS disease is present. Dr Ross pointed out that, because nearly all patients with brain metastases will eventually die of their disease, therapy aims at preventing events that would shorten survival or decrease quality of life, with palliation the primary goal of therapy.

Most of the data on brain metastases come from retrospective analyses of series of patients with melanoma. There are no prospective, phase III trials studying therapy for brain metastases originating from melanoma. However, recursive partitioning analysis (RPA) can effectively stratify patients, allowing some conclusions to be drawn regarding therapy.[16] This method was employed in the studies discussed below.

The median survival time for patients with brain metastases from melanoma is extremely short, at about 4 months[16-18] and is similar to survival for patients with brain metastases from other sites.[17-19] However, there is some evidence that several subsets of patients tend to have better outcomes. Factors that may increase the odds of an improved outcome include good KPS, resectability (which usually implies a single lesion), a lack of comorbid extracranial disease (rare

Sidebar 5

Palliative and Hospice Care

Palliative and hospice care are defined as treatments that enhance comfort and quality of life during the last phase of a patient's life. Palliative care is generally intended to aid in activities of daily living for patients who are experiencing some degree of incapacitation, while hospice care is end-stage palliative care, intended for patients who are virtually certain to die of their disease within months.[31] Because malignant melanoma is largely incurable, most facets of treatment involve palliative care. Palliative care:

- Must reflect the patient's preferences, values, and symptoms
- Includes symptom relief, easing of pain, and improvements in quality of life
- Includes physical, social, psychological, and spiritual support for the patient and caregivers
- Does not include medical therapy or adverse event management
- Can be provided in home, hospice, or hospital settings
- Should be discussed early, before it is actually needed, to allow the patient time to understand and prepare for the transition to palliative or hospice care
- Should involve the primary caregiver

During active therapy, palliative care is usually provided by the patient's medical team, primarily the oncology nursing staff. Between periods of therapy, responsibility usually falls to a separate palliative care team affiliated with the hospital, a home care agency, or a hospice agency.

Communication and education are 2 key roles of palliative care, both at home and in the hospital. Patient education and communication between the patient and the health care system often rely on palliative care providers. Palliative care providers are often:

- an accessible, friendly, and understanding link with the health care system
- effective patient advocates
- in closer contact with the patient than the rest of the medical team
- highly familiar with the patient's situation and needs
- the patient's primary source of information and education

Education

Education can be based on information from many sources, including the hospital, the National Institutes of Health, and pharmaceutical manufacturers. To be effective in patient education, palliative care providers need to ask many questions and repeat information as needed. This is especially critical because patients with melanoma often do not understand information the first time it is presented because of the complexity of the information and the emotional impact of their disease.

For patients living at home, palliative care becomes a combination of nursing and social work. It begins with an assessment of the patient's support structures and needs. In addition to providing medical, physical, and occupational therapy, the palliative care team may do the following:

- Advise and assist patients and caregivers in coping with pain, weakness, activities of daily living, and mental deficits
- Provide social and economic advice and assistance, such as advice on obtaining insurance and on identifying specialized equipment and furniture
- Provide psychological and social support to patients and caregivers

Additional information on palliative and hospice care is available from the National Hospice and Palliative Care Organization (www.nhpco.org).

in melanoma), the youth of the patient, and a long disease-free interval. Both surgery and radiotherapy are also associated with increased survival, but it is unclear whether this results from therapy or a selection bias.[16-19]

Other important considerations in selecting therapy for brain metastases are the number and location of metastatic lesions. Dr Flaherty feels that there is good evidence that surgical resection provides longer survival than WBRT for single operable lesions,[20] although there are exceptions when comorbidity is present. For single lesions, the combination of resection and WBRT gives better local control and possibly better survival than resection or WBRT alone.[21,22] For patients with a limited number of metastases, WBRT, SRS, or the combination of SRS and WBRT may provide survival benefits. A comparison of WBRT alone to WBRT followed by SRS found that the combination improved survival for patients with a single unresectable metastasis and improved the KPS for all patients.[23] A phase III study is underway, comparing SRS with or without follow-up WBRT for brain metastases from all primary sites, another metastatic site, or from the metastatic brain lesions(s).[24]

Although no phase III trials focus on therapy for brain metastases from melanoma alone, data from studies involving series of patients with solid tumors show that the benefits of surgery, SRS, and WBRT for brain metastases from melanoma parallel those for other types of solid tumors. These data suggest that a combination of local therapy using surgery or SRS with WBRT is a reasonable choice for patients with a limited number of metastatic lesions, good performance status, and well-controlled extracranial disease.[17,23]

Dr Ross raised the question of the potential toxicities of WBRT for patients with melanoma. In his experience, adverse events such as dementia or other mental status changes due to radiotherapy are rare. Dr Flaherty commented that adverse events due to WBRT typically do not appear for a year or more. For patients with brain metastases from melanoma, survival times greater than 1 year are a rare luxury, so the problem seldom arises. Dr Olencki reported that he has encountered no toxicity in his patients from WBRT in the first year after therapy.

The faculty raised several questions on the use of SRS in combination with other systemic therapies. Some institutions have used SRS as a follow-up to surgery. Dr Flaherty commented that he knows of no data supporting the combination of SRS and systemic therapy and would only recommend it as part of a clinical trial. Several faculty members discussed the order in which SRS and WBRT should be used. No randomized controlled trials have addressed this question, and the faculty did not reach a consensus. In the absence of definitive data, Dr Flaherty typically uses SRS followed by WBRT. Dr Olencki typically uses the opposite order but mentioned informal discussions that suggested that the order was not important. Dr Ross commented that early treatment of index lesions with SRS could help prevent adverse events such as bleeding or stroke-like symptoms that could have a significant negative impact on the patient's quality of life.

Dr Ballo inquired whether any systemic agents are known to decrease the incidence of brain metastases. According to Dr Flaherty, no such agents have been identified. Temozolomide may have a small benefit, and a European trial of fotemustine found that it may provide significant protection against brain metastases. However, fotemustine is not available in the United States.

PALLIATIVE AND HOSPICE CARE

Case Presentation Revisited

The patient received WBRT and SRS. He tolerated the treatment well and was free of CNS symptoms 2 months after the completion of therapy. However, an evaluation found that the liver metastasis was progressing. The patient's LDH was 950 U/L, and his KPS was 60% and declining.

The faculty members were asked whether they would recommend hospice care to this patient and whether it should have been recommended earlier. A large majority (78%) felt that hospice care would be appropriate at this stage. Relatively few (22%) felt that the patient had been overtreated and would have recommended hospice care earlier. Laura Stover, RN, BSN, commented that she would recommend formal palliative or hospice care at this stage because of the patient's declining performance status. A patient's transition to hospice care can be difficult, and there are no guidelines to aid physicians in aiding patients through the transition. Dr Flaherty commented that he approaches the subject by discussing the need for hospice with the patient and his or her caregivers. During the conversation, he reviews the benefits and toxicities that the patient experienced, reviews the possibilities for further therapy, and continues to discuss the patient's goals and the role of hospice care. Sidebar 5 discusses palliative and hospice care in more detail.

Conclusions

Metastatic melanoma typically has a poor prognosis and remains a substantial challenge in oncology. Generally, the faculty recommended an aggressive approach to staging and treatment, while introducing palliative care and hospice

discussions early in the process. High-dose IL-2 has produced good responses in appropriate candidates. Chemotherapy may also benefit selected patients, while recent phase III trials with biochemotherapy have been generally disappointing. For patients who have failed available standard regimens, the faculty would move quickly to clinical trials, using such agents as BAY 43-9006, other Phase I trials, and vaccines. In addition, surgical and radiologic management of brain metastases may have a disease-modifying or palliative effect, depending on the patient's status. The transition to palliative care and hospice care is an important element of care to improve the quality of life and aid in end-of life transitioning for the patient and his/her caregivers.

References

1. Balch C, Houghton AN, Peters LJ. Cutaneous melanoma. In: DeVita VT, editor. In: Cancer: Principles and Practice of Oncology. 4th ed. Philadelphia: *J.B. Lippincott*, 1993; 1612-1661.
2. Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J Clin Oncol.* 2001;19:3635-3648.
3. Proleukin® [package insert]. Emeryville, Ca. *Chiron Corporation*; 2000.
4. National Comprehensive Cancer Care Network. Clinical practice guidelines in oncology-v.1.2004: *Melanoma.* National Comprehensive Care Network, Inc. 2004.
5. Atkins MB, Kunkel L, Sznol M, et al. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. *Cancer J Sci Am.* 2000;6(suppl 1):S11-S14.
6. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol.* 1999;17:2105-2116.
7. Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol.* 1999;17:2745-2751.
8. Anderson CM, Tabacof J, Legha SS. Malignant Melanoma: Biology, Diagnosis and Management. In: Pazdur, editor. In:Medical Oncology: *A Comprehensive Review.* 2nd ed. Huntington, NY: PRR, 1995; 493-509.
9. Mastrangelo MJ, Bellet RE, Kane MJ, Berd D. Chemotherapy of melanoma. In: Perry, editor. In:The Chemotherapy Sourcebook. Baltimore, Md: *Wiiliams & Wilkins*, 1992; 886-907.
10. Falkson CI, Ibrahim J, Kirkwood JM, et al. Phase III trial of dacarbazine versus dacarbazine with interferon alpha-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon alpha-2b and tamoxifen in patients with metastatic malignant melanoma: an Eastern Cooperative Oncology Group study. *J Clin Oncol.* 1998;16:1743-1751.
11. Eton O, Legha SS, Bedikian AY, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. *J Clin Oncol.* 2002;20:2045-2052.
12. Atkins MB, Lee S, Flaherty LE, et al, for the US Melanoma Intergroup. A prospective randomized phase III trial of concurrent biochemotherapy (BCT) with cisplatin, vinblastine, dacarbazine (CVD), IL-2 and interferon alpha-2b (IFN) versus CVD alone in patients with metastatic melanoma (E3695): an ECOG-coordinated intergroup trial [abstract 2847]. *Proc Am Soc Clin Oncol.* 2003;22:708.
13. Kolch W, Kotwaliwale A, Vass K, et al. The role of Raf Kinases in malignant transformation. Expert Reviews in Molecular Medicine, Cambridge University Press, 2002. Available at http://www.expertreviews.org/02004386a.pdf. Accessed February 2, 2005.
14. Ahmad T, Marais R, Pylke L, et al. BAY 43-9006 in patients with advanced melanoma: the Royal Marsden experience [abstract 7506]. *Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings* (Post-Meeting Edition). 2004;22.
15. Flaherty KT, Brose M, Schuchter L, et al. Phase I/II trail of Bay43-9006, carboplatin (C) and paclitaxel (P) demonstrates preliminary antitumor activity in the expansion cohort of patients with metastatic melanoma [abstract 7507]. *Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings* (Post-Meeting Edition). 2004;22.
16. Buchsbaum JC, Suh JH, Lee SY, et al. Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study. *Cancer.* 2002;94:2265-2272.
17. Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol.* 2004;22:1293-1300.
18. Bafaloukos D, Gogas H. The treatment of brain metastases in melanoma patients. *Cancer Treat Rev.* 2004;30:515-520.
19. Broadbent AM, Hruby G, Tin MM, et al. Survival following whole brain radiation treatment for cerebral metastases: an audit of 474 patients. *Radiother Oncol.* 2004;71:259-265.
20. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322:494-500.
21. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA.* 1998;280:1485-1489.
22. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys.* 1994;29:711-717.
23. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet.* 2004;363:1665-1672.
24. Clinical Trials. Available at http://www.clinicaltrials.gov. Accessed November 11, 2004.
25. Leahy MG, Pitfield D, Popert S, et al. Phase I study comparing continuous infusion of recombinant interleukin-2 by subcutaneous or intravenous administration. *Eur J Cancer.* 1992;28A:1049-1051.
26. Tagliaferri P, Barile C, Caraglia M, et al. Daily low-dose subcutaneous recombinant interleukin-2 by alternate weekly administration: antitumor activity and immunomodulatory effects. Am *J Clin Oncol.* 1998;21:48-53.
27. Eton O, Rosenblum MG, Legha SS, et al. Phase I trial of subcutaneous recombinant human interleukin-2 in patients with metastatic melanoma. *Cancer.* 2002;95:127-134.
28. Agarwala SS, Glaspy J, O'Day SJ, et al. Results from a randomized phase III study comparing combined treatment with histamine dihydrochloride plus interleukin-2 versus interleukin-2 alone in patients with metastatic melanoma. *J Clin Oncol.* 2002;20:125-133.
29. Agarwala SS, Kirkwood JM. Temozolomide, a novel alkylating agent with activity in the central nervous system, may improve the treatment of advanced metastatic melanoma. *Oncologist.* 2000;5:144-151.
30. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. *J Clin Oncol.* 2000;18:158-166.
31. The National Hospice and Palliative Care Organization. Hospice & palliative care information: an explanation of palliative care. Available at http://www.nhpco.org. Accessed January 10, 2005.
32. McDermott DF, Mier JW, Lawrence DP, et al. A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin 2, and interferon alpha-2B in patients with metastatic melanoma. *Clin Cancer Res.* 2000;6:2201-2208.
33. Antoine EC, Benhammouda A, Bernard A, et al. Salpêtrière Hospital experience with biochemotherapy in metastatic melanoma. *Cancer J Sci Am.* 1997;3(suppl 1):S16-S21.
34. Richards JM, Mehta N, Ramming K, et al. Sequential chemoimmunotherapy in the treatment of metastatic melanoma. *J Clin Oncol.* 1992;10:1338-1343.
35. Legha SS, Ring S, Eton O, et al. Development and results of biochemotherapy in metastatic melanoma: the University of Texas M.D. Anderson Cancer Center experience. *Cancer J Sci Am.* 1997;3(suppl 1):S9-15.
36. Keilholz U, Goey SH, Punt CJ, et al. Interferon alfa-2a and interleukin-2 with or without cisplatin in metastatic melanoma: a randomized trial of the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. *J Clin Oncol.* 1997;15:2579-2588.
37. Atkins MB, O'Boyle KR, Sosman JA, et al. Multiinstitutional phase II trial of intensive combination chemoimmunotherapy for metastatic melanoma. *J Clin Oncol.* 1994;12:1553-1560.
38. O'Day SJ, Gammon G, Boasberg PD, et al. Advantages of concurrent biochemotherapy modified by decrescendo interleukin-2, granulocyte colony-stimulating factor, and tamoxifen for patients with metastatic melanoma. *J Clin Oncol.* 1999;17:2752-2761.

CME Evaluation Form

Please use the scale below to answer these questions.
Fill in the circle completely. You may use pen or pencil to fill in the circles.

	Very Low	Low	Moderate	High	Very High

1. To what extent were the objectives of the educational activity achieved?
   O O O O O
2. To what extent were you satisfied with the overall quality of the educational activity?
   O O O O O
3. To what extent was the content of the program relevant to your practice?
   O O O O O
4. To what extent did the activity enhance your knowledge of the subject area?
   O O O O O
5. To what extent did the activity change the way you think about clinical care/professional responsibilities?
   O O O O O
6. To what extent will you make a change in your practice/professional responsibilities as a result of your participation in this educational activity?
   O O O O O
7. Which of the following best describes the impact of this activity on your performance? **(Please use the scale below in answering this question.)**
   - O This program will not change my behavior because I am already currently conducting my professional responsibilities in a manner consistent with the information presented in this educational activity.
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   O O O O O
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11. Please indicate your degree:
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    O Nurse O Nurse Practitioner O Other
12. Was there any particular content that was irrelevant to your practice? If yes, why? _____
13. What types of information should be used to determine topics for this activity if repeated? _____
14. Would you prefer a different learning format (discussions, skills training, formal course)? _____
15. In the event that content exhibited commercial bias, please describe the specifics. _____
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Case Re-evaluation

Please circle the answer that best describes your current view of the case.

1. Did your opinions on management of patients with metastatic melanoma change after completing this exercise?
   A. Yes B. No
2. What therapy would you have recommended for this patient when bilateral pulmonary nodules were confirmed?
   A. Chemotherapy (DTIC based single-agent or multi-agent)
   B. High-dose IL-2
   C. Biochemotherapy (CVD + IL2/IFN)
   D. Phase I clinical trial
   E. Observation until symptoms develop
   F. Hospice
3. What was the most important factor influencing any changes in your opinion on question 2?
   A. Clinical data on response rates
   B. Clinical data on durable response rates
   C. Tolerability and adverse event profile
   D. All of the above
   E. No change in opinion
   F. Other (Please describe) _____
4. When would you have first discussed palliative and hospice care with this patient?
   A. Initial suspicion of melanoma
   B. Upon discussion of therapies and prognosis after first detection of distant metastatic disease
   C. Progression of metastatic disease after therapy
   D. Development of brain metastases
   E. Disease progression and declining functional score
5. Do you have any additional comments, questions, or observations on any changes in your strategy for managing malignant melanoma? _____

Melanoma Care Centers in the United States

Below is a list of melanoma care centers in the United States where you can refer your patients and access other resources to improve your practice.

NORTHEAST

Melanoma Program
Norris Cotton Cancer Center
Dartmouth Hitchcock Medical Center
Lebanon, NH
603-650-5534

Skin Oncology Program
Boston Medical Center, Boston, MA
617-638-7131
Physician in charge: Marie-France Demierre, MD

The Melanoma Program at Massachusetts General Hospital
Pigmented Lesion Clinic, Boston, MA
617-724-6082

Multidisciplinary Melanoma Clinic
University of Connecticut Health Center
Farmington, CT
860-679-4600

Pigmented Lesion Clinic
Yale Dermatology Consultants
New Haven, CT
203-785-4632

Roswell Park Cancer Institute
Buffalo, NY
716-845-7614

The Tumor Vaccine Program
Albert Einstein College of Medicine
New York, NY
718-430-2000

Melanoma Disease Management Team
Memorial Sloan-Kettering Cancer Center, New York, NY
212-610-0766
www.mskcc.org

Pigmented Lesion Section
New York University Medical Center, Oncology Section, New York, NY
212-263-5260
www.med.nyu.edu/derm

Comprehensive Cancer Center
Our Lady of Mercy Medical Center
New York, NY
718-920-1100

The Melanoma and Soft Tissue Oncology Program at
The Cancer Institute of New Jersey
UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ
732-235-6777

Melanoma and Skin Cancer Program
University of Pittsburgh Cancer Institute
Hillman Cancer Center, Pittsburgh, PA
412-692-4724

Pigmented Lesion Group
Hospital of the University of Pennsylvania, Philadelphia, PA
215-662-6926

MIDWEST

Multidisciplinary Melanoma Clinic
Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI
734-936-6360
www.cancer.med.umich.edu/clinic/melclinic.htm

Pigmented Lesion Clinic
Henry Ford Hospital, Detroit, MI
313-916-4060

Multidisciplinary Melanoma Clinic
Karmanos Cancer Institute
Wayne State University, Detroit, MI
313-745-9166

Multidisciplinary Melanoma and Pigmented Lesion Clinic
University of Cincinnati Medical Center
Cincinnati, OH
513-584-8900

MetroHealth Medical Center
Cancer Care Center Melanoma Program, Cleveland, OH
216-778-4795 (surgical oncology)
216-778-5802 (medical oncology)

The Melanoma Center At The James
Ohio State University, Columbus, OH
614-293-7531 (medical)
614-293-5644 (surgical)

Wagner & Associates Plastic and Reconstructive Surgery Consultants of Indiana, Indianapolis, IN
317-621-2520
317-621-2580

Interdisciplinary Melanoma Clinic
Indiana University Cancer Center, Indiana University Medical Center
Indianapolis, IN
317-278-7449

Cardinal Bernardin Cancer Center
Loyola University Chicago, Chicago, IL
708-327-2078
www.luhs.org

Pigmented Lesion Center
Rush University, Chicago, IL
312-563-2321
www.rush.edu/rumc/page-R12605.html

Melanoma and Pigmented Lesion Center
University of Minnesota
Minneapolis, MN
612-625-5199

Multidisciplinary Melanoma Group
St. Louis University Health Sciences Center/SLUCare, St. Louis, MO
314-268-5320

SOUTH

The Melanoma and Pigmented Lesion Clinic
Johns Hopkins Hospital, Baltimore, MD
410-614-1022

Melanoma Center
Washington Cancer Institute
The Washington Hospital Center
Washington, DC
202-877-2551
www.whc.mhg.edu

Blumenthal Cancer Center
Carolina Medical Center
Charlotte, NC
704-355-2757

Dermatologic Surgery Unit, Department of Dermatology
Wake Forest University School of Medicine, Winston-Salem, NC
336-716-6276

The Melanoma Clinic/Pigmented Lesion Clinic
Duke Comprehensive Cancer Center
Durham, NC
919-684-2137

Brown Cancer Center, University Hospital at University of Louisville
Norton Cancer Center at Norton University, Louisville, KY
502-852-1897

The Dermatology Clinic
Vanderbilt University Medical Center
Nashville, TN
615-322-6485

Emory Surgery, Melanoma, and Pigmented Lesion Clinic
Emory University, Atlanta, GA
404-778-3354
404-778-5225

H. Lee Moffitt Cancer Center
Cutaneous Oncology Clinic, Tampa, FL
813-972-8485
813-972-8400 ext 1968 (new patients)

Lakeland Regional Cancer Center
Cutaneous Oncology Program
Lakeland, FL
863-603-6565

The Pigmented Lesion Clinic
University of Miami School of Medicine
Miami, FL
305-243-4183

Melanoma Skin Center
Division of Internal Medicine, Department of Dermatology
M.D. Anderson Cancer Center
Houston, TX
713-745-1113

WEST

Melanoma Multidisciplinary Clinic
Huntsman Cancer Institute
Salt Lake City, UT
801-408-3555 (referrals)

Cutaneous Oncology
University of Colorado Cancer Center
Aschutz Cancer Pavilion, Aurora, CO
720-848-0300

The Melanoma Center
UCSF Clinical Cancer Center
San Francisco, CA
415-885-7546

Northern California Melanoma Center
San Francisco, California
415-353-6535

Pigmented Lesion and Multidisciplinary Melanoma Clinics
Stanford University Medical Center
Stanford, CA
650-725-5255

The Angeles Clinic and Research Institute
Affiliated with the John Wayne Cancer Institute
Santa Monica, CA
310-231-2178

The Pigmented Lesion Clinic
UCLA Dermatology Center
Los Angeles, CA
310-825-6911

CHAO Family Comprehensive Cancer Center-Melanoma Clinic
University of California, Irvine Medical Center, Orange, CA
714-456-8171

Seattle Cancer Care Alliance
University of Washington, Seattle, WA
206-288-2168 (patient referrals)

CME Post-test Questions

Please answer each question on the space provided on page 14.

1. Which of the following metastasis sites is associated with the shortest median survival in metastatic melanoma?
   A. Subcutaneous tissues
   B. Lung
   C. Other visceral sites
   D. Differences in survival are not statistically significant

2. Which one of these therapies is associated with the longest duration of response?
   A. Dacarbazine (DTIC)
   B. High dose IV Interleukin-2 (IL-2)
   C. Low dose subcutaneous IL-2
   D. Biochemotherapy with DTIC, IL-2, and interferon alfa-2b

3. What is the objective response rate produced by IL-2 therapy for metastatic melanoma?
   A. 4%
   B. 16%
   C. 32%
   D. 58%

4. Which of the following patients would be considered a good candidate for IL-2 therapy?
   A. 35-year-old male, EPS 0, brain and liver metastases, cardiac stress test and pulmonary function tests not done
   B. 68-year-old female, EPS 2, skin metastases, cardiac stress test not done, passed pulmonary function test
   C. 46-year-old female, EPS 1, lymph node metastases, failed cardiac stress test, passed pulmonary function test, myocardial infarct 2 years ago
   D. 53-year-old male, EPS 0, lung metastases, passed cardiac stress test and pulmonary function test

5. The key phase III trial comparing combination chemotherapy with single-agent chemotherapy in malignant melanoma found that the response rate for combination chemotherapy in comparison to single-agent chemotherapy is:
   A. Significantly worse
   B. Not statistically different
   C. Significantly better
   D. The two trials had inconsistent results

6. With regard to ECOG E3695, a large Phase III trial that compared chemotherapy and biochemotherapy regimens for patients with metastatic melanoma, which one of the following statements is true?
   A. Both response rates and survival were significantly better for biochemotherapy
   B. Both response rates and survival were significantly worse for biochemotherapy
   C. Survival rates did not differ between biochemotherapy and chemotherapy
   D. Partial response rates were higher in the chemotherapy arm

7. The commonly accepted standard therapy for patients with melanoma that has metastasized to the brain is:
   A. Surgical resection of the tumor
   B. Whole brain radiation therapy (WBRT)
   C. Stereotactic radiosurgery (SRS)
   D. A combination of the above
   E. There is no commonly accepted standard

8. According to the faculty, the therapy for melanoma brain metastases should aim to:
   A. Control the disease and thereby prolong survival
   B. Prevent events that would shorten survival or decrease quality of life
   C. Relieve pain
   D. Eliminate existing tumors and prevent further brain metastases
   E. There is no commonly accepted standard

9. For patients with metastatic melanoma, when should palliative and hospice care first be discussed?
   A. During the initial discussion of the patient's overall prognosis and treatment options
   B. When the patient's ECOG performance score becomes 2
   C. When brain metastases appear
   D. As soon as melanoma is diagnosed

10. Palliative care is defined as:
    A. Treatment that enhances comfort and quality of life during the end of life
    B. Therapy to relieve pain
    C. Management of adverse events
    D. Treatment to maximize the tolerability of curative therapies

Visit www.MelanomaCare.org
to view electronically or pass on to colleagues

Please answer these questions BEFORE OPENING this newsletter.

The following questions refer to the case study of a patient with metastatic melanoma outlined on the front cover. Please circle the answers that most represent your opinion, detach this perforated page, and fax to 973-682-9077. Or, if you prefer, you can visit the Melanoma Care Consortium at www.MelanomaCare.org, answer these questions, read the article, answer the post-test questions, and apply for CME credit online.

1. Would you recommend a biopsy of one of the pulmonary nodules in this patient?
A. Yes
B. No

2. Which therapy would you recommend for this patient at this stage?
A. Chemotherapy (DTIC based single-agent or multi-agent)
B. High-dose IL-2
C. Biochemotherapy (cisplatin/vinblastine/DTIC [CVD] + IL-2/IFN)
D. Phase I clinical trial
E. Observation until symptoms develop
F. Hospice

3. If the patient accepted therapy but progressed after the therapy was complete, which therapy would you then recommend?
A. Chemotherapy (DTIC based single-agent or multi-agent)
B. High-dose IL-2
C. Biochemotherapy (CVD + IL-2/IFN)
D. Phase I clinical trial
E. Observation until symptoms develop
F. Hospice

4. Which therapy would you recommend if the patient developed two brain metastases?
A. Surgical resection of both lesions followed by observation
B. Surgical resection of both lesions followed by whole brain radiotherapy (WBRT)
C. Surgical resection of both lesions followed by SRS (stereotactic radiosurgery)
D. WBRT alone
E. SRS alone
F. WBRT then SRS
G. Palliation alone with steroids and hospice referral

5. At which point would you recommend hospice care for this patient?
A. Initial diagnosis of melanoma
B. When discussing therapy after detection of distant metastatic disease
C. Progression of metastatic disease after therapy
D. Development of brain metastases
E. Disease progression and declining functional score

Please retain this sheet because it includes the CME post test questions on page 15.

MELANOMA CARE
OPTIONS

MARCH 2005

Fostering an Interdisciplinary Approach to Melanoma Care

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