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Treatment of Metastatic Melanoma: An Overview

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Abstract

The 10-year survival rate for patients with metastatic melanoma is less than 10%. Although surgery and radiation therapy have a role in the treatment of metastatic disease, systemic therapy is the mainstay of treatment for most patients. Single-agent chemotherapy is well tolerated but is associated with response rates of only 5% to 20%. Combination chemotherapy and biochemotherapy may improve objective response rates but do not extend survival and are associated with greater toxicity. Immunotherapeutic approaches such as high-dose interleukin-2 are associated with durable responses in a small percentage of patients. In this article, we review the treatments for metastatic melanoma including promising investigational approaches.

Metastatic melanoma continues to be a challenging disease to treat, with an estimated 8,420 related deaths in the United States in 2008.[1] The 10-year survival rate for patients with metastatic melanoma is less than 10%.[2] More than 3 decades after its initial approval by the US Food and Drug Administration (FDA) in 1975, dacarbazine continues to be the standard of care for most patients with this disease. High-dose interleukin-2 (HD IL-2 [Proleukin]), approved by the FDA in 1998 for metastatic melanoma, benefits a small subset of patients. Attempts to improve upon the survival of patients with metastatic disease have met with failure, and the need for successful new therapies for metastatic melanoma cannot be overemphasized. However, our understanding of the biology of this disease is steadily increasing, and many promising therapeutic approaches are currently under investigation. We discuss the various systemic therapeutic approaches to the treatment of metastatic melanoma below.

Prognostic Factors for Metastatic Melanoma

Many factors have been proposed to influence the prognosis in patients with metastatic melanoma. The impact of the initial site of metastasis on survival was studied in a multivariate analysis of 1,521 patients with stage IV melanoma. Three groups of patients were identified: those with cutaneous, nodal, or gastrointestinal tract metastases; those with isolated pulmonary metastases; and those with liver, brain, or bone metastases.[3] The median survivals in these three groups were 12.5, 8.3, and 4.4 months, respectively. The 5-year actuarial survivals were

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14%, 4%, and 3%, respectively. In addition to the site of disease, the presence of an elevated serum lactate dehydrogenase (LDH) has also been associated with poor prognosis.[4,5] The 2002 American Joint Committee on Cancer (AJCC) staging system of cutaneous melanoma classifies patients with metastatic disease into three categories based on the site of metastases and serum LDH level (see Table 1).[2]

Other factors that have been associated with shorter survival include older age, poor performance status, male sex, greater number of metastatic sites, shorter disease-free interval, hypoalbuminemia, pretreatment neutrophilia, and leukocytosis.[3-7] The identification of valid prognostic factors is important to the design and interpretation of clinical trials in metastatic melanoma.

Roles of Surgery, Radiation Therapy, and Systemic Therapy

The presence of distant metastases usually reflects hematogenous dissemination of melanoma cells. The cornerstone of treatment for metastatic melanoma is systemic therapy to address the subclinical sites of metastases as well. Locoregional treatment modalities such as surgery or radiation are usually reserved for palliation of symptoms due to local tumor growth.

Surgery

Resection of distant metastases may also be considered for selected patients in whom a survival benefit might be expected with surgical rather than medical treatment. Surgery may potentially improve outcomes in patients with fully resectable oligometastatic disease.

In a report of 144 patients who underwent surgical resection of non-regional metastatic melanoma, the overall 5- and 10-year survival rates were 20% and 14%, respectively.[8] Patients with a solitary metastasis confined to the subcutaneous, nonregional lymph nodes or lung were most likely to benefit from aggressive surgical intervention. In another series of 77 patients undergoing surgical resection of metastatic disease, the overall 5-year survival rate was 10%.[9] Patients with solitary lesions had a 5-year survival rate of 12%, compared with 0% for patients with multiple lesions. Patients with complete resection had a 5-year survival rate of 15%, compared with 4% for patients with incomplete resection. Patients with complete resection of solitary lesions had a 5-year survival of 18%. However, the retrospective and nonrandomized nature of these reports makes it difficult to distinguish the true benefit of surgical intervention from the differences in natural history of disease.

Radiation Therapy

Melanoma is considered a relatively radioresistant tumor, but patients may derive clinical benefit from radiation of symptomatic metastases. Radiation therapy is usually used as an adjunct to the use of systemic therapy. Radiation therapy (whole-brain irradiation and/or stereotactic radiosurgery) is especially useful in patients with central nervous system (CNS) metastases, as most systemic therapies have limited penetration into the CNS.

Systemic Therapy

Systemic therapy is the mainstay of therapy for most patients with stage IV melanoma. Systemic therapies include cytotoxic chemotherapy, immunotherapy, or a combination approach such as biochemotherapy. In addition, many novel therapies are currently under investigation.

Cytotoxic Chemotherapy

Cytotoxic chemotherapy has been used for the treatment of metastatic melanoma for over 3 decades. Chemotherapeutic agents with modest antitumor efficacy in metastatic melanoma include alkylating agents (dacarbazine, temozolomide [Temodar], nitrosoureas), the platinum analogs, and the microtubular toxins. These agents have been used alone or in combination.

Single-Agent Chemotherapy

Dacarbazine—An alkylating agent, dacarbazine (5-[3,3-dimethyl-1-triazenyl]-imidazole-4-carboxamide, or DTIC) is the only chemotherapeutic agent approved by the FDA for treatment of melanoma. A pooled analysis of 23 randomized, controlled trials showed that the objective response rate (ORR) for 1,390 patients receiving dacarbazine alone was 15.3%. The majority of these responses were partial (11.2% partial responses [PR], 4.2 % complete responses [CR]).[10] Responses are seldom durable, and fewer than 2% of patients treated with dacarbazine alone are alive at 6 years.[11] Since dacarbazine monotherapy has not been investigated in a placebo-controlled trial, there is insufficient evidence to suggest an overall survival benefit with dacarbazine. The primary purpose of dacarbazine therapy for metastatic melanoma is palliation.

Dacarbazine is typically administered intravenously at a dose of 150 to 200 mg/m^2/d for 5 days or at a single dose of 800 to 1,000 mg/m^2, with doses repeated every 3 to 4 weeks. The latter schedule is more convenient and is well tolerated by most patients. Common toxicities include mild nausea and vomiting, myelosuppression, and fatigue, and most patients are able to maintain their baseline quality of life.

Despite its modest efficacy and lack of data for survival benefit, dacarbazine continues to be the “standard treatment” of metastatic melanoma. No other therapy has yet been shown to have a significant survival benefit over dacarbazine.

Temozolomide—An orally administered analog of dacarbazine, temozolomide has been extensively tested in melanoma. Like dacarbazine, temozolomide is converted to the active alkylating metabolite MTIC (3-methyl-[triazen-1-yl]-imidazole-4-carboxamide). Unlike dacarbazine, however, this conversion is spontaneous, nonenzymatic, and occurs at a physiologic pH in all tissues to which the drug is distributed. Besides having excellent oral bioavailability, temozolomide penetrates into the CNS and may potentially prevent or treat melanoma brain metastases. These attractive features have prompted extensive investigation of temozolomide in metastatic melanoma.

A phase III trial randomized 305 patients to receive temozolomide (200 mg/m^2/d orally for 5 days every 4 weeks) vs dacarbazine (250 mg/ m^2/d intravenously for 5 days every 3 weeks).[12] The median overall survival (OS) and ORR for patients treated with temozolomide (7.7 months and 14%, respectively) were not statistically different from those treated with dacarbazine (6.4 months and 12%, respectively).

The results of another multicenter phase III trial that randomized 859 patients to receive dacarbazine vs an extended dosing schedule of temozolomide (150 mg/m^2/d on 7 consecutive days every 14 days) were recently reported.[13] The investigators found no significant differences between dacarbazine and temozolomide in ORR (10% and 14%, respectively), progression-free survival (PFS, 2.1 and 2.3 months, respectively), or OS (9.3 and 9.1 months, respectively).

Temozolomide has also been substituted for dacarbazine in various combination chemotherapy or biochemotherapy regimens in an effort to reduce the high rate of isolated CNS relapse in

patients exhibiting major responses.[14] However, the recently reported results of a phase III trial comparing cisplatin/IL-2/temozolomide vs cisplatin/IL-2/dacarbazine did not show any benefit of temozolomide in preventing brain metastases.[15]

Hence, temozolomide has not proven to be superior to dacarbazine. The choice between the two drugs is usually guided by the desired route of administration, cost differences, and the presence or absence of brain metastases.

Antimicrotubular Agents—Vinca alkaloids (inhibitors of microtubular assembly) such as vindesine and vinblastine, and taxanes (inhibitors of microtubule disassembly) such as paclitaxel have modest single-agent activity in patients with metastatic melanoma.[16,17] Vinblastine has been incorporated in various combination chemotherapy and biochemotherapy regimens. Paclitaxel, used as a single agent or in combination with other agents, has antitumor activity (ORR = 16%–26%) in patients with metastatic melanoma, including patients whose disease has progressed on prior chemotherapies.[17-19] Weekly administration of paclitaxel at a dose of 80 to 100 mg/m^2 (on days 1, 8, and 15 every 4 weeks) is well tolerated by most patients. Alternatively, a higher dose can be administered once every 3 to 4 weeks.

Associated toxicities include fatigue, alopecia, myelosuppression, neuropathy, myalgias, and hypersensitivity reactions. An albumin-bound, nanoparticle form of paclitaxel (ABI-007, or Abraxane) had an ORR of 27% in 34 chemotherapy-naive patients with metastatic melanoma in a phase II trial.[20]

Platinum Analogs—Cisplatin and carboplatin have modest activity in patients with metastatic melanoma. Single-agent cisplatin given at conventional doses yields a response rate of less than 10%. However, a phase II study that used a higher dose (150 mg/m^2) of cisplatin in combination with amifostine reported an ORR of 53%, although the responses were short-lived.[21] A response rate of 19% was observed with carboplatin in a phase II study in chemotherapy-naive patients with metastatic melanoma.[22] Carboplatin has also been used in combination with paclitaxel in previously treated patients.[19]

Nitrosoureas—Nitrosoureas such as carmustine (BCNU), lomustine (CCNU), and fotemustine have single-agent activity comparable to dacarbazine, although they cause more myelosuppression and alopecia. Fotemustine rapidly crosses the blood-brain barrier and has been found to have encouraging activity in patients with brain metastases.[23] When compared to dacarbazine in a phase III trial involving 229 patients with metastatic melanoma, fotemustine was associated with a higher ORR (15% vs 7%, respectively) and a trend toward improved survival (7.3 vs 5.6 months, respectively).[24] In patients without brain metastases at inclusion, the median time to development of brain metastases was 22.7 months in the fotemustine arm vs 7.2 months in the dacarbazine arm. Fotemustine has not been approved by the FDA but is available in Europe.

Combination Chemotherapy

The modest antitumor activity of the chemotherapeutic agents mentioned above led to investigation of combinations of these agents to improve outcomes. Single-institution studies suggested that combination chemotherapy might lead to an increase in the response rate and possibly survival.

The combination of cisplatin, dacarbazine, BCNU, and tamoxifen (CDBT), also known as the Dartmouth regimen, was initially reported to have an ORR of 55%.[25,26] However, a phase III multicenter trial that randomized 240 patients to the CDBT regimen vs dacarbazine monotherapy did not show a statistically significant benefit in favor of the combination.[27] Despite a modest difference in ORR in favor of CDBT over dacarbazine (16.8% and 9.9%,

respectively; $P = .13$), there was no significant difference in OS (7.7 and 6.3 months, respectively; $P = .52$). Myelosuppression, fatigue, nausea, and vomiting were significantly higher in the CDBT arm.

Another combination that includes cisplatin, vinblastine, and dacarbazine (CVD), had an ORR of 40% in a phase II study.[28] The CVD regimen was later used as a backbone for combining with IL-2 and interferon to develop biochemotherapy regimens.[29]

The combination of paclitaxel and carboplatin (PC) has been reported to have antitumor activity in patients with metastatic melanoma, including patients who have received prior chemotherapy.[19,30] The PC regimen was recently used as the comparator arm in two randomized, placebo-controlled, phase III trials testing PC vs PC plus sorafenib (Nexavar). In one of these trials involving patients who had received prior dacarbazine or temozolomide, patients who received PC alone had an ORR of 11%, median PFS of 17.9 weeks, and median OS of 42 weeks.[31]

In summary, combinations of cytotoxic agents may yield somewhat higher response rates than dacarbazine monotherapy, but are associated with greater toxicity and do not extend survival significantly.

Immunotherapy

Cytotoxic chemotherapy may have a palliative benefit in some patients with metastatic melanoma, but it usually does not lead to durable responses and has not been proven to have a survival benefit.[11] Preclinical and clinical data have revealed the susceptibility of melanoma to approaches designed to modulate the immune system. Some immunotherapeutic approaches have led to durable complete responses in a small subset of patients, although it has been challenging to predict which patients will respond to immunotherapy. The successes and failures of melanoma immunotherapy have contributed profoundly to our understanding of basic immunology.

Interleukin-2

IL-2 is a lymphokine that stimulates T-cell proliferation and function; augments natural killer cell proliferation and cytotoxic activity; and triggers the release by activated lymphocytes of cytokines such as interferon gamma, tumor necrosis factor, and others. High-dose bolus IL-2 (HD IL-2) was approved by the FDA in 1998 for the treatment of metastatic melanoma due to the potential for durable complete responses in a small number of patients.

In a pooled analysis of 270 patients treated with HD IL-2, the ORR was 16% (CR 6%, PR 10%).[32,33] Sixty percent of the complete responders had durable responses that were ongoing at the time of the report (duration > 42 months to > 122 months). Forty-four percent of responders were long-term survivors beyond 5 years (range, >70 months to >150 months). None of the responding patients experienced disease progression after 5 years. Also, some patients who had relapsed after having a complete response or were partial responders with minimal residual disease underwent surgical resection of the disease and achieved prolonged relapse-free survival, thus suggesting the potential for long-term control of micrometastatic disease by HD IL-2.

HD IL-2 is administered at a dose of 600,000 to 720,000 IU/kg by IV bolus every 8 hours on days 1 to 5 (cycle 1) and days 15 to 19 (cycle 2), with a maximum of 28 doses per each two-cycle course. Response evaluation is usually performed 4 weeks after the second cycle. Courses of HD IL-2 may be repeated in patients with evidence of tumor regression. The administration

of HD IL-2 requires hospitalization with intensive monitoring and is mostly limited to specialized centers with personnel who are experienced in the management of this regimen.

Major toxicities associated with HD IL-2 include fever, chills, hypotension, increased capillary permeability, cardiac arrhythmias, oliguria, volume overload, delirium, and rash. Bacterial sepsis can also complicate HD IL-2 administration, and antibiotic prophylaxis is recommended. The risk of multiorgan complications usually limits HD IL-2 administration to younger patients with excellent performance status and organ function.

Due to the toxicities associated with HD IL-2, it would be helpful to limit its administration to patients who are more likely to respond. However, pretreatment prediction of responses to HD IL-2 has been an elusive goal so far. A large retrospective analysis of 305 patients who received HD IL-2 alone could not identify any pretreatment factors that were strongly associated with increased ORR or long-term survival.[34] An analysis of 379 patients who received HD IL-2 in combination with vaccines identified those patients with cutaneous and/or subcutaneous metastases only as having a significantly higher chance of responding, as compared to patients with disease in other sites (46% vs 13%, respectively; $P = .00005$).[34] However, responses with HD IL-2 have been noted in patients with visceral metastases and/or large tumor burdens.[33,34]

Interferon Alfa-2b

Interferon alfa-2b (IFN-α, Intron A), approved by the FDA for adjuvant therapy of resected high-risk melanoma, is associated with modest antitumor activity (ORR 22%, CR < 4%) in patients with metastatic melanoma.[35] Responses, however, are limited to patients with low-volume disease in cutaneous or soft-tissue sites and are sometimes delayed, with onset many months after initiation.[35] The common toxicities associated with IFN-α, such as fever, chills, fatigue, myalgias, psychocognitive impairment, and autoimmune events, adversely affect patient quality of life, especially with long-term administration. Pegylated IFN-α (PEG-Intron) permits more convenient administration with good tolerability and has been suggested to have similar efficacy in metastatic disease.[36] Due to the low likelihood of response and the cumulative toxicities, IFN-α monotherapy has limited utility in the treatment of stage IV melanoma. However, the antitumor activity of IFN-α has led to extensive investigation of its use in combination with other therapies.

To summarize, HD IL-2 may lead to durable complete responses in a subset of patients and should be considered in patients who are likely to tolerate it. The success of HD IL-2 in inducing durable complete responses in some patients with metastatic melanoma has provided “proof of concept” for the field of immunotherapy, and has fuelled extensive investigation of novel immunotherapeutic approaches.

Biochemotherapy

The term biochemotherapy refers to regimens that combine cytotoxic agents with IFN-α and/or IL-2. Early single-institution trials of biochemotherapy demonstrated promising antitumor activity. This led to the rapid development of many such regimens and subsequently to an extensive investigation comparing these regimens to chemotherapy alone. The pivotal randomized trials comparing combinations of chemotherapy with IL-2 and/or IFN-α to chemotherapy alone are listed in Table 2.

As is evident from the results of these trials, biochemotherapy is sometimes associated with a higher response rate, but this has not resulted in significant improvement in overall survival. These findings were further confirmed in a meta-analysis of 18 trials involving 2,621 patients.[46] The results of this meta-analysis suggested a clear improvement in ORR with

biochemotherapy (odds ratio = 0.59; 95% confidence interval [CI] = 0.49–0.72; $P < .00001$) but no benefit in OS (odds ratio = 0.99; 95% CI = 0.91–1.08; $P = .9$).[46] The increased ORR with biochemotherapy comes at the cost of significantly increased toxicity compared to chemotherapy alone.

Biochemotherapy may provide a palliative benefit in patients who are symptomatic and/or have rapidly progressive disease. However, the lack of survival benefit with biochemotherapy suggests that alternative therapies such as HD IL-2 or investigational agents should be considered for such patients once their disease has been stabilized. Biochemotherapy requires a reduction in the IL-2 dose to combine it safely with chemotherapy, and hence, the possibility of a durable CR may be compromised. Indeed, preclinical and clinical evidence suggests the importance of dose-intensity of IL-2 for achieving durable responses. A recent report suggested that 16% of patients whose disease had progressed after receiving biochemotherapy had a complete remission with subsequent HD IL-2.[47] Most responders to biochemotherapy eventually experience disease progression, often in the central nervous system.[41] This has led to substitution of temozolomide for dacarbazine in many biochemotherapy regimens. However, the recently reported results of a phase III trial comparing cisplatin/IL-2/temozolomide vs cisplatin/IL-2/dacarbazine did not show any benefit of temozolomide in preventing brain metastases.[15]

Reference Guide

Therapeutic Agents Mentioned in This Article

Allovectin-7

Amifostine

Carboplatin

Carmustine (BCNU)

Cisplatin

Cyclophosphamide

Dacarbazine

Fludarabine

Fotemustine

gp100

Interferon alfa-2b (IFN-α, Intron A)

Interferon alfa-2b, pegylated (PEG-Intron)

Interleukin (IL)-2 (Proleukin)

Ipilimumab

Lomustine (CCNU)

Paclitaxel

Paclitaxel, albumin-bound (Abraxane)

Sorafenib (Nexavar)

Tamoxifen

Temozolomide (Temodar)

Tremelimumab

Vinblastine

Vindesine

Vitespen

Brand names are listed in parentheses only if a drug is not available generically and is marketed as no more than two trademarked or registered products. More familiar alternative generic designations may also be included parenthetically.

To summarize, biochemotherapy may increase response rates compared to chemotherapy alone but is associated with increased toxicity without a definite survival benefit.

Novel Investigational Therapies

Multiple attempts to improve upon existing therapies for metastatic melanoma may not have been successful in phase III trials, but have added significantly to our understanding of the disease. The molecular alterations important to the pathogenesis of melanoma continue to be elucidated, and there has been a steady progress in our knowledge of the biology of this disease.[48] Novel therapies, many of which target specific molecular pathways, are being tested. Some of these promising therapies that are currently being investigated in phase III trials are summarized in Table 3.

Some of the novel immunotherapeutic approaches deserve special mention, as promising antitumor activity has been observed.

Anti-CTLA-4 Antibody

The cytotoxic T-lymphocyte antigen (CTLA)-4 is expressed on activated T lymphocytes and counteracts positive stimulatory signals to these cells mediated through other T-cell receptors, hence acting as a negative regulator of T-cell activation. CTLA-4 is also constitutively expressed on regulatory T cells that inhibit excessive immune stimulation. Monoclonal antibodies that bind to CTLA-4 may potentiate immune responses against cancer cells. Anti-CTLA-4 antibodies (ipilimumab and tremelimumab) are currently being evaluated in clinical trials in melanoma (see Table 3) and have been associated with encouraging antitumor activity.

In a pooled analysis of two phase II trials of ipilimumab that enrolled 139 patients, objective responses were observed in 23 patients (17%), including three complete responses that were ongoing at last follow-up (23+, 52+, and 53+ months).[50] The overall survival in this analysis was 15.7 months, which compares favorably to historical cohorts. Responses to anti-CTLA-4 antibodies are sometimes delayed in onset and are often associated with development of immune-related adverse events, primarily enterocolitis and hypophysitis. Results of a phase III trial comparing dacarbazine plus ipilimumab vs dacarbazine alone are eagerly awaited. Anti-CTLA-4 antibodies may prove particularly useful in combination with other strategies designed to stimulate antitumor immune responses such as adoptive T-cell therapy or vaccination approaches.

Adoptive Cell Therapy

Adoptive cell therapy (ACT) involves collection of lymphocytes from the patient (peripheral blood lymphocytes or tumor-infiltrating lymphocytes [TIL]), in vitro selection/expansion/activation of collected lymphocytes, and subsequent infusion of processed lymphocytes back into the patient to induce an immune response against the cancer cells. A recent report that demonstrates the promise of ACT for metastatic melanoma investigated host lymphodepletion

(using cyclophosphamide plus fludarabine with or without total-body irradiation) followed by autologous TIL transfer and HD IL-2.[54] An ORR of 56% was observed in 93 patients. Among the 10 patients who achieved a complete response, no relapses were reported with a median follow-up of 31 months.

Another example of successful use of ACT involved a novel approach that isolated and expanded autologous CD4+ T-cell clones with specificity for the melanoma-associated antigen NY-ESO-1.[55] When these cells were infused into a patient with refractory metastatic melanoma, who had not undergone any previous conditioning or cytokine treatment, the transferred CD4+ T cells mediated a durable clinical remission and led to endogenous responses against melanoma antigens other than NY-ESO-1.

Vaccination

Various vaccination strategies to induce active immunity targeting cancer cells are currently being tested for the treatment of metastatic melanoma. These strategies have included vaccination with peptides (eg, gp100), dendritic cells, nucleic acids (eg, Allovectin-7), and heat shock protein complexes (eg, vitespen).

A phase III trial comparing the combination of HD IL-2 plus vaccination with gp100 peptides vs HD IL-2 alone has recently completed accrual, and results are awaited. Another phase III trial is comparing standard chemotherapy (dacarbazine or temozolomide) vs intralesional injections of Allovectin-7 (a plasmid DNA encoding the major histocompatibility complex [MHC] heavy chain class I antigen HLA-B7 and ß-2 microglobulin proteins that results in synthesis and expression of the complete MHC complex on the cell surface). This follows the encouraging results seen in a phase II study of intralesional Allovectin-7 in 127 patients, where the ORR was 12% with a median OS of 21.3 months.[56]

In addition, multiple other approaches that target specific molecular pathways are in various stages of testing for metastatic melanoma. With the underlying heterogeneity in melanoma, it is unlikely that one approach will apply to all patients. As with most cancers, the key to the treatment of metastatic melanoma will be identification of specific subsets of the patient population that are more likely to respond to a specific therapy.

Summary

Treatment of metastatic melanoma remains a challenge. While surgery and radiation therapy may play a role in the palliation of symptoms from local tumor growth, systemic therapy is the mainstay of treatment for metastatic melanoma. Treatment with HD IL-2 may induce durable responses in a small subset of patients and should be considered in eligible patients. Chemotherapeutic approaches may have a palliative benefit. Single-agent chemotherapy is usually well tolerated. Combination chemotherapy and biochemotherapy have not improved survival but may lead to increased response rates at the cost of higher toxicity. Many novel therapeutic approaches appear promising, and participation in clinical trials should be considered the standard of care.

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Table 1

Subcategories of Metastatic Disease, as Defined in the 2002 AJCC Staging System for Cutaneous Melanoma, and Survival Rates

Classification	Site	Serum LDH	1-yr Survival	2-yr Survival
M1a	Distant skin, subcutaneous, or nodal metastases	Normal	59%	37%
M1b	Lung metastases	Normal	57%	23%
M1c	All other visceral metastases	Normal	41%	24%
	Any distant metastasis	Elevated		

AJCC = American Joint Committee on Cancer; LDH = lactate dehydrogenase.

Adapted from Balch CM et al.[2]

Table 2

Pivotal Randomized Controlled Trials of Chemotherapy vs Biochemotherapy in Metastatic Melanoma

Author	N	Regimen	ORR/CR	Median OS	Comments on Biochemotherapy Arm
Thomson,[37] 1993	170	DTIC	17% / 2%	8.9 mo	No significant improvement in ORR or survival
		DTIC + IFN	21% / 7%	7.6 mo	
Bajetta,[38] 1994	266	DTIC	20% / 5%	11 mo	Improved response duration; no significant improvement in ORR or survival
		DTIC + IFN 9MU	28% / 8%	13 mo	
		DTIC + IFN 3MU	23% / 7%	11 mo	
Falkson,[39] 1998	271	DTIC ± tamoxifen	16% / 4%	8.4 mo	No significant improvement in ORR or survival
		(DTIC ± tamoxifen) + IFN	20% / 9%	9.3 mo	
Rosenberg,[40] 1999	102	DTIC + cisplatin + tamoxifen	27% / 8%	15.8 mo	Trend toward improved ORR ; however, trend toward worsened OS
		DTIC + cisplatin + tamoxifen + IL-2 + IFN	44% / 6%	10.7 mo	
Eton,[41] 2002	183	CVD (cisplatin + vinblastine + DTIC)	25%[a] / 2%	9.2 mo	Significantly improved ORR; trend toward improved OS; two patients with durable CRs (at > 75 mo and > 48 mo)
		CVD + IL-2 + IFN (sequential biochemotherapy)	48%[a] / 7%	11.9 mo	
Ridolfi,[42] 2002	176	DTIC + cisplatin ± BCNU	20% / 3%	9.5 mo	No significant improvement in ORR or OS
		(DTIC + cisplatin ± BCNU) + sc IL-2 + IFN	25% / 3%	11 mo	
Kaufmann,[43] 2005	282	Temozolomide	13%[a] / 2%	8.4 mo	Significantly improved ORR; however, no significant improvement in OS
		Temozolomide + IFN	24%[a] / 8%	9.7 mo	
Bajetta,[44] 2006	151	CVD (cisplatin + vinblastine + DTIC)	21%/0%	12 mo	No significant improvement in ORR or OS
		CVD + sc IL-2 + IFN	33%/4%	11 mo	
Atkins,[45] 2008	395	CVD (cisplatin + vinblastine + DTIC)	14%/5%	8.7 mo	No significant improvement in ORR or survival
		CVD + IL-2 + IFN (concurrent biochemotherapy)	19%/2%	9.0 mo	

[a] Statistically significant difference.

BCNU = carmustine; CR = complete response; DTIC = dacarbazine; IFN = interferon; IL = interleukin; MU = million units; ORR = objective response rate; OS = overall survival; sc = subcutaneous.

Table 3

Novel Therapies Under Investigation in Treatment of Patients With Metastatic Melanoma

Drugs (Mechanism of Action)	Key Clinical Trials/Treatment Arms	N	ORR	OS	Comments
Anti-CTLA-4 monoclonal antibodies: Tremelimumab and ipilimumab (cause immune stimulation through blockade of immune checkpoints)	Phase III: tremelimumab[49]	655			No significant difference in ORR and overall survival; durable CRs in some patients
	Tremelimumab		9%	11.8 mo	
	DTIC or temozolomide		10%	10.7 mo	
	Two phase II trials: ipilimumab (pooled analysis)[50]	139			Impressive OS; durable CRs; delayed responses seen; phase III trial ongoing
	Ipilimumab ± gp100 vaccination		17%	15.7 mo	
Antisense oligonucleotide: Oblimersen (suppresses production of anti-apoptotic bcl-2)	Phase III[51]	771			Improved ORR and time to progression with oblimersen; no significant difference in OS; another phase III trial ongoing
	DTIC + oblimersen		14% [a]	9.0 mo	
	DTIC		8% [a]	7.8 mo	
Small-molecule kinase inhibitor: Sorafenib (blocks many pathways including Raf, VEGFR, PDGFR)	Phase III[31] (previously treated patients)	270			Negative phase III trial in previously treated patients; improved time to progression in the phase II trial in treatment-naive patients; other phase III trials ongoing
	Paclitaxel + carboplatin + sorafenib		10%	9.7 mo	
	Paclitaxel + carboplatin		11%	9.7 mo	
	Phase II randomized[52] (treatment-naive patients)	101			
	Sorafenib + DTIC		24%	10.6 mo	
	DTIC		12%	11.9 mo	
Inducer of oxidative-stress and apoptosis; synergizes with paclitaxel: Elesclomol or STA-4783 (enhanced immune-mediated cytotoxicity through upregulation of heat-shock proteins?)	Phase II randomized[53]	81			Encouraging results in randomized phase II trial; phase III trial in chemotherapy-naïve patients ongoing
	STA-4783 + paclitaxel		15%	12.0 mo	
	Paclitaxel		4%	7.8 mo	

[a] Statistically significant difference.

CR = complete response; CTLA = cytotoxic T-lymphocyte antigen; DTIC = dacarbazine; ORR = objective response rate; OS = overall survival; PDGFR = platelet-derived growth factor receptor; VEGFR = vascular endothelial growth factor receptor.