

15 Treatment of disseminated melanoma

The outcome for patients with stage IV melanomas is poor. The median survival is only six to nine months, with an estimated five-year survival of 5–10% depending on the prognostic factors, the site of metastasis, the number of metastatic sites, and elevated serum LDH levels.^{1,2}

The standard chemotherapy has been single agent dacarbazine (DTIC) that has response rates reported at 5–20%, but only 5% are complete responses and of short duration.^{3,4} Recently fotemustine was shown to produce higher overall response rate compared with dacarbazine, but with only a trend towards overall survival. Unlike DTIC and temozolomide, fotemustine is associated with higher risk of myelosuppression⁵.

The oral alkylating agent temozolomide has equivalent efficacy to dacarbazine (median survival 7.7 months versus 6.4 respectively).⁶ Temozolomide resulted in better health-related quality-of-life outcomes than dacarbazine, both in functional improvements and decreased symptoms.⁷

Combination chemotherapy does not improve survival over single agents and may not improve palliation of more toxic than single agents.⁸ For example, the Dartmouth regimen (cisplatin, carmustine, DTIC and tamoxifen) has a slightly increased response rate but there is no improvement in survival when compared to dacarbazine alone.⁴ The combination of cisplatin and temozolomide did not improve the outcome compared to temozolomide alone.⁹

The addition of tamoxifen to chemotherapy is ineffective.¹⁰ The biological agent interferon-alpha achieved single agent response rates around 15%, while IL2 phase II trials ranged between 3% and 50%.^{11,12} Randomised trials of the combination showed no advantage over single agents.¹³ Combining interferon-alpha with chemotherapy did not improve survival. IL2 was combined with dacarbazine only in phase II trials.¹⁴ Similarly, adding interferon-alpha to temozolomide improved the response rate but did not translate into a survival advantage. Randomised studies of adding either or both interferon and interleukin to combination chemotherapy has not resulted in improved survival of patients with metastatic melanoma.^{15,16} To date no other biological treatment, either vaccines or targeted therapies such as Bcl-2 antisense therapies, have been effective alone or demonstrated survival advantages in randomised trials which add them to chemotherapy.¹⁷

Radiotherapy can improve symptoms from the effect of local tumours. The sites commonly requiring treatment in melanoma are bone, brain, subcutaneous lesions, bulky lymph nodes, liver and adrenal metastases. Whilst many of these can be treated with short fractionation regimens such as 8 Gy in one fraction (bone metastases)¹⁸ or 20 Gy in five fractions (brain metastases),¹⁹ larger and bulky tumours such as those involving lymph nodes or widespread cutaneous deposits may require more lengthy schedules, such as 40 Gy in fifteen fractions or 45 Gy in twenty fractions.

15.1 Brain metastases

For patients who have brain metastasis with favourable prognostic signs including the presence of a single brain metastasis, no extracranial disease, good performance status (PS) and initial presentation with brain metastasis, resection seems to be better than WBRT.²⁰ Median survival ranges from 1.8 months to 10.5 months depending on prognostic factors.²¹ Patients with multiple surgically accessible lesions and little or no extracranial disease may also have an improved prognosis when treated with resection. For patients with surgically inaccessible or multiple metastasis and medical comorbidities, SRS (stereotactic radio surgery) may offer better survival than WBRT.^{21–25} Complete or partial response occurs in 55% of the patients and freedom from progression is achieved in 90–95% after SRS.²⁶ Median survival was better for a solitary lesion than multiple metastases.²⁷ The SIR score (Score Index for Radiosurgery) impacts on survival.²⁸ After surgery or SRS, adjuvant WBRT could improve local control but has no clear survival benefit.^{23,29,30}

For poor prognostic patients, options include WBRT, chemotherapy, steroids or BSC (best supportive care). In one study WBRT alone had a median survival of 3.4 months compared to 2.1 months for BSC alone.²² Steroids given 2–7 days prior to radiotherapy improved symptoms in 73% of the patients.³¹ Surgery could be useful in relieving symptoms from large lesions.

The role of chemotherapy is mainly explored in small phase II trials. In a phase II trial of 151 patients, temozolomide had a response rate of 7% and stable disease of 29%, with an overall survival of 3.5 months in previously untreated patients.³² Other agents studied were thalidomide, and docetaxel alone or in combination.³³ Two small phase II studies examined the role of radiotherapy concurrent with chemotherapy using temozolomide and fotemustine with MS of 8 months.^{34,35} Avril reported RR of 5.9% for fotemustine, compared with DTIC in a phase III trial of metastatic melanoma where 18% of patients had brain metastasis.⁵ Problems with phase II studies were illustrated by an Avril study in which the previously reported phase II response rate of nearly 30% was not replicated in this larger phase III study.

15.2 Surgery

In a phase III trial of adjuvant therapy, surgical resection of selected patients with metastatic melanoma in up to five sites leads to a five year survival of 42.5%.³⁶ Improvement in survival has been reported for metastasis to skin, subcutaneous soft tissue, distant lymph nodes, lung, brain, adrenal glands, liver and gastrointestinal system.^{37–44} One of the most important prognostic factors for survival is the presence of a solitary metastasis.⁴⁵ Surgery for further recurrence can also be useful. In a small series, 20% of patients who underwent a second complete resection achieved a disease-free survival of more than five years.⁴⁶

Evidence summary	Level	Reference
Single agent fotemustine, dacarbazine or temozolomide can be used for palliation of patients with disseminated melanoma	II	3, 6, 37
Biological agents such as interferon-alpha and interleukin-2 yield single agent response rates but do not improve survival alone or when added to single agent or combination chemotherapy. No vaccine has proven effective	II	11, 12, 15, 16
Radiotherapy is effective in providing relief of symptoms in patients with metastatic melanoma where metastases involve bone, brain, soft tissue, liver and adrenal	IV	18
Hypo-fractionated schedules may be more effective in soft tissue disease but not at all sites	IV	19
For good prognosis limited brain metastases with no extracranial disease, surgery improves survival compared to whole brain radiotherapy	IV	23, 24
For good prognosis surgically inaccessible brain metastases with no extracranial disease, stereotactic radiosurgery improves survival	IV	23–28
Surgery or radiosurgery for solitary or few brain metastases of any histology followed by whole brain radiotherapy is effective in reducing intracranial relapse but not improving overall survival	II	29, 30
Patients with resectable metastases have prolonged survival after resection. In patients with metastases limited to skin, subcutaneous tissue, distant lymph nodes, lung, adrenal gland liver, and/or gastrointestinal system, surgery can improve survival	IV	36–45

Recommendations

	Grade
1. Patients with metastatic melanoma be referred for consideration of chemotherapy and/or palliative care to improve their symptoms	C
2. Patients with localised symptoms from melanoma metastasis be referred for radiotherapy	C
3. To improve survival, patients with limited or no extracranial disease and with favourable prognosis brain metastases be considered for surgical resection and if unresectable, for stereotactic radiosurgery. Patients with unfavourable prognostic metastases receive palliation with surgery, whole brain radiotherapy, chemotherapy, steroids or palliative care	C
4. Patients with surgically operable metastases be considered for resection	C

References

1. Barth A, Wanek LA, Morton DL. Prognostic factors in 1,521 melanoma patients with distant metastases. *J Am Coll Surg* 1995; 181(3):193–201.
2. Buzaid AC, Ross MI, Balch CM, Soong S, McCarthy WH, Tinoco L et al. Critical analysis of the current American Joint Committee on Cancer staging system for cutaneous melanoma and proposal of a new staging system. *J Clin Oncol* 1997; 15(3):1039–1051.
3. Hill GJ, Krentenz ET, Hill HZ. Dimethyl triazeno imidazole carboxamide and combination therapy for melanoma. IV. Late results after complete response to chemotherapy (Central Oncology Group protocols 7130, 7131, and 7131A). *Cancer* 1984; 53(6):1299–1305.
4. Chapman PB, Einhorn LH, Meyers ML, Saxman S, Destro AN, Panageas KS et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. *J Clin Oncol* 1999; 17(9):2745–2751.
5. Avril MF, Aamdal S, Grob JJ, Hauschild A, Mohr P, Bonerandi JJ et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *J Clin Oncol* 2004; 22(6):1118–1125.
6. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S 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(1):158–166.
7. Kiebert GM, Jonas DL, Middleton MR. Health-related quality of life in patients with advanced metastatic melanoma: results of a randomized phase III study comparing temozolomide with dacarbazine. *Cancer Invest* 2003; 21(6):821–829.
8. Eigentler TK, Caroli UM, Radny P, Garbe C. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. *Lancet Oncol* 2003; 4(12):748–759.
9. Bafaloukos D, Tsoutsos D, Kalofonos H, Chalkidou S, Panagiotou P, Linardou E et al. Temozolomide and cisplatin versus temozolomide in patients with advanced melanoma: a randomized phase II study of the Hellenic Cooperative Oncology Group. *Ann Oncol* 2005; 16(6):950–957.
10. Agarwala SS, Ferri W, Gooding W, Kirkwood JM. A phase III randomized trial of dacarbazine and carboplatin with and without tamoxifen in the treatment of patients with metastatic melanoma. *Cancer* 1999; 85(9):1979–1984.
11. Coates A, Rallings M, Hersey P, Swanson C. Phase-II study of recombinant alpha 2-interferon in advanced malignant melanoma. *J Interferon Res* 1986; 6(1):1–4.
12. Philip PA, Flaherty L. Treatment of malignant melanoma with interleukin-2. *Semin Oncol* 1997; 24(1 Suppl 4):S32–S38.
13. Sparano JA, Fisher RI, Sunderland M, Margolin K, Ernest ML, Sznol M et al. Randomized phase III trial of treatment with high-dose interleukin-2 either alone or in combination with interferon alfa-2a in patients with advanced melanoma. *J Clin Oncol* 1993; 11(10):1969–1977.
14. Reeves E, Bridge P, Appleyard R. The current role of systemic therapy in the management of malignant melanoma of the skin: an overview. *Journal of Radiotherapy in Practice* 2005; 4:161–175.
15. Bajetta E, Del Vecchio M, Nova P, Fusi A, Daponte A, Sertoli MR et al. Multicenter phase III randomized trial of polychemotherapy (CVD regimen) versus the same chemotherapy (CT) plus subcutaneous interleukin-2 and interferon-alpha2b in metastatic melanoma. *Ann Oncol* 2006; 17(4):571–577.
16. Keilholz U, Punt CJ, Gore M, Kruit W, Patel P, Lienard D et al. Dacarbazine, cisplatin, and interferon-alfa-2b with or without interleukin-2 in metastatic melanoma: a randomized phase III trial (18951) of the European Organisation for Research and Treatment of Cancer Melanoma Group. *J Clin Oncol* 2005; 23(27):6747–6755.

17. Bedikian AY, Millward M, Pehamberger H, Conry R, Gore M, Trefzer U et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 2006; 24(29):4738–4745.
18. Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986; 6(4):247–255.
19. Ziegler JC, Cooper JS. Brain metastases from malignant melanoma: conventional vs. high-dose-per-fraction radiotherapy. *Int J Radiat Oncol Biol Phys* 1986; 12(10):1839–1842.
20. Sampson JH, Carter JH, Jr., Friedman AH, Seigler HF. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. *J Neurosurg* 1998; 88(1):11–20.
21. Buchsbaum JC, Suh JH, Lee SY, Chidel MA, Greskovich JF, Barnett GH. 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(8):2265–2272.
22. Fife KM, Colman MH, Stevens GN, Firth IC, Moon D, Shannon KF et al. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol* 2004; 22(7):1293–1300.
23. Wronski M, Arbit E. Surgical treatment of brain metastases from melanoma: a retrospective study of 91 patients. *J Neurosurg* 2000; 93(1):9–18.
24. Konstadoulakis MM, Messaris E, Zografos G, Androulakis G, Karakousis C. Prognostic factors in malignant melanoma patients with solitary or multiple brain metastases. Is there a role for surgery? *J Neurosurg Sci* 2000; 44(4):211–218.
25. Yu C, Chen JC, Apuzzo ML, O'Day S, Giannotta SL, Weber JS et al. Metastatic melanoma to the brain: prognostic factors after gamma knife radiosurgery. *Int J Radiat Oncol Biol Phys* 2002; 52(5):1277–1287.
26. Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD. Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival. *Int J Radiat Oncol Biol Phys* 1998; 42(3):581–589.
27. Grob JJ, Regis J, Laurans R, Delaunay M, Wolkenstein P, Paul K et al. Radiosurgery without whole brain radiotherapy in melanoma brain metastases. *Club de Cancerologie Cutanee. Eur J Cancer* 1998; 34(8):1187–1192.
28. Selek U, Chang EL, Hassenbusch SJ, III, Shiu AS, Lang FF, Allen P et al. Stereotactic radiosurgical treatment in 103 patients for 153 cerebral melanoma metastases. *Int J Radiat Oncol Biol Phys* 2004; 59(4):1097–1106.
29. Tsao MN, Lloyd NS, Wong RK, Rakovitch E, Chow E, Laperriere N. Radiotherapeutic management of brain metastases: a systematic review and meta-analysis. *Cancer Treat Rev* 2005; 31(4):256–273.
30. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998; 280(17):1485–1489.
31. Katz HR. The relative effectiveness of radiation therapy, corticosteroids, and surgery in the management of melanoma metastatic to the central nervous system. *Int J Radiat Oncol Biol Phys* 1981; 7(7):897–906.
32. Agarwala SS, Kirkwood JM, Gore M, Dreno B, Thatcher N, Czarnetski B et al. Temozolomide for the treatment of brain metastases associated with metastatic melanoma: a phase II study. *J Clin Oncol* 2004; 22(11):2101–2107.
33. Bafaloukos D, Tsoutsos D, Fountzilias G, Linardou H, Christodoulou C, Kalofonos HP et al. The effect of temozolomide-based chemotherapy in patients with cerebral metastases from melanoma. *Melanoma Res* 2004; 14(4):289–294.
34. Ulrich J, Gademann G, Gollnick H. Management of cerebral metastases from malignant melanoma: results of a combined, simultaneous treatment with fotemustine and irradiation. *J Neurooncol* 1999; 43(2):173–178.

35. Hofmann M, Kiecker F, Wurm R, Schlenger L, Budach V, Sterry W et al. Temozolomide with or without radiotherapy in melanoma with unresectable brain metastases. *J Neurooncol* 2006; 76(1):59–64.
36. Morton D, Mozzillo N, Thompson J, et al. An international randomized phase III trial of Bacillus Calmette-Guerin plus allogeneic melanoma vaccine (MCV) or placebo after complete resection of melanoma metastatic to regional or distant sites. *J Clin Oncol* 2007; 25(18S [June 20 supplement]):8508.
37. Karakousis CP, Velez A, Driscoll DL, Takita H. Metastasectomy in malignant melanoma. *Surgery* 1994; 115(3):295–302.
38. La Hei E, Thompson J, McCaughan B, Petersen-Schaefer K, Ramanaden D, Coates A. Surgical resection of pulmonary metastatic melanoma: A review of 83 thoracotomies. *Asia Pacific Heart J* 1996; 5(2):111–114.
39. Tafra L, Dale PS, Wanek LA, Ramming KP, Morton DL. Resection and adjuvant immunotherapy for melanoma metastatic to the lung and thorax. *J Thorac Cardiovasc Surg* 1995; 110(1):119–128.
40. Hsueh EC, Essner R, Foshag LJ, Ollila DW, Gammon G, O'Day SJ et al. Prolonged survival after complete resection of disseminated melanoma and active immunotherapy with a therapeutic cancer vaccine. *J Clin Oncol* 2002; 20(23):4549–4554.
41. Branum GD, Epstein RE, Leight GS, Seigler HF. The role of resection in the management of melanoma metastatic to the adrenal gland. *Surgery* 1991; 109(2):127–131.
42. Rose DM, Essner R, Hughes TM, Tang PC, Bilchik A, Wanek LA et al. Surgical resection for metastatic melanoma to the liver: the John Wayne Cancer Institute and Sydney Melanoma Unit experience. *Arch Surg* 2001; 136(8):950–955.
43. Khadra MH, Thompson JF, Milton GW, McCarthy WH. The justification for surgical treatment of metastatic melanoma of the gastrointestinal tract. *Surg Gynecol Obstet* 1990; 171(5):413–416.
44. Ollila DW, Essner R, Wanek LA, Morton DL. Surgical resection for melanoma metastatic to the gastrointestinal tract. *Arch Surg* 1996; 131(9):975–979.
45. Fletcher WS, Pommier RF, Lum S, Wilmarth TJ. Surgical treatment of metastatic melanoma. *Am J Surg* 1998; 175(5):413–417.
46. Ollila DW, Hsueh EC, Stern SL, Morton DL. Metastasectomy for recurrent stage IV melanoma. *J Surg Oncol* 1999; 71(4):209–213.