Drugs 1998 Jun; 55 (6): 791-799
0012-6667/98/0006-0791/$09.00/0

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Current Treatment Options for Malignant Melanoma

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Contents

Summary

The incidence of malignant melanoma has increased at an alarming rate over the past few decades. Indications are that it will continue to rise in the foreseeable future. Primary prevention of malignant melanoma through education of the general public regarding the hazards of sun exposure is important in an attempt to reduce the incidence of the disease in the future. It can, however, be expected to take many years before a decrease in the number of cases of this disease is seen. Until such time, the medical oncologist will be faced with an increasing number of referrals for both adjuvant therapy and treatment of metastatic disease.

Many agents have been investigated as possible postsurgical adjuvant therapies in patients with malignant melanoma. To date, interferon-α (IFN-α) given initially intravenously in high doses followed by subcutaneous therapy for 1 year, is the only treatment that has been shown to increase disease-free and overall survival in patients with high-risk melanomas. Patients falling into this group should still, wherever possible, be enrolled in prospectively randomised clinical trials.

Although the prognosis for patients with metastatic melanoma remains poor, some progress in the management of this disease has been made. It has not yet been conclusively proven that combination chemotherapy yields superior results

to single agent dacarbazine (DTIC) [which has for many years formed the cornerstone of therapy].

Immunotherapy involving IFNs and interleukin-2 (IL-2) alone or in combination has yielded similar results to those achieved with chemotherapy alone. The combination of chemotherapy plus immunotherapy appears to hold promise, with high response rates and often durable remissions reported, albeit at the expense of considerable treatment-related toxicity. Novel therapies including tumour vaccines and gene therapy also hold promise for the future management of this disease.

The incidence of malignant melanoma has increased at an alarming rate over the past few decades. At present, over 40 000 new cases are diagnosed annually in the US, resulting in over 7000 deaths per year. All indications are that this increase will continue for the foreseeable future.

Primary prevention of malignant melanoma, through education of the general public regarding the hazards of sun exposure, is important in an attempt to reduce the incidence of the disease in the future. Earlier recognition of precursor lesions, especially dysplastic nevi, may also contribute to a decrease in the number of new cases of melanoma. Similarly, the early recognition of established melanomas can be expected to decrease the mortality from this disease in the future.

Unfortunately, it can be expected to take a number of years before a decline in the number of new cases of this disease is seen. Until such time, the practising medical oncologist can expect to be faced with an increasing number of referrals for both adjuvant therapy and treatment of advanced disease.

1. Adjuvant Therapy for Malignant Melanoma

The majority of primary melanomas with a depth of <1.5mm can be cured by wide local excision alone. Deep primary tumours (>4mm), however, have a risk of recurrence of approximately 50%, and those metastatic to regional nodes have a risk of recurrence of 60 to 85%.[1] Consequently, trials investigating the possible benefit of systemic adjuvant therapy have focused on this group of patients. In these patients, the tumour burden is still low and therefore theoretically more susceptible to chemotherapy or manipulation of the immune system.

Many agents, both cytotoxic and cytostatic, chemotherapy, biotherapy or combinations have been investigated as possible postsurgical adjuvant therapies in patients with malignant melanoma. This review concentrates on the most significant of these agents.

1.1 Chemotherapy

1.1.1 Dacarbazine (DTIC)

As a result of the activity of dacarbazine (DTIC) in metastatic disease, a number of trials have examined a possible role for this agent in the adjuvant setting. A trial conducted by the World Health Organization (WHO) failed to show any benefit for patients treated with dacarbazine compared with placebo for deep primary lesions or patients with regional nodal metastases.[2] The European Organisation for Research and Treatment of Cancer (EORTC) trial, which again randomised patients to receive either dacarbazine or placebo, failed to show any differences in relapse-free or overall survival after a mean 3 years of follow-up.[3] Similarly, in a trial conducted by the Central Oncology Group, patients who received adjuvant dacarbazine for American Joint Committee on Cancer (AJCC) stage II, III and IV melanoma had a worse outcome compared with control patients.[4]

1.1.2 Vindesine

The vinca alkaloid vindesine has also been evaluated in the adjuvant treatment of malignant melanoma. In a nonrandomised trial, Retsas et al.[5] found a highly significant improvement in disease-

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free and overall survival in patients treated with vindesine following resection of regional lymph nodes compared with patients followed by observation alone. Although an interim analysis of these results has confirmed a statistically significant benefit for vindesine-treated patients,[6] other investigators have failed to reproduce these results.[7]

1.1.3 Levamisole

Levamisole has also been evaluated as an adjuvant treatment following excision of a primary melanoma. In a trial conducted by the National Cancer Institute of Canada, Quirt et al.[8] were able to demonstrate a reduction of 29% in both the death rate ($p = 0.08$) and the recurrence rate ($p = 0.09$) in a cohort of patients who were randomised to receive adjuvant levamisole as opposed to observation alone. Other studies, however, have failed to confirm a benefit for the adjuvant use of this drug. Loutfi et al.[9] failed to demonstrate any benefit in prolonging either disease-free or overall survival in 156 patients randomised to receive either adjuvant levamisole or placebo. Of note in this study was the severe toxicity which led to discontinuation of levamisole in 32 patients. Spitler[10] was also unable to demonstrate any differences in disease-free or overall survival in 203 patients randomised to receive either levamisole or placebo as postsurgical adjuvant therapy for malignant melanoma. *In conclusion*, it is doubtful whether levamisole has any role in adjuvant therapy for melanoma.

1.1.4 Other Chemotherapy

The National Cancer Institute (NCI) in Bethesda, Maryland, US found no benefit for the adjuvant use of semustine (methyl CCNU) in patients with high risk primary lesions or regional nodal metastases.[11]

1.2 Nonspecific Immunotherapy

1.2.1 Bacillus Calmette Guérin (BCG)

Activity by Bacillus Calmette Guérin (BCG) as nonspecific immunotherapy for malignant melanoma was first reported by Morton et al.[12] These investigators noted that among patients treated by intralesional BCG administration, a response was commonly seen in noninjected lesions, thus implying a systemic immune response. Since that time, BCG has been evaluated as a postsurgical adjuvant therapy in a number of randomised clinical trials.[8,11,13-17] Although some of these trials have suggested small benefits for certain subsets of patients, many of them have employed small patient numbers in their treatment arms and have shown, overall, no significant benefit for the use of BCG. A large WHO trial revealed no survival benefit for patients treated with adjuvant BCG. Subset analysis did, however, reveal benefit for those patients who received BCG either alone or in combination with dacarbazine and who had a negative tuberculin skin test before the start of therapy.[18]

1.2.2 Granulocyte Macrophage Colony–Stimulating Factor (GM-CSF)

Cytokines such as granulocyte macrophage colony–stimulating factor (GM-CSF) can enhance local activation of immune effector cells. In a small study by Spitler et al.,[19] GM-CSF administered as postsurgical adjuvant therapy resulted in a statistically significant prolongation of disease-free and overall survival. Although encouraging, these results require confirmation in large randomised studies.

1.2.3 Corynebacterium parvum

A number of trials have examined a possible role for *Corynebacterium parvum* as nonspecific immunotherapy for high risk melanomas. Although some smaller studies showed benefit, which approached significance,[20,21] the European adjuvant study failed to demonstrate this.[22]

1.3 Specific Immunotherapy

1.3.1 Interferon (IFN)

Much interest has been focused on the use of interferon (IFN) in the adjuvant setting for patients with malignant melanoma.

In a trial conducted by the North Central Cancer Treatment Group (83-7052), patients with primary lesions of Breslow depth 1.69mm (T3), >4mm (T4) and those with nodal metastases (N1) were

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randomised to receive IFNα-2a 20 million units intramuscularly 3 times weekly for a period of 3 months, versus observation. Analysis of this trial revealed no significant prolongation of disease-free or overall survival.[23] The WHO Melanoma Program Trial 16 evaluated IFNα-2a at a dosage of 3 million units subcutaneously 3 times weekly for 3 years versus observation. Analysis of this trial suggested no significant impact of therapy on either relapse-free or overall survival.[24] The SWOG trial 86-42 demonstrated a lack of activity of IFN-γ in the adjuvant setting for patients with malignant melanoma.[25]

The ECOG trial E 1684 randomised patients with AJCC stage IIb or III melanoma to receive either adjuvant IFNα-2b or observation following resection of the primary lesion. Patients receiving IFN treatment received initial high dose intravenous therapy (20 million U/m^2/day) 5 days weekly for 4 weeks followed by 10 million U/m^2 subcutaneously 3 times weekly for a further 11 months. Patients in the IFN-treated group had significantly more toxicity but demonstrated a significant prolongation of time to treatment failure (1.7 *vs* 0.98 years; p = 0.023 – one sided) as well as overall survival (3.8 *vs* 2.8 years; p = 0.0237– one sided).[26]

The issues of dosage, duration and regimen of IFN administration are still uncertain; however, the E 1690 study, which compared the above 2 arms with a lower dose of IFN given for a longer period of time (3 million units subcutaneously 3 times weekly for 2 years), will answer some of these questions. This trial completed accrual in 1995 and results will be available soon.

1.4 Tumor Vaccines

In recent years a variety of antigens expressed by melanoma cells (melanoma-associated antigens, MAA) have been characterised. These antigens differ from those present on normal melanocytes and have limited expression on most normal tissue.[27] It is hoped that immunising the host with these antigens may lead to enhanced cellular and tumoural immune responses against the melanoma cells. Numerous phase II studies have been reported showing some activity of these vaccines in patients with AJCC stage IV disease.[28-30] These preparations are now being evaluated in the adjuvant setting. Vaccination with the ganglioside GM2 has been shown to induce the production of immunoglobulin M (IgM) antibodies in patients with melanoma.[31] In a study by Livingston et al.[32] in which patients received BCG with or without GM2, disease-free survival was significantly increased in those receiving GM2.[32] An ECOG-led Intergroup study, E 1694, is currently accruing patients who are randomised to receive either high dose IFNα (as administered in E 1684) or vaccination with ganglioside GM2.

2. Therapy for Metastatic Malignant Melanoma

Metastatic malignant melanoma is a relatively chemoresistant neoplasm. Prognosis for patients with metastatic disease remains dismal, with a median survival of around 6 months.[33] Less than 10% of patients remain alive 5 years after the diagnosis of metastatic disease.[34] Patients with localised metastatic disease should be considered candidates for surgical resection of lesions wherever possible, as some may remain free of disease for a number of years. Therapeutic strategies for disseminated disease include chemotherapy (both single agent and combination), immunotherapy and, more recently, the use of vaccines and gene therapy.

2.1 Chemotherapy (Single Agent)

2.1.1 Dacarbazine

Since its introduction in the 1970s, dacarbazine has formed the cornerstone of conventional chemotherapy for metastatic malignant melanoma. Response to dacarbazine as a single agent is of the order of 20%.[35] Metastases to the skin and subcutaneous tissues, and lymph node involvement show the most favourable response. Dacarbazine does not cross the blood-brain barrier and is therefore inactive against cerebral metastases. Complete re-

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sponses are rare (4%), and small minorities of complete responders sustain prolonged remissions.[36]

2.1.2 Temozolamide

Temozolamide, a drug closely related to the active metabolite of dacarbazine, has shown activity in the treatment of metastatic melanoma. This agent is well tolerated and is available in oral form. In a phase II trial, Bleehen et al.[37] reported an overall response rate of 21% in 56 chemonaïve patients. Further studies of this agent appear to be warranted.

2.1.3 Nitrosoureas

The nitrosoureas, carmustine (BCNU), lomustine (CCNU) and semustine, have been extensively studied in melanoma. Due to their lipid solubility, enabling these agents to cross the blood-brain barrier, it was hoped that they might have an effect on cerebral metastases. Unfortunately, this has not proven to be correct. The nitrosoureas in general have shown a lower response rate than dacarbazine. In trials conducted by the ECOG, overall response rates of 11 to 15% were documented.[38,39] The recently developed cloroethyl nitrosourea fotemustine is highly lipophillic and readily penetrates the blood-brain barrier. In 140 patients with cerebral metastases treated with this agent, an overall response rate of 24.3% was recorded.[40] In a study at our institution an overall response rate of 9.7% was obtained in 31 patients treated with fotemustine. Two of the responses were documented in patients with cerebral metastases.[41] Regimens combining this agent with dacarbazine have unfortunately yielded increased toxicity without additional response.[42-47]

2.1.4 Other Agents

The vinca alkaloids vincristine, vinblastine and vindesine have consistently been associated with response rates of 10 to 15% when used as single agents in patients with metastatic malignant melanoma.[48] Considerably higher response rates have been reported when they are used in combination with other drugs.[49]

A variety of other chemotherapeutic agents have been evaluated in patients with metastatic malignant melanoma. Cisplatin and its analogues carboplatin and zeniplatin have only modest activity in metastatic disease, despite considerable toxicity.[50-53] Activity of the taxanes (paclitaxel and docetaxel) in metastatic melanoma is also modest with responses of around 15% reported.[54-56] Other agents including gemcitabine[57] and didemnin-B[58] are inactive in advanced melanoma.

2.2 Combination Chemotherapy

The most widely used combination chemotherapy regimen in metastatic malignant melanoma is the regimen described by Del Prete et al. using dacarbazine, BCNU, cisplatin and tamoxifen,[59] sometimes referred to as the Dartmouth regimen. Response rates in excess of 50% were subsequently reported by other authors utilising this regimen.[60-62] The Intergroup trial E 91140 is presently accruing patients for randomisation to either the above combination or single agent dacarbazine and will definitively answer the question whether this combination is truly superior.

Although tamoxifen alone has negligible activity in metastatic melanoma it is postulated that its addition augments the activity of other agents and may delay the onset of cisplatin resistance.[63] A number of other trials have shown no benefit for the addition of tamoxifen to conventional chemotherapy in patients with metastatic melanoma. The recently published NCI Canada Melanoma Trial Group was unable to demonstrate benefit for the addition of tamoxifen to carmustine, dacarbazine and cisplatin.[64] In the ECOG-led intergroup trial E 3690 the addition of tamoxifen to dacarbazine failed to improve either time to treatment failure or overall survival.[65]

The combination of cisplatin, vinblastine and dacarbazine (CVD) has also been frequently used in the setting of metastatic disease. Response rates as high as 40% have been reported in non-randomised, single institution studies.[49] In randomised studies, however, CVD remains equivalent to, but more toxic than, dacarbazine alone.

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2.3 High Dose Chemotherapy with Autologous Bone Marrow/Stem Cell Support

Much interest has focused on the possible role of high dose chemotherapy followed by autologous bone marrow or peripheral blood stem cell support in patients with metastatic malignant melanoma. Agents evaluated have included dacarbazine, nitrosoureas and alkylating agents. Although response rates of as high as 50 to 60% have been reported, complete responses are infrequent and the toxicity of the high dose regimens employed has been considerable. Duration of response is generally short-lived, with a median of around 6 months.[66-68]

2.4 Immunotherapy

2.4.1 IFNα

Although the main indication for IFN therapy in malignant melanoma appears to be in the adjuvant setting, IFNα has activity in disseminated disease. Response rates of approximately 16% can be expected. Patients with cutaneous and soft tissue disease are most likely to benefit from IFN therapy, and uninterrupted regimens regardless of rate of administration have yielded results superior to those from intermittent treatment.[69]

2.4.2 Interleukin-2 (IL-2)

The cytokine interleukin-2 (IL-2) has also been shown to have activity in patients with metastatic melanoma. Incubation of lymphoid cells with IL-2 results in the activation of these cells to so-called lymphokine activated killer (LAK) cells. Initial trials using IL-2 plus LAK cells were conducted by Rosenberg et al.[70] at the NCI, and encouraging results prompted expansion of the original study to include other institutions, which confirmed these results. Single agent IL-2 has been evaluated by the IL-2 Working Group and a response rate of only 5% reported.[71] Treatment with IL-2 is associated with considerable toxicity, predominantly severe hypotension often requiring inotropic support and renal dysfunction (usually reversible).

2.4.3 IL-2 Plus IFN

The combined use of IFNα which augments melanoma cell expression of histocompatibility antigens, and IL-2 to increase T cell activation, seems a logical approach in the therapy of malignant melanoma. Using the above combination response rates as high as 41% have been reported, at the expense of severe toxicity.[72]

The IL-2 working group compared treatment with IL-2 alone and the combination of IL-2 plus IFNα. Disappointing response rates of 5 and 10%, respectively, were observed.[71]

2.5 Combined Chemotherapy/ Immunotherapy

Many trials have combined the use of chemotherapy and immunotherapy in patients with metastatic malignant melanoma. In a study at our institution comparing dacarbazine combined with IFNα with dacarbazine alone, Falkson et al.[73] demonstrated a response rate of 53.1% for the combination arm compared to only 20% in patients receiving single agent dacarbazine. Patients treated with the combination of the 2 agents had a median survival of 17.6 months compared with 9.6 months for those receiving dacarbazine alone. Other studies using similar if not identical regimens have not, however, produced the same results.[74-76] The ECOG trial E 3690, which accrued 271 patients, also showed no significant difference in either time to treatment failure or overall survival across all 4 treatment arms, while those arms containing IFN had considerably more toxicity.[65]

Using sequential biochemotherapy (CVD plus IL-2 and IFNα), Legha et al.[49] reported a 60% response rate in a group of 62 patients. This included 14 complete responses. The median duration of complete response was greater than 3 years, with a number of patients remaining disease-free for longer periods. As with other combination regimens utilising IL-2, severe toxicity was seen with 15% of patients requiring admission to an intensive care unit.

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3. Future Directions

3.1 Gene Transfer Therapy

The genetic structure of a malignant cell can be altered by gene transfer techniques, allowing the cell to be destroyed by the immune system. This technique has been used to transfect the HLA-B7 gene into melanoma cells by Nabel and co-workers.[77] Some melanoma cells, which take up the HLA-B7 gene, are subsequently destroyed by the immune system. Rosenberg[78] at the NCI was able to transfect the tumour necrosis factor (TNF) gene into tumour-infiltrating lymphocytes (TIL) using a retroviral vector. Since that time, the genes encoding for a number of other cytokines have been successfully transfected into TIL1.

4. Conclusion

In summary, to date adjuvant IFNα given at first intravenously in high doses followed by subcutaneous therapy for a year is the only treatment that has been shown to increase disease-free and overall survival in patients with high risk melanomas. Patients falling into this group should still, wherever possible, be enrolled in prospectively randomised clinical trials.

For patients with metastatic malignant melanoma, single agent dacarbazine remains the cornerstone of therapy. They should also, however, wherever possible, be treated in trials which employ new agents and/or innovative approaches.

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