Seminars in Surgical Oncology 12:429–435 (1996)

Treatment of Melanoma Metastases in the Brain

MATTHEW G. EWEND, MD, LISA A. CAREY, MD, AND HENRY BREM, MD
From the Departments of Neurosurgery (M.G.E., H.B.) and Oncology (L.A.C., H.B.), Johns Hopkins University School of Medicine, Baltimore, Maryland

Melanoma is prone to spread to the brain and is the third most common source of intracranial metastasis. Patients usually present with signs and symptoms of increased intracranial pressure, a new focal neurologic deficit, or seizures. Contrasted magnetic resonance imaging (MRI) is the single most valuable imaging modality. Surgical therapy is the appropriate choice for single lesions that are accessible, especially if they are causing significant mass effect or are located in the posterior fossa. Patients with several intracranial metastases who undergo resection of all lesions may have a similar prognosis to those with a single resected lesion. Stereotactic radiosurgery appears to provide good local control of small lesions. External beam radiotherapy may provide some benefit to patients, and is often used in conjunction with surgery or stereotactic radiosurgery. To date, chemotherapy has been limited because of chemo-resistance and drug delivery issues. Future directions for treatment may include local sustained delivery of either chemotherapy or immunoregulatory molecules.

KEY WORDS: **melanoma, brain, neoplasm metastasis, surgery, stereotaxic techniques, radiosurgery, radiation therapy, chemotherapy**

INTRODUCTION

Intracranial melanoma is a problem frequently encountered by neurosurgeons, although it is virtually always a manifestation of metastatic disease rather than the initial presentation [1]. Indeed, melanoma is the third most common cause of intracranial metastasis, behind carcinomas of the lung and breast [2]. In patients with melanoma who have undergone treatment of a primary lesion, the brain is the third most common site of distant recurrence. Only recurrence in the skin and distant lymph nodes occurs more frequently [3]. The brain is the first site of metastasis in 25% of patients [4]. In addition, one fourth of intracranial melanoma metastases are solitary [3]. Of patients with metastatic melanoma, 12–20% develop a clinically significant central nervous system (CNS) lesion, while autopsy series have revealed that 36–54% have CNS lesions [3].

The strong propensity for melanoma to metastasize to the brain may be due to secretion of degradative enzymes that allow it to cross the tight capillary junctions which compose the blood-brain barrier. For example, cultured cell lines derived from melanoma tumors metastatic to the brain were shown to express degradative enzymes at increased levels compared to nonmetastatic cell lines or lines derived from tumors metastatic to sites outside the CNS. These enzymes were found to destroy the basement membrane [5].

Intracranial melanoma is a major cause of morbidity and mortality. Brain metastases resulting from other types of cancers often respond to therapy and are well controlled. Melanoma patients with brain metastases frequently have widespread systemic disease, yet up to 91% of these patients die of intracranial disease despite aggressive therapy [2,4,6–8]. In addition, intracranial melanoma lesions have a high propensity to bleed [9]. Without treatment, the median survival for patients with brain metastases from melanoma is 3–4 weeks [2,10]. At present, surgery, radiation therapy (whole brain or focused radiation), and systemic chemotherapy remain the mainstays of therapy for intracranial melanoma. However, no single therapy has been shown to have consistent long-lasting benefit.

This review details the presentation, immediate management, and definitive therapeutic options for melanoma

Address reprint requests to Henry Brem, MD, Department of Neurosurgery, Hunterian 817, Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205.

in the brain. Immunologic approaches are addressed in a separate article in this issue.

CLINICAL PRESENTATION

The average patient with intracranial melanoma is 53 years old [11], and more than one half (58–71%) are men [2,6]. The higher incidence in men may reflect the worse prognosis of primary lesions of the head, neck, and trunk, which occur more frequently in males [3,6]. Intracranial metastasis tends to occur in patients who had deeper primary lesions. In one study, 71% of those with intracranial metastases had Clark's levels IV (1.5–4 mm deep) and V (>4 mm deep) primary melanomas, with a mean lesion thickness of 3.5 mm [2]. The median time between diagnosis of melanoma and presentation of a brain metastasis is approximately 2.5–4 years [2,4,11,12]. In one series, however, 17% of patients developed intracranial metastases more than 10 years after the initial diagnosis.

Intracranial brain metastasis from melanoma is rarely found without a history of signs or symptoms [11]; rather, it usually presents with signs of increased intracranial pressure (ICP) including headache, nausea, and vomiting [4]. Other common symptoms include change of mental status, focal neurologic deficits such as weakness or cranial nerve deficits, and seizures [3]. The incidence of seizures is 25–50% [3,4,13]. Hemorrhage occurs in 27% of patients with intracranial lesions as determined by neuroimaging [6], although pathologic examination of resected lesions suggests that up to 71% have evidence of prior hemorrhage [14]. Of all lesions that metastasize to the brain, melanoma is the most likely to bleed [9]. If the lesion obstructs cerebrospinal fluid flow, hydrocephalus can develop, resulting in signs and symptoms of increased intracranial pressure.

Brain metastasis from melanoma is likely of hematogenous origin, and as a result, its distribution mirrors the blood flow and weight of the brain [15]. In 75% of cases, the lesion is in the cerebral cortex [16]. Most commonly, the parietal lobe is involved (42–45%), followed by the frontal lobe (21%), and the remainder of the cortex (10–28%). The cerebellum (5%) is the next most common site for metastasis, with brain stem and spinal cord lesions occasionally occurring [6,9,11]. Also reported are rare cases of meningeal metastasis [17] as well as carcinomatous meningitis [18].

Up to 70% of patients treated initially for brain metastasis develop CNS recurrence either locally or at distant sites. Increased ICP and focal neurologic deficits are common presentations for recurrence just as for initial disease. Patients treated for intracranial melanoma and who are maintained on anticonvulsants rarely have seizures unless they have suffered a recurrence. Therefore, a patient with previously treated intracranial melanoma who has a seizure should always be evaluated for recurrent disease regardless of seizure history [19].

DIAGNOSIS

Brain metastasis is seldom the first manifestation of malignant melanoma. More commonly the patient presents with either clinical evidence of elevated ICP, a new neurologic deficit, or seizure, and a careful history reveals a past diagnosis of melanoma. Any patient with a history of melanoma and new neurologic signs or symptoms should undergo a neuroimaging examination. Intracranial melanoma metastases are typically small (most are 1.1–4 cm), frequently multiple (75%), and tend to occur at the gray-white junction. Larger lesions are less common and usually solitary; patients with multiple lesions rarely have any single tumor >4 cm [20].

Of the imaging modalities, magnetic resonance imaging (MRI) with and without contrast is preferred because of its increased sensitivity in detecting lesions [19]. Typically, the tumor appears bright on T1-weighted images (Fig. 1a,b) and dark on T2-weighted images (Fig. 1c). This appearance is thought to be due to the presence of melanin in the tumor rather than associated hemorrhage [21]. Subclinical hemorrhage does occur frequently in these lesions, however, and the presence of different stages of blood breakdown products can alter either the T1-weighted or T2-weighted signal [14]. Most lesions larger than 1.5 cm have surrounding edema [14]. MRI is particularly useful in detecting multiple lesions, an important factor in selecting therapy. Computed tomography (CT) scan with contrast can also be used to diagnose brain metastases. On CT (Fig. 1d), melanoma lesions are frequently slightly hyperdense compared to the brain and do exhibit moderate contrast enhancement. CT is often more readily available in emergent situations, and will show large lesions, hemorrhage, or significant edema. An uncontrasted CT obtained from an emergency room, however, is insufficient to rule out intracranial disease.

For patients who carry a diagnosis of melanoma but have a normal neurologic examination, routine screening of the CNS with neuroimaging rarely identifies metastasis and is not recommended [3]. Merimsky et al. [20] found that metastases in asymptomatic patients tended to be smaller (<1 cm); however, it is not clear that early detection alters survival, nor is the prevalence of positive scans in the neurologically asymptomatic melanoma population known.

INITIAL MANAGEMENT

Patients who present initially with signs of increased ICP or new neurologic deficits and a history of melanoma should be evaluated rapidly for possible brain metastases. There are four major components to the treatment paradigm: stabilization, neuroimaging, treatment of edema and seizures, and definitive therapy (Fig. 2).

First, the critically ill patient should be stabilized. Patients with severely increased ICP should be managed

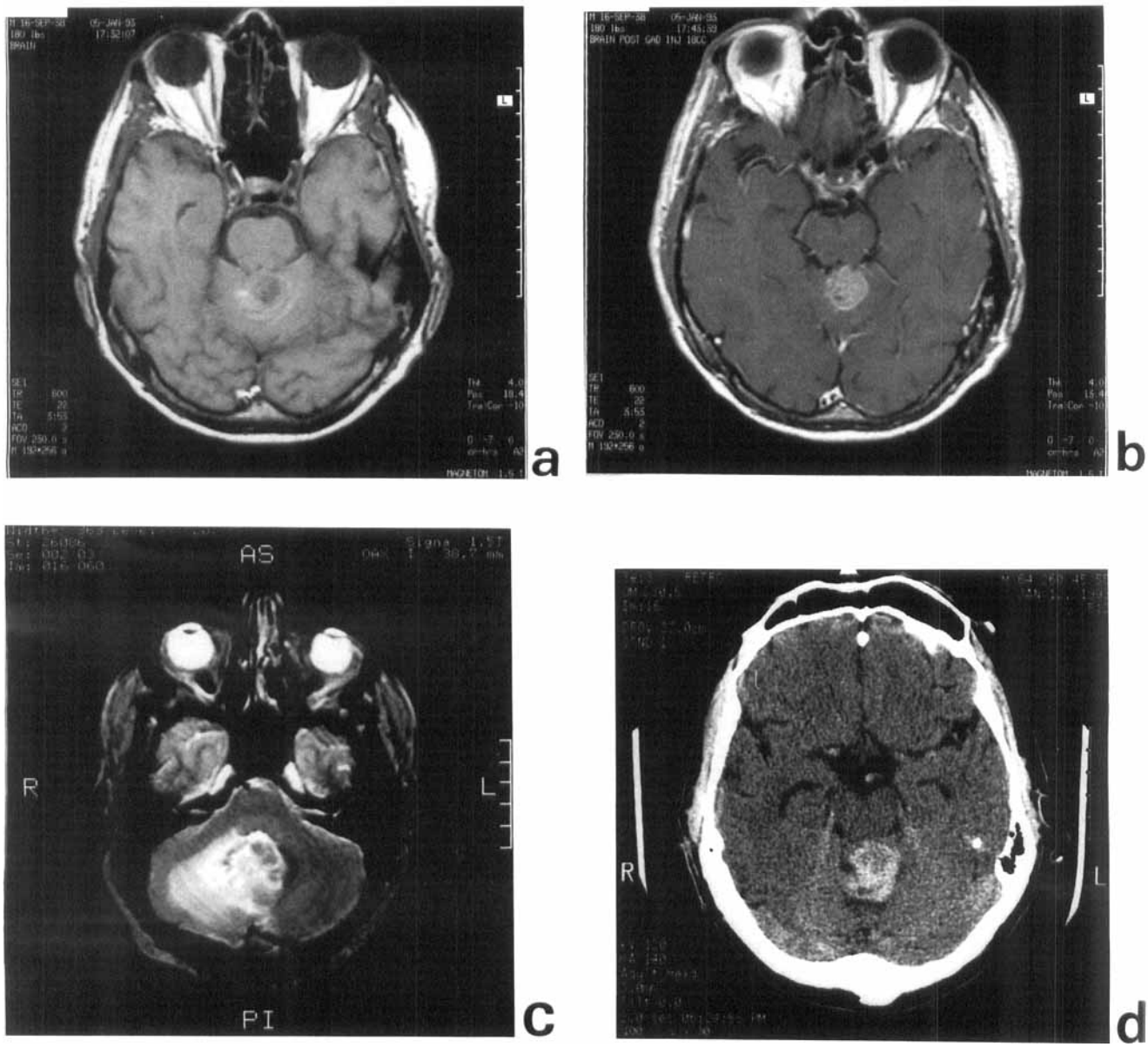

Fig. 1. Four images of melanoma in the brain are presented. The location of tumor, the posterior fossa, is less common then a supratentorial location, but the imaging characteristics pictured here are otherwise typical. **a:** T1-weighted MRI shows a heterogenous lesion. Some areas of the tumor are brighter than in the normal brain while other areas of the tumor are dark in comparison to the normal brain. **b:** When contrast is given, T1-weighted MRI shows strong enhancement. **c:** T2-weighted MRI shows that the tumor itself is dark, with surrounding edema appearing as bright. **d:** Unenhanced CT scan shows a lesion that is well circumscribed and hyperintense to surrounding brain.

immediately by tracheal intubation, hyperventilation to reduce pCO_2 and decrease intracranial blood volume, and mannitol therapy to reduce cerebral edema [22]. ICP management in patients with severe ICP elevation should precede neuroimaging. In patients who are awake and alert, or in those who return to a normal level of consciousness after a seizure, MRI or CT can usually be safely obtained without additional therapy. In a patient with new neurologic deficit or seizures and a history of melanoma, lumbar puncture should not be performed without a neuroimaging study to confirm an open cerebrospinal fluid pathway.

Steroid therapy can extend survival for patients with intracranial metastasis [10]. Once an imaging study is obtained that reveals intracranial disease thought to be melanoma, patients are started on intravenous dexamethasone at 16–40 mg per day divided into four to six doses. Fluid restriction is also of value in passively reducing brain edema. Given the high incidence of seizures in melanoma patients, anticonvulsant prophylaxis is recommended [19]. After initial management of edema and seizures, further therapeutic decisions must take into account factors such as patient age, extent of intracranial and systemic disease, and the desires of the patient.

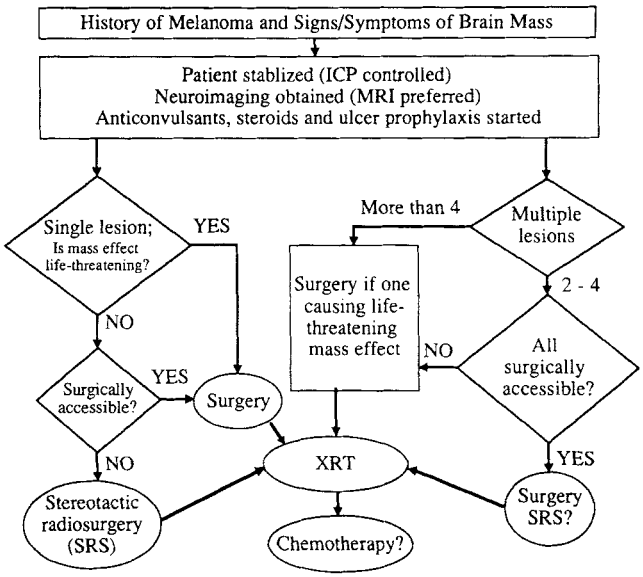

Fig. 2. Treatment paradigm for patients with intracranial metastatic melanoma. XRT = external beam whole brain radiotherapy. All other abbreviations as in the text.

SURGERY

Surgical resection is the first-line therapy for lesions associated with a risk of herniation either from the tumor's mass effect or from bleeding into the tumor. Posterior fossa tumors are also generally treated with surgery, since there is relatively little room for swelling or mass effect within the tight confines of the posterior fossa.

Solitary intracranial lesions that are not life-threatening are also frequently treated by surgery [2,3,11], which is generally followed by radiation therapy. Median survival after surgical resection alone ranges from 5 to 15 months with or without subsequent radiation therapy [2,3,11]. Several factors are predictive of more than 1-year survival following surgery: a single lesion, no extracranial metastasis, unknown primary before surgery, and longer than a 5-year interval between diagnosis of melanoma and presentation of intracranial disease. The reported 2-year survival after surgery ranged from 0 to 25% and 3-year survival ranged from 0 to 15% [11]. In addition to an apparent survival benefit, quality of life as measured by Karnofsky performance scores also improves after surgery [11]. Many authors recommend surgery for solitary lesions that are surgically accessible [2,3,11,23], although, as discussed below, stereotactic radiosurgery can also be used for control of local disease.

Recently, there has been increased interest in the role of surgery in treating multiple metastases. Bindal et al.[24] reported on a series of patients with varying numbers of brain metastases who underwent surgical resection of all lesions. This series, while not entirely of melanoma patients, was weighted toward melanoma. They compared patients with multiple metastases who had all lesions resected to patients with multiple metastases in whom at least one but not all metastases were resected and to patients with single metastases that were resected. Patients who had all of their multiple metastases resected had a median survival equivalent to patients who had a solitary metastasis resected (14 months). Patients who had surgery but had at least one unresected metastasis had a lower median survival of 6 months. On the basis of these results, the authors recommended surgical resection of multiple metastases when all metastases can be surgically approached and the patient's expected survival is longer than 3 months.

In several small reported series [7,11], surgical resection of recurrent metastases of various histologic types including melanoma has been performed with favorable results. Interestingly, recurrent melanoma had a poorer outcome from surgery than did most other tumor types. In spite of this, the authors recommend reoperation for a young patient with recurrent intracranial melanoma who has good functional status and who is free of systemic disease [7].

Standard neurosurgical techniques are used in intracranial melanoma resection. Frameless stereotaxis image guidance systems are useful in planning the flap location in order to minimize the size of the craniotomy for single lesions or to design a flap to include multiple lesions [25]. Once the dura is open, the lesion is not always immediately apparent, since melanoma metastases favor the gray-white junction and can be hidden by the overlying cortex. At this stage of the operation, frameless stereotaxis and/or intraoperative ultrasound are invaluable for identifying the location of the lesion. Efforts are then made to reach the lesion through the nearest sulcus whenever possible, thereby minimizing the damage to the normal brain. Once found, the lesions are frequently discrete nodules which appear black, making them distinct from the normal surrounding brain. Since the frontal and parietal lobes are frequently involved, identification of the motor strip is an important issue. Strip electrocorticography is useful in determining the location of the motor strip by identification of phase reversal. Moreover, because of the propensity toward bleeding characteristic of melanoma, adequate intravenous access and arterial monitoring should be obtained prior to starting the craniotomy. After the first 72 hours following surgery, steroids are tapered as quickly as possible. Patients usually spend 12–24 hours in intensive care, and are often discharged home in 4–7 days.

RADIATION THERAPY

There are three main rationales for radiotherapy for intracranial melanoma metastasis. First, following resection, radiation may slow regrowth of any microscopic tumor foci at the margins of the resection bed. Second, radiation may prevent growth of small tumor foci elsewhere in the brain. Third, radiation after tumor resection is effective for other types of intracranial metastasis [19]. Unfortunately, melanoma is traditionally considered a radioresistant

tumor. It has been suggested that melanoma is radiosensitive, but that larger fractions than are conventionally used are required in order to achieve an effect [26]. Supporting this is the finding that large single fractions of focused radiotherapy, delivered as stereotactic radiosurgery (discussed below) are as effective against radioresistant tumors, including melanoma, as they are against radiosensitive tumors such as lung cancer [27]. The potential for neurotoxicity with higher fractional doses is of major concern, and conclusive data demonstrating that higher dose fractions of whole brain radiation are more effective for intracranial melanoma are not available [4].

The best data on the role of radiation were collected in patients who had first undergone surgical resection [19]. In a nonrandomized trial, patients received either 2,400–4000 cGy in 200–300 cGy fractions or no radiation therapy. Median survival at 9 months did not differ between the two groups; however, the median time to CNS recurrence was 26 months for those who received radiation after surgery vs. 5.7 months for those treated only with surgical resection. Eighty-five percent of those not receiving radiation died of CNS disease as compared to 24% of those who were irradiated. In addition, the CNS relapse rate was 37% in the irradiated group and 69% in the nonirradiated group. In patients with no other active systemic disease at the time of surgical resection and whole brain irradiation, median survival was over 19 months.

Patients treated with radiation therapy and steroids, but without surgery, have been shown to have a dismal outcome, with a median survival of only 10–14 weeks, although they had clear symptomatic improvement of headache, weakness, and mental status changes [13,28]. There is also some evidence that radiation may diminish meningeal relapse [19].

On the basis of these data, many, but not all, authors recommend radiation therapy, usually 3,000–5,000 cGy in 180–300 cGy doses, following surgical resection of a solitary metastasis [2,3,19]. Palliative radiation can also be offered for multiple metastases not amenable to surgical resection [3].

STEREOTACTIC RADIOSURGERY

Single fraction, high-dose, focused radiotherapy, termed "stereotactic radiosurgery," has been used in several series for treatment of intracranial melanoma metastasis [12,16,27,29]. Intracranial metastases are relatively good targets for stereotactic radiation delivered by either the gamma knife or the linear accelerator because the lesions are usually small (<4 cm), discrete, and circular [8]. Stereotactic radiosurgery is an attractive option because it is minimally invasive, can reach lesions that are surgically unapproachable, and usually can be performed as an outpatient procedure [27].

Local control rates for small intracranial melanomas (less than 3 cm) are as high as 97% at 7 months following stereotactic radiosurgery and whole brain radiotherapy. In that series, no patient died of progression of a stereotactically radiated lesion [12]. The authors felt that, despite an unfavorable population with 90% of patients with active systemic disease, their results were equivalent to or better than many reported surgical series. Similar results are reported in other series [16,29]. Alexander et al. [27] reviewed 241 patients treated with stereotactic radiosurgery for intracranial metastases of various primaries including melanoma. There was no difference in response between radioresistant tumors such as melanoma and more radiosensitive tumors including lung tumors. They achieved local control of the tumors in 85% of lesions at 1 year and 65% of lesions at 2 years. Age over 60 years and the presence of active systemic disease correlated negatively with survival. Lesions that were themselves recurrent or infratentorial were more likely to recur following stereotactic radiosurgery. Overall, patients survived 9.4 months, with 31% dying of intracranial disease (25% of deaths due to progression of a treated lesion). Six percent of patients had seizures in the first 2 days following the stereotactic radiation. At least one-third of patients with posterior fossa lesions had self-limited nausea and vomiting following the therapy. The 30-day mortality was 2%, with no deaths directly attributable to the stereotactic radiosurgery. A multicenter randomized trial comparing stereotactic radiosurgery and direct surgery is currently under way.

CHEMOTHERAPY

In general, melanoma has not proven to be a chemosensitive tumor. The only drug approved by the Food and Drug Administration (FDA) for melanoma, dacarbazine (DTIC), has a 20% response rate [3]. Unfortunately, brain metastases rarely respond to DTIC [3,30,31]. The Dartmouth regimen, DTIC, carmustine (BCNU), cisplatin, and tamoxifen, has achieved a response rate of 46% [32] and is the recommended first-line therapy for systemic melanoma [32]. This regimen, however, has been relatively unsuccessful in treating brain metastases; in one Southwest Oncology Group (SWOG) study, DTIC and cisplatin generated an 11% response rate in patients with brain metastases, with a median survival of only 4.3 months [33].

Nitrosoureas, particularly BCNU, have shown activity against melanoma and there was hope that their lipid solubility would increase penetration into the brain and improve chemotherapy of intracranial melanoma. Unfortunately, clinical trial results have been disappointing [30]. Because of concern that the nitrosoureas were not being efficiently delivered across the blood-brain barrier, a more lipophilic nitrosourea, fotemustine, was developed and has been tested in several trials [34–37]. A response rate of 24% has been reported for intracranial disease [36]. The drug is well tolerated and can be given on an outpatient basis. At present, it appears to be the most

promising single agent for systemic treatment of melanoma in the brain [38].

Case reports of patients with CNS metastases responding to 5-fluorouracil and alpha-interferon or DTIC and gamma-interferon have been reported [39,40]. In most cases, however, systemic therapies that appear promising, such as DTIC and alpha-interferon, have been successful for extracranial disease but left the brain vulnerable to involvement, leading the authors to recommend prophylactic radiation therapy [41].

OTHER THERAPIES

Numerous other therapies have been reported as single cases or small series but their efficacy remains unproven. They include boron capture [3] and thermoradiotherapy [42]. A trial of the radiosensitizing agent iododeoxyuridine (IUdR) is underway but no results are currently available [3].

New Directions

New surgical techniques such as stereotactic craniotomy, frameless stereotaxy, and intraoperative ultrasound are making surgical removal safer and more effective. Surgical treatment of multiple metastases has been reported to improve survival and is being evaluated at multiple centers. The role of stereotactic radiosurgery is currently being defined, especially for local control of small lesions. Chemotherapy has some benefit systemically, but issues of drug delivery have hampered efforts to treat intracranial disease. A similar problem has been faced in the treatment of primary brain gliomas. Nitrosoureas given systemically have shown minimal efficacy in treating glioma [43]. Like intracranial melanoma, drug delivery into the CNS is thought to be a limiting factor. This issue of drug delivery is presently being addressed through the use of surgically implanted, biodegradable polymers that release the nitrosourea BCNU. These polymers have been shown to be safe and effective in treating patients at both their initial presentation and recurrence of malignant glioma [44]. The BCNU polymer, GLIADEL®, has been approved by the FDA for widespread usage under a Treatment Investigational New Drug Protocol. Preclinical studies have demonstrated that a BCNU-loaded polymer can also prolong survival in animal models of brain metastases from melanoma [45]. Human trials of the BCNU polymer for the treatment of intracranial melanoma are being planned.

Another approach for treating intracranial melanoma involves local immune therapy with cytokines. Numerous animal studies have been performed using cytokine delivery to treat intracranial tumors, including melanoma. Locally delivered immunoregulatory molecules such as interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interleukin-4 (IL-4) have all been effective models in our laboratory and have also been used by others [46–48]. Advancement to clinical trials will require effective delivery systems for these complex proteins. Transfected cells, either tumor cells or bystander cells, and controlled delivery devices such as microspheres have been used in animals to deliver cytokines and may prove useful in treating patients. Indeed, autologous tumor cells have been used to deliver GM-CSF in human renal cell cancer patients. Intracranial evaluation is being planned.

SUMMARY

Intracranial metastasis remains an important source of morbidity and mortality for patients with melanoma. Although the incidence of melanoma is relatively low compared with that of carcinoma of the lung or breast, the tumor is prone to spread to the brain and is thus the third most common source of intracranial metastasis. Patients usually present with signs and symptoms of increased ICP, a new focal neurologic deficit, or seizures. The combination of these symptoms with a history of melanoma should raise a high degree of suspicion. Contrast MRI is the single most valuable imaging modality. Surgical therapy is the appropriate choice for single lesions that are accessible, especially if they are causing significant mass effect or are located in the posterior fossa. Evidence is accumulating that patients with several intracranial metastases who undergo surgical resection of all lesions have a similar prognosis as those with a single resected lesion. Stereotactic radiosurgery appears to provide good local control of small lesions; its role is still being defined. It is the treatment of choice for surgically inaccessible lesions. External beam radiotherapy may provide some benefit to patients, and is often used in conjunction with surgery or stereotactic radiosurgery. It is usually offered as palliative therapy in patients with widespread intracranial metastases. Chemotherapy to date has been limited because of chemoresistance and difficulty in drug delivery. Fotemustine appears to be the most promising agent, with a 25% response rate. Future directions for treatment of this tumor may include polymer implants for local sustained delivery of chemotherapy or immunoregulatory molecules.

ACKNOWLEDGMENTS

The authors thank Dr. Roland Lee for his assistance with the CT and MRI scans presented, and Dr. Steve Gruber for helpful discussion. We also thank Dr. Pamela Talalay for reviewing the manuscript. We acknowledge the support of the NIH National Research Service Award CA-09574, of which Dr. Matthew Ewend is a recipient; the support of the National Cooperative Drug Discovery Group (UO1-CA52857) of the National Cancer Institute of the NIH; and the support of the New Approaches to Brain Tumor Therapy (NABTT; UO1-CA62474)) of the National Cancer Institute of the NIH. Dr. Brem is a consultant to Guilford Pharmaceuticals Inc.

REFERENCES

1. Hulick PR: Brain metastases as the presenting manifestation of malignant melanoma: A case report. Del Med J 67:231–234, 1995.
2. Saha S, Meyer M, Krementz ET, et al.: Prognostic evaluation of intracranial metastasis in malignant melanoma. Ann Surg Oncol 1:38–44, 1994.
3. Balch CM, Houghton AN, Peters LJ: Cutaneous Melanoma. In DeVita VT Jr, Hellman S, Rosenberg SA (eds): "Cancer: Principle and Practice of Oncology." Philadelphia: Lippincott Company, 1993, 1612–1661.
4. Choi KN, Withers HR, Rotman M: Intracranial metastases from melanoma. Cancer 56:1–9, 1985.
5. Nicolson GL, Nakajima M, Herrmann JL, et al.: Malignant melanoma metastasis to brain: Role of degradative enzymes and responses to paracrine growth factors. J Neurooncol 18:139–149, 1993.
6. Mendez IM, Del Maestro RF: Cerebral metastases from malignant melanoma. Can J Neurol Sci 15:119–123, 1988.
7. Bindal RK, Sawaya R, Leavens ME, et al.: Reoperation for recurrent metastatic brain tumors. J Neurosurg 83:600–604, 1995.
8. Davey P, O'Brien P: Disposition of cerebral metastases from malignant melanoma: Implications for radiosurgery. Neurosurgery 28:8–14; discussion 14–15, 1991.
9. Galicich JH, Arbit E, Wronski M: Metastatic brain tumors. In Wilkins RH, Rengachary SS (eds): "Neurosurgery." New York: McGraw-Hill, 1996, 807–822.
10. Stridsklev IC, Hagen S, Klepp O: Radiation therapy for brain metastases from malignant melanoma. Acta Radiol Oncol 23:231–235, 1984.
11. Jonsson PE, Hafstrom L, Stromblad LG: Surgical management of brain metastases. In Lejeune FJ, Chaudhuri PK, Gupta TK (eds): "Malignant Melanoma: Medical and Surgical Management." New York: McGraw-Hill, 1994, 253–258.
12. Somaza S, Kondziolka D, Lunsford LD, et al.: Stereotactic radiosurgery for cerebral metastatic melanoma. J Neurosurg 79:661–666, 1993.
13. Byrne TN, Cascino TL, Posner JB: Brain metastasis from melanoma. J Neurooncol 1:313–317, 1983.
14. Woodruff WW, Djang WT, McLendon RE, et al.: Intracerebral malignant melanoma: High-field-strength MR imaging. Radiology 165:209–213, 1987.
15. Wright DC: Surgical treatment of brain metastases. In Rosenberg SA (ed): "Surgical Treatment of Metastatic Cancer." Philadelphia: Lippincott, 1987, 165–222.
16. Coffey RJ, Flickinger JC, Bissonette DJ, Lunsford LD: Radiosurgery for solitary brain metastases using the cobalt-60 gamma unit: Methods and results in 24 patients. Int J Radiat Oncol Biol Phys 20:1287–1295, 1991.
17. Rodriguez y Baena R, Gaetani P, Danova M, et al.: Primary solitary intracranial melanoma: Case report and review of the literature. Surg Neurol 38:26–37, 1992.
18. Merimsky O, Inbar M, Gerard B, Chaitchik S: Fotemustine—An advance in the treatment of metastatic malignant melanoma. Melanoma Res 2:401–406, 1992.
19. Hagen NA, Cirrincione C, Thaler HT, DeAngelis LM: The role of radiation therapy following resection of single brain metastasis from melanoma. Neurology 40:158–160, 1990.
20. Merimsky O, Reider-Groswasser I, Inbar M, et al.: Cerebral metastatic melanoma: Correlation between clinical and CT findings. Melanoma Res 2:385–391, 1992.
21. Dewulf P, Demaerel P, Wilms G, et al.: Cerebral metastatic malignant melanoma: CT and MR findings with pathological correlation. J Belge Radiol 76:318–319, 1993.
22. Brem H, Grossman S, Hanley DF: Intracranial masses. In Harvey AH, Johns RJ, McKusick VA, et al. (eds): "Principles and Practice of Medicine." Norwalk, CT: Appleton & Lange, 1988, 1052–1057.
23. Stevens G, Firth I, Coates A: Cerebral metastases from malignant melanoma. Radiother Oncol 23:185–191, 1992.
24. Bindal RK, Sawaya R, Leavens ME, Lee JJ: Surgical treatment of multiple brain metastases. J Neurosurg 79:210–216, 1993.
25. Sipos EP, Tebo SA, Zinreich SJ, et al.: In vivo accuracy testing and clinical experience with the ISG viewing wand. Neurosurgery 39:194-204, 1996.
26. Overgaard J: The role of radiotherapy in recurrent and metastatic malignant melanoma: A clinical and radiobiological study. Int J Radiat Oncol Biol Phys 12:867–872, 1986.
27. Alexander E 3rd, Moriarty TM, Davis RB, et al.: Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastasis. J Natl Cancer Inst 87:34–40, 1995.
28. Carella RJ, Gelber R, Hendrickson F, et al.: Value of radiation therapy in the management of patients with cerebral metastases from malignant melanoma. Cancer 45:679–683, 1980.
29. Buatti JM, Friedman WA, Bova FJ, Mendenhall WM: Treatment selection factors for stereotactic radiosurgery of intracranial metastases. Int J Radiat Oncol Biol Phys 32:1161–1166, 1995.
30. Ho RC: Medical management of stage IV malignant melanoma. Cancer 75 (2 Suppl):735–741, 1995.
31. Kirkwood JM, Agarwala SS: Systemic cytotoxic and biologic therapy of melanoma. PPO Updates 8:1–16, 1993.
32. Mastrangelo MJ, Bellet RE, Berd D: Aggressive chemotherapy for melanoma. PPO Updates 5:1–11, 1991.
33. Fletcher WS, Daniels DS, Sondak VK, et al.: Evaluation of cisplatin and DTIC in inoperable stage III and IV melanoma: A Southwest Oncology Group study. Am J Clin Oncol 16:359–362, 1993.
34. Merimsky O, Inbar M, Reider-Groswasser I, Chaitchik S: Fotemustine with or without dacarbazine for brain metastases of malignant melanoma. Eur J Cancer 27:1066, 1991.
35. Calabresi F, Aapro M, Becquart D, et al.: Multicenter phase II trial of the single agent fotemustine in patients with advanced malignant melanoma. Ann Oncol 2:377–378, 1991.
36. Khayat D, Giroux B, Berille J, et al.: Fotemustine in the treatment of brain primary tumors and metastases. Cancer Invest 12:414–420, 1994.
37. Khayat D, Avril MF, Gerard B, et al.: Fotemustine: An overview of its clinical activity in disseminated malignant melanoma. Melanoma Res 2:147–151, 1992.
38. Merimsky O, Inbar M, Reider-Groswasser I, Chaitchik S: Brain metastases of malignant melanoma in interferon complete responders: Clinical and radiological observations. J Neurooncol 12:137–140, 1992.
39. Phuphanich S, Jacobs M, Spiers A: Response of recurrent brain metastases in malignant melanoma to 5-fluorouracil and interferon-alpha therapy. J Neuroimaging 4:114–116, 1994.
40. Schadendorf D, Worm M, Czarnetzki BM: Brain metastases of metastatic malignant melanoma: Response to DTIC and interferon-gamma. J Neurooncol 16:77–79, 1993.
41. Merimsky O, Chaitchik S: Our experience with interferon-alpha: Metastatic malignant melanoma. Mol Biother 4:135–138, 1992.
42. Sneed PK, Stauffer PR, Gutin PH, et al.: Interstitial irradiation and hyperthermia for the treatment of recurrent malignant brain tumors. Neurosurgery 28:206–215, 1991.
43. Kornblith PL, Walker M: Chemotherapy for malignant gliomas. [published erratum appears in J Neurosurg 69:645, 1988]. J Neurosurg 68:1–17, 1988.
44. Walter KA, Tamargo RJ, Olivi A, et al.: Intratumoral chemotherapy. Neurosurgery 37:1128–1145, 1995.
45. Ewend MG, Williams JA, Tobassi K, et al.: Local delivery of chemotherapy and concurrent external beam radiotherapy prolongs survival in metastatic brain tumor models. Cancer Research, 1996 (in press).
46. Golumbek PT, Lazenby AJ, Levitsky HI, et al.: Treatment of established renal cancer by tumor cells engineered to secrete interleukin-4. Science 254:713–716, 1991.
47. Dranoff G, Jaffee E, Lazenby A, et al.: Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting anti-tumor immunity. Proc Natl Acad Sci USA 90:3539–3543, 1993.
48. Glick RP, Lichtor T, Kim TS, et al.: Fibroblasts genetically engineered to secrete cytokines suppress tumor growth and induce antitumor immunity to a murine glioma *in vivo*. Neurosurgery 36:548–555, 1995.