Published in final edited form as:

J Natl Compr Canc Netw. 2014 May ; 12(5): 611–615.

BRAF^{V600E} mutant melanoma presenting with cardiac involvement

Douglas B. Johnson, MD^a and Jeffrey A. Sosman, MD^a

^aDepartment of Hematology/Oncology, Vanderbilt University Medical Center, Nashville TN.

Abstract

Melanoma is an aggressive skin cancer with limited treatment options historically. Approximately 50% of melanomas harbor BRAF^{V600} mutations. This report describes a 32 year old man with metastatic BRAF^{V600} mutant melanoma who presented with cardiac involvement. Recently developed treatment options for patients with BRAF mutant melanoma include BRAF inhibitors (vemurafenib, dabrafenib), MEK inhibitors (trametinib), and immune-based therapeutics (interleukin-2 or ipilimumab), but the most effective strategy for first-line therapy is heavily debated. Opinions vary over treatment selection but the consensus of experts favors immune-based therapies initially for asymptomatic patients with low-volume disease and BRAF inhibitors for patients with highly symptomatic or rapidly progressing disease. In this case, the cardiac involvement by melanoma, while clinically uncommon, presents challenging management decisions.

Keywords

Melanoma; cardiac; metastasis; ipilimumab; vemurafenib; braf

Case Report

A 32 year-old man developed axillary swelling in early 2011. A 6×5cm mass was excised and found to be consistent with melanoma. He underwent a completion axillary lymph node dissection with two additional lymph nodes involved by melanoma; extracapsular extension was not identified (TxN2b, AJCC stage IIIB). Detailed physical exam did not reveal a primary site of melanoma; staging PET/CT scan and brain MRI showed no disseminated metastases. He was treated with high dose interferon alpha for one year which was completed in mid-2012. One month later, he noted supraclavicular fullness and monocular blurred vision. CT scans demonstrated a cardiac mass, enlarged supraclavicular and axillary lymph nodes, and a mass in the chest wall; brain MRI revealed a 3 × 1.5cm retro-orbital mass. Molecular testing revealed a BRAF^{V600E} mutation. Echocardiogram showed a 3.5cm mass adherent to the right atrial free wall without valvular regurgitation or impaired flow (Figure 1); cardiac MRI demonstrated a 4.7 × 3.8 cm mass filling nearly the entire right

Corresponding Author: Douglas B. Johnson, 777 Preston Research Building, Nashville, TN 37232. Phone: 205-317-3791. Fax: 615-343-7602. douglas.b.johnson@vanderbilt.edu.

Disclosures: Dr. Sosman is on the advisory board for Bristol-Myers-Squibb and Genentech.

atrium with tricuspid valve involvement (Figure 2). He underwent radiation therapy, with 3,250cGy administered in 5 fractions to his atrial mass and 3,500cGy to his retro-orbital mass. He subsequently initiated vemurafenib 960mg twice daily.

Two months after starting vemurafenib, restaging scans showed slight decrease in his lymphadenopathy but unchanged orbital, cardiac, and chest wall masses. One month later, he developed worsening blurred vision, proptosis, and chest wall pain. Scans demonstrated widespread progression of his metastatic disease although his atrial mass appeared unchanged in size on echocardiogram. He was enrolled on a clinical trial evaluating combination therapy with a MEK inhibitor (AZD6244) and an Akt inhibitor (MK2206). Two months later he developed progressive eye and chest wall pain, fatigue, and hypoxia with exertion. Imaging showed further progression of disease including two new brain metastases for which he underwent stereotactic radiosurgery. Cardiac MRI demonstrated slight enlargement of his atrial metastasis; CT angiogram did not reveal pulmonary embolism or parenchymal abnormalities. He underwent resection of his orbital mass for palliation of his refractory pain and proptosis and was initiated on ipilimumab. After receiving two doses, he developed anorexia and nausea, intermittent confusion, and progressive functional decline. He was referred to hospice care and subsequently died in May 2013.

Discussion

Malignant melanoma is an aggressive cutaneous malignancy that caused over 9000 deaths in 2012.¹ A wide variety of clinical presentations may occur when patients develop metastatic or recurrent disease. These range from local or in-transit skin involvement, isolated single organ metastases, or widely disseminated metastatic disease. Melanoma may involve essentially every organ including the heart. The presence of visceral metastases portends a poor prognosis, although recently approved therapeutic options may induce disease regression and extend survival for a prolonged duration in a minority of patients. Two important management issues for clinicians treating metastatic melanoma are illustrated by this case: selection of first-line therapy for BRAF^{V600E} mutant melanoma and the management of cardiac metastases.

First line therapy: immune therapy vs. targeted therapy

Therapeutic options for advanced melanoma fall into two broad categories. Targeted small molecule inhibitors are effective in patients with BRAF V600E mutant melanoma, a cohort which comprises approximately 50% of all melanoma patients.^{2, 3} Vemurafenib, a specific BRAF inhibitor, induces rapid and often dramatic tumor regression in most patients with objective RECIST responses in 50–60% of patients and improved overall survival compared to cytotoxic chemotherapy.^{4, 5} Dabrafenib, another selective BRAF inhibitor, was approved in May 2013 and appears to have fairly equivalent activity in BRAF V600 mutant melanoma.⁶ Trametinib, a MEK inhibitor, also demonstrates a survival advantage in BRAF mutant melanoma with a response rate in the 20–30% range and was approved in May 2013.⁷ Combined inhibition of BRAF and MEK with dabrafenib and trametinib induces responses in >70% and appears to delay the onset of acquired resistance with a median

progression free survival of 9.4 months compared to 5.8 months for dabrafenib monotherapy ($p < 0.001$).⁸ Unfortunately, resistance to these agents inevitably develops and almost all patients progress within two years of starting therapy. The other major class of therapeutics is immune-based and includes ipilimumab and interleukin-2 (IL-2) which have activity regardless of BRAF mutational status. Ipilimumab is a monoclonal antibody which blocks the immune checkpoint CTLA-4 (cytotoxic T lymphocyte antigen 4) and demonstrated a survival advantage in melanoma patients compared to an experimental peptide vaccine.⁹ In contrast to small molecule inhibitors, ipilimumab may induce delayed responses which may even be preceded by tumor enlargement. Autoimmune toxicities including colitis, endocrinopathies, hepatitis, and dermatitis may complicate therapy. High dose interleukin-2 (IL-2) has been used for many years and induces prolonged disease-free survival in 6–8% of patients.¹⁰ Its severe associated toxicities necessitate inpatient administration at an experienced center and may only be used in patients with normal organ function.¹¹ These immune-based therapies induce disease regression in a minority of patients, although these responses are often durable.^{10, 12, 13}

The most effective first-line treatment strategy for patients with BRAF V600 mutant melanoma has not been clearly defined since the agents have not been compared directly in a prospective fashion. It also remains unclear whether the initial therapy influences the anti-tumor efficacy of subsequent treatments. An intergroup trial is currently in early planning stages to address the best sequence of therapy with a randomized phase III clinical trial in untreated melanoma patients comparing the best combination of targeted agents to the best immunotherapy approach followed by planned crossover at disease progression. This will provide critical insight into management of melanoma patients. In the interim, several retrospective studies provide some guidance for clinicians.

A retrospective analysis evaluated 43 patients treated with vemurafenib; 16 had previously been treated with immune therapy (IL-2 in the majority).¹⁴ The group initially treated with immune therapy demonstrated favorable outcomes with a 75% response rate to vemurafenib and 31 month median overall survival (OS). By contrast, the 10 patients who received first-line vemurafenib followed by ipilimumab at disease progression had a median OS of 2.2 months; 5 patients died prior to completing ipilimumab therapy. An additional retrospective study evaluated 28 patients treated with vemurafenib followed by ipilimumab. Twelve of these patients experienced rapid disease progression and were unable to receive all 4 doses of ipilimumab due to symptomatic deterioration.¹⁵ Brain metastases, elevated LDH, and ECOG performance status of 1 predicted a poor response to ipilimumab. These studies suggest that the efficacy of immune-based therapies in the setting of BRAF inhibitor resistance is limited for at least a subset of patients.

Subgroup analyses from multicenter phase III trials involving ipilimumab and vemurafenib may also help guide clinical practice. Ipilimumab demonstrated improved survival compared to a peptide vaccine. A much greater magnitude of benefit was observed in patients with stage IIIc, IVa, and IVb disease compared to stage IVc with a hazard ratio of 0.47 (0.27–0.82) vs. 0.72 (0.53–0.97).⁹ Conversely, vemurafenib was clearly superior to chemotherapy for patients with stage IVc melanoma whereas the benefit appeared less for patients with stage IIIc, IVa, and IVb (hazard ratio 0.32 (0.21–0.50) vs. 0.64 (0.29–1.38)).⁴

Finally, if immune-based therapy is selected for initial therapy, it is not clear whether IL-2 or ipilimumab is superior. Ipilimumab is generally more tolerable and can be administered to a more elderly and frail population than IL-2, although the volume of experience is less and responses are not truly evaluable until 24 weeks following therapy initiation (unless rapid and obvious disease progression occurs earlier). IL-2 has been used for many years, and responses may be evaluable at approximately 8 weeks, although severe acute toxicities limit its use to selected patients at experienced centers. Analysis of the pivotal ipilimumab vs. peptide vaccine trial demonstrated similar survival benefit in those with prior IL-2 vs those without prior IL-2.⁹ However, there are theoretical concerns about the converse treatment order, that IL-2 might induce delayed immune-related adverse events from ipilimumab, or that the subsequent use of IL-2 may be precluded by ongoing ipilimumab toxicity.

Taken together, general consensus by key opinion leaders is that patients who are relatively asymptomatic with low volume BRAF^{V600} mutant melanoma should receive immune-based therapies as first-line therapy for the chance of a long term benefit, either with ipilimumab or IL-2.¹⁶ Patients who are highly symptomatic, with large volume or rapidly progressing disease should usually be treated initially with vemurafenib or dabrafenib. Patients whose disease presentation falls in the middle of this spectrum may be treated with immune-based therapies or BRAF inhibitors. The advent of newer immune checkpoint inhibitors targeting the programmed cell death-1 receptor or its ligand (PD-1/PD-L1; including nivolumab, MK-3475, MPDL3280A) as monotherapy or in combination with ipilimumab may change this paradigm in the near future as both rapid and durable responses have been observed in early trials.^{17–19}

Cardiac Metastases in Melanoma

Melanoma has a propensity for cardiac involvement, generally through hematogenous spread. Lung and breast carcinomas also commonly involve the heart usually through direct extension of the tumor. Autopsy series show an incidence of cardiac metastases in up to 64% in patients who die with metastatic melanoma.^{20–22} Involvement is often multifocal and may involve the pericardium, epicardium, or myocardium, usually on the right side.²³ The vast majority of cases are clinically silent and most commonly are not even detectable by imaging. Even massive involvement (“charcoal heart”) may confer few symptoms.^{24, 25} Occasionally, asymptomatic metastases may be detected with staging CT or PET scans. In symptomatic patients, more definitive imaging with echocardiogram or cardiac MRI may be performed for surgical planning or to evaluate for outflow obstruction.²³ When clinically apparent, these cardiac metastases most commonly cause dyspnea and peripheral edema from obstruction of forward flow or pericardial effusion. Chest discomfort and tachycardia may also be presenting symptoms; infrequent cases of acute aortic occlusion from melanoma embolism, heart block, and acute coronary syndrome have also been reported.^{26–28}

Therapeutic options for cardiac metastases include systemic therapies or local measures. Systemic therapies are generally preferred for asymptomatic lesions. BRAF inhibitors often cause rapid disease regression in patients with BRAF V600E mutant melanoma and may be

an effective treatment even in patients with symptomatic cardiac involvement. Ipilimumab is another therapeutic option although symptomatic lesions have an extremely high risk of progression prior to benefit even in responding patients. IL-2 causes significant cardiac stress and generally is not administered in the setting of symptomatic cardiac metastases.

Surgical resection of cardiac metastases may be an effective palliative option and even curative in occasional cases. Resection is not commonly performed given the invasive nature of the surgery and usual presence of concurrent widespread metastatic disease. However, appropriately selected patients may derive prolonged benefits from resection which may allow for administration of systemic therapy.²⁹ Additionally, referral to a cardiothoracic surgeon is strongly encouraged for the rare cases of isolated cardiac involvement, as resection may be potentially curative.³⁰ Surgical techniques are evolving and include aggressive strategies such as cardiac autotransplantation.³¹ Radiation therapy is an additional therapeutic options which may cause tumor shrinkage or prolonged stabilization and has been utilized successfully in a case report.³² Our patient appeared to derive palliative benefit from radiation with minimal growth of his atrial mass over several months despite widespread systemic worsening. Clinicians should consider referring patients with symptomatic cardiac metastases to a cardiothoracic surgeon or radiation oncologist for local treatment. Additionally, cardiac involvement should be on the differential diagnosis when melanoma patients present with cardiopulmonary complaints. Nevertheless, until systemic therapy is greatly improved, the control of cardiac metastases will remain difficult and will confer a poor prognosis in most cases.

Acknowledgments

Research Support: Douglas Johnson: K12 CA 0906525

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin.* 2013; 63:11–30. [PubMed: 23335087]
2. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med.* 2005; 353:2135–2147. [PubMed: 16291983]
3. Lovly CM, Dahlman KB, Fohn LE, et al. Routine multiplex mutational profiling of melanomas enables enrollment in genotype-driven therapeutic trials. *PLoS One.* 2012; 7:e35309. [PubMed: 22536370]
4. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011; 364:2507–2516. [PubMed: 21639808]
5. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med.* 2012; 366:707–714. [PubMed: 22356324]
6. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet.* 2012; 380:358–365. [PubMed: 22735384]
7. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. *N Engl J Med.* 2012; 367:107–114. [PubMed: 22663011]
8. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations. *N Engl J Med.* 2012
9. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010; 363:711–723. [PubMed: 20525992]

10. Rosenberg SA, Yang JC, Topalian SL, et al. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. *JAMA*. 1994; 271:907–913. [PubMed: 8120958]
11. Schwartzentruber DJ. Guidelines for the safe administration of high-dose interleukin-2. *J Immunother*. 2001; 24:287–293. [PubMed: 11565830]
12. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. 1999; 17:2105–2116. [PubMed: 10561265]
13. Prieto PA, Yang JC, Sherry RM, et al. CTLA-4 blockade with ipilimumab: long-term follow-up of 177 patients with metastatic melanoma. *Clin Cancer Res*. 2012; 18:2039–2047. [PubMed: 22271879]
14. Ackerman A, McDermott DF, Lawrence DP, et al. Outcomes of patients with malignant melanoma treated with immunotherapy prior to or after vemurafenib. *J Clin Oncol*. 2012; 30:8569.
15. Ascierto PA, Simeone E, Giannarelli D, et al. Sequencing of BRAF inhibitors and ipilimumab in patients with metastatic melanoma: a possible algorithm for clinical use. *J Transl Med*. 2012; 10:107. [PubMed: 22640478]
16. Jang S, Atkins MB. Which drug, and when, for patients with BRAF-mutant melanoma? *Lancet Oncol*. 2013; 14:e60–e69. [PubMed: 23369684]
17. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012; 366:2443–2454. [PubMed: 22658127]
18. Hamid O, Robert C, Daud A, et al. Safety and Tumor Responses with LAMBROLIZUMAB (Anti-PD-1) in Melanoma. *N Engl J Med*. 2013
19. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2013
20. Glancy DL, Roberts WC. The heart in malignant melanoma. A study of 70 autopsy cases. *Am J Cardiol*. 1968; 21:555–571. [PubMed: 5650736]
21. Klatt EC, Heitz DR. Cardiac metastases. *Cancer*. 1990; 65:1456–1459. [PubMed: 2306690]
22. MacGee W. Metastatic and invasive tumours involving the heart in a geriatric population: a necropsy study. *Virchows Arch A Pathol Anat Histopathol*. 1991; 419:183–189. [PubMed: 1926759]
23. Allen BC, Mohammed TL, Tan CD, et al. Metastatic melanoma to the heart. *Curr Probl Diagn Radiol*. 2012; 41:159–164. [PubMed: 22818836]
24. Waller BF, Gottdiener JS, Virmani R, et al. The "charcoal heart;" melanoma to the cor. *Chest*. 1980; 77:671–676. [PubMed: 7363689]
25. Savoia P, Fierro MT, Zaccagna A, et al. Metastatic melanoma of the heart. *J Surg Oncol*. 2000; 75:203–207. [PubMed: 11088053]
26. de Vasconcelos VT, Arias VE, Ikeda S. Cardiac metastasis of melanoma presenting as acute aortic occlusion. *J Thromb Thrombolysis*. 2013
27. Auer J, Schmid J, Berent R, et al. Cardiac metastasis of malignant melanoma mimicking acute coronary syndrome. *Eur Heart J*. 2012; 33:676. [PubMed: 21846676]
28. Cheng G, Newberg AB, Alavi A. Metastatic melanoma causing complete atrioventricular block--the role of FDG PET/CT in diagnosis. *Clin Imaging*. 2011; 35:312–314. [PubMed: 21724126]
29. Gibbs P, Cebon JS, Calafiore P, et al. Cardiac metastases from malignant melanoma. *Cancer*. 1999; 85:78–84. [PubMed: 9921977]
30. Kontozis L, Soteriou M, Papamichael D, et al. Isolated right atrial metastasis of malignant melanoma mimicking a myxoma. *Hellenic J Cardiol*. 2011; 52:281–284. [PubMed: 21642081]
31. Leja MJ, Kim M, Perryman L, et al. Metastatic melanoma to the intracavitary left ventricle treated using cardiac autotransplantation technique for resection. *Methodist DeBakey Cardiovasc J*. 2011; 7:44–46. [PubMed: 22143478]
32. Magnuson WJ, Halligan JB. Successful treatment of melanoma metastatic to the left atrium using external beam radiation therapy. *Oncology (Williston Park)*. 2010; 24:650–653. [PubMed: 20669802]

Figure 1.
Right atrial mass (denoted by arrow) demonstrated on transthoracic echocardiogram, apical view