Developments in the treatment of advanced melanoma
Sloot, Sarah

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2017

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 27-04-2019
BRAF inhibition for advanced locoregional BRAF V600E mutant melanoma: a potential neoadjuvant strategy
Abstract

Selective BRAF inhibitors (BRAFi) yield objective responses in 50% of patients with metastatic BRAF V600E mutant melanoma. Adding a MEK inhibitor increases this response rate to 70%. Limited data are available on the outcomes of unresectable stage III patients, and it remains unclear whether BRAF-targeted therapy can be utilized as a neoadjuvant strategy. Data on patients with advanced locoregional BRAF V600E mutant melanoma treated with BRAF-targeted therapy at Moffitt Cancer Center were analyzed to determine response rates, subsequent resection rates after tumor downsizing, pathologic responses, and patient survival. Fifteen patients with locoregional disease treated with BRAF-targeted therapy, either BRAFi alone (vemurafenib; 11 patients) or a combination of a BRAFi and a MEK inhibitor (dabrafenib plus trametinib or placebo; four patients), were identified. The median age was 50 years; the median follow-up was 25.4 months. The median BRAF-targeted therapy treatment duration was 6.0 months (range 1.2-29.4 months). Response Evaluation Criteria in Solid Tumors-based evaluation demonstrated objective response in 11 patients (73.3%). Six patients underwent resection of the remaining disease after therapy. Pathological analysis showed complete pathologic response (n = 2), partial pathologic response (n = 2), or no pathologic response (n = 2). Four of six patients undergoing surgery have been alive for more than two years, including three patients currently free from active disease. No complications attributable to BRAF-targeted therapy were observed in the perioperative period. Dose reduction or discontinuation because of toxicities occurred in 10/15 patients. Neoadjuvant BRAF-targeted therapy may be effective in advanced locoregional BRAF V600E mutant melanoma patients in increasing resectability, yielding pathological responses, and achieving prolonged survival.

Introduction

Of the 73,870 cases of melanoma estimated to be diagnosed in the USA in 2015, ~9% of patients present initially with regional lymph node or in-transit metastases.1 Data from the Multicenter Selective Lymphadenectomy Trial I of patients with resected 1.2-3.5 mm deep melanomas demonstrated a 10% locoregional recurrence rate in those who underwent sentinel lymph node biopsy and 19% in those who underwent observation of the nodal basin.2,3 Most locoregional disease is amenable to resection aiming to render the patient free from disease.4 However, some patients present with unresectable bulky adenopathies because of surgical limitations such as involvement of neurovascular structures. Similarly, as many as 24% of patients with recurrent locoregional melanoma have satellite and/or in-transit disease not amenable to complete resection.5 Radiation, intralesional injection, hyperthermic isolated limb perfusion, and isolated limb infusion may be of benefit to some patients, but the majority of patients with locoregional melanoma recurrence ultimately require systemic therapy.6,7 Several phase 2 clinical trials have been conducted in resectable stage III melanoma patients using neoadjuvant systemic therapy, including temozolomide, high-dose interferon, or biochemotherapy.8-10 Objective response rates are suboptimal for use as a neoadjuvant strategy in patients with unresectable stage III disease. BRAF-targeted therapy may represent a more effective means for tumor debulking/cytoreduction and subsequent definitive surgery. Phase 3 studies of BRAF inhibitors vemurafenib and dabrafenib have shown objective response rates of 50% in metastatic BRAF V600E mutant melanoma patients, with ~90% of patients showing tumor regression on waterfall plots.11,12 Even higher objective response rates (up to 68%) are achievable with strategies combining a BRAF inhibitor (BRAFi) and an MEK inhibitor (MEKi).13-17 Although unresectable stage III patients comprised 2-9% of the cohorts in these studies, no data have been reported on response rates, conversion rates to the resectable state, and tolerability for this subpopulation. To address outcomes of unresectable stage III melanoma treated with BRAF-targeted therapy, we retrospectively analyzed data on advanced locoregional BRAF V600E mutant melanoma patients treated with BRAFi or BRAFi/MEKi.
Materials and methods

After approval by the Institutional Review Board of the University of South Florida, data on patients treated with BRAF-targeted therapy ( vemurafenib or dabrafenib ± trametinib) for unresectable locoregional BRAF V600E mutant melanoma at Moffitt Cancer Center from 2011 to 2013 were collected. Patients were systematically identified through BRAF test results, pharmacy prescription records, protocol enrollment, and survey of surgical and medical oncologists in the Department of Cutaneous Oncology. Patients with unresectable locoregional disease, defined as in-transit metastases, bulky adenopathies that could not be resected without compromise of neurovascular structures, or regional lymph node metastases that were beyond standard surgical parameters (e.g. axillary disease with chest wall invasion), were included. Patients were excluded if they did not receive initial full dose levels of vemurafenib (960 mg orally twice daily) or dabrafenib (150 mg orally). Demographic and baseline data collected included sex, age, location and extent of disease, serum lactate dehydrogenase (LDH) level, and type of BRAF-targeted therapy received. Data on clinical outcomes included duration of systemic treatment, best radiographic response as measured by Response Evaluation Criteria In Solid Tumors (RECIST 1.1 on computed tomography, PET/computed tomography, and/or MRI), toxicities, surgical outcomes, and survival. When surgery was performed, the resected specimens were analyzed for pathologic response. Pathologic parameters assessed included percentage of viable tumor and presence of necrosis. Pathologic response was graded as follows: (i) complete pathologic response if no viable tumor cells were observed, (ii) partial pathologic response if 10-99% of the tumor area was necrotic but still contained viable tumor cells, and (iii) no pathologic response if less than 10% of the tumor was necrotic/regulated. As the data are exploratory in nature, the results are presented in a descriptive manner. GraphPad Prism 6.02 (GraphPad, La Jolla, California, USA) and IBM SPSS 21.0 (SPSS Inc., Chicago, Illinois, USA) were utilized for analyses.

Results

Baseline characteristics

A total of 15 patients met the inclusion criteria. The median age at initiation of BRAF-targeted therapy was 50 years; nine patients were male, and most patients had advanced nodal disease alone (12 patients) or in combination with in-transit disease (two patients). No patient had received prior systemic therapy for unresectable disease. BRAF genotyping was performed by pyrosequencing (12/15) and real-time PCR/Cobas (2/15). For the remaining patient, genotyping was performed at an external institution and the method was unspecified. Eleven patients received vemurafenib alone, three patients received dabrafenib plus trametinib (clinicaltrials.gov: NCT01584648). LDH levels at the start of treatment were available for 10/15 patients, with 4/10 patients having an LDH level above the normal limit. BRAF-targeted therapy was not restarted after surgery unless the disease progressed.

Patient outcomes

The median follow-up was 25.4 months from initiation of BRAF-targeted therapy. RECIST-based evaluation of the best overall response demonstrated an objective response in 11 patients (73.3%; one complete response, ten partial responses). Two patients had stable disease and two patients had progressive disease. Patients received BRAF-targeted therapy for a median duration of 6.0 months (range 1.2-29.4 months). Two patients remain on active treatment with BRAF-targeted therapy. Reasons for discontinuation include recommendation for surgical resection of disease (4/13), toxicity (2/13) and disease progression (7/13). Of the 11 patients treated with vemurafenib, eight patients required a dose reduction because of toxicities (fatigue, rash, hand-foot syndrome, arthralgias, elevated transaminases). Two of four patients treated with dabrafenib/trametinib discontinued therapy after less than two months because of acute uveitis and a combination of arthralgias, fevers, and rash, respectively. Six patients with partial response underwent resection of residual disease after a median time on BRAF-targeted therapy of 4.7 months (range 1.2-8.9 months). In the nine patients not undergoing resection of the disease, the median treatment duration was 6.0 months (range 2.3-29.4 months). A total of five patients died of the disease, and the median overall survival by Kaplan-Meier evaluation has not yet been reached (Figure 1). The estimated 2-year survival was 68%.

All six patients undergoing surgery after BRAF-targeted therapy were rendered grossly free from disease. All LDH levels were within the normal range after BRAF-targeted therapy before surgery. The median time from discontinuation of BRAF-targeted therapy to surgery was 20 days (range 5-227 days). No unexpected complication occurred during surgery nor in the postoperative period that could have been attributed to prior exposure to BRAF-targeted therapy. Of the six patients documented to be alive past 24 months, four discontinued therapy and underwent surgical resection. Two patients have not relapsed 24.9 and 39.5 months post resection. Interestingly, both patients received dabrafenib plus trametinib for 1.2 and 1.4 months, respectively, before discontinuation because of toxicity. One additional patient has remained free from active disease for 25.6 months from his surgery after receiving stereotactic radiosurgery for two brain metastases two months after his nodal resection. The fourth patient had disease relapse and underwent craniotomy for a brain metastasis, followed by several lines of systemic therapy (ipilimumab, chemotherapy, nivolumab). Of the remaining two surgical patients, one succumbed to widespread disease recurrence despite restarting vemurafenib and the other was lost to follow-up.

Overall survival

Histopathologic evaluation of resected disease after BRAF-targeted therapy demonstrated partial to complete pathologic response in four of six patients (Figure 2). In two patients, complete pathologic response was observed; one had no melanoma cells within the 51
BRAF inhibition as a potential neoadjuvant strategy

...axillary nodes examined and the other had no viable melanoma cells in nine pelvic lymph nodes and subcutaneous fat, although some nodes exhibited nodular aggregates of melanin-laden macrophages and necrosis. Two patients had a partial pathologic response (defined as 10-99% necrosis). Of these, one patient had 15 axillary nodes resected, and two of these lymph nodes showed focal areas of viable tumor amidst abundant necrosis. The other patient had 28 axillary nodes resected, two of which had rare viable tumor cells in an otherwise necrotic background. Before BRAF-targeted treatment, this patient had three lymph nodes excised, demonstrating greater than 80% involvement by viable melanoma with extracapsular extension. The remaining two patients showed no pathologic response despite radiographic evidence of tumor shrinkage. One demonstrated tumor involvement of 75% of the total area and extracapsular extension in three of four pelvic lymph nodes; the other showed metastatic disease in 25 of 26 axillary nodes and 4/12 cervical nodes, with variable necrosis ranging from none to areas of complete necrosis, but averaging less than 10% of tumor necrosis. In the four patients with a partial or complete pathologic response, the resected tissue was characterized by large, geographic areas of necrosis and melanin deposition, both in the extracellular compartment and in the macrophages, rimmed by a lymphohistiocytic infiltrate (Figure 2). Within the necrotic regions, occasional ghost-like remnants of nonviable tumor cells could be seen.

Discussion

The role of neoadjuvant systemic therapy in advanced locoregional melanoma patients is not well defined. Past prospective studies with temozolomide, interferon, and biochemotherapy in resectable stage III patients have demonstrated tumor burden reduction and occasional pathologic complete responses. However, response rates have been suboptimal and patients often experience significant toxicities. These studies did not include patients with unresectable melanoma. Several case reports of patients with metastatic BRAF V600E mutant melanoma given neoadjuvant vemurafenib have shown success in cytoreduction and subsequent resection of their disease. Therefore, the use of a BRAF-targeted therapy as a neoadjuvant approach is an attractive, but largely untested, strategy to render patients surgical candidates and to achieve a disease-free status.

Our case series of 15 patients with unresectable, advanced locoregional BRAF V600E mutant melanoma treated with BRAF-targeted therapy showed an objective RECIST-based response rate greater than 70%. This response rate is on a par with that reported from the phase 3 studies of vemurafenib and dabrafenib ± trametinib, in which objective radiographic responses were seen in 50-70% of all metastatic BRAF V600E mutant melanoma patients. Compared with the 16-26% objective radiographic response rates observed in the neoadjuvant studies of temozolomide and biochemotherapy in resectable stage III melanoma, the higher response rate with BRAF-targeted therapy likely represents a more effective strategy in both resectable and unresectable stage III melanoma patients. In addition, six of 15 unresectable
BRAF inhibition as a potential neoadjuvant strategy

Three patients with radiologic partial responses after BRAF-targeted therapy. Patient A: target lesion in right axilla (a1), treated for 4.0 months (a2), resulting in a complete pathologic response. Post-treatment lymph node excision shows an area of necrosis, with cholesterol clefts peripherally and fibrosis centrally (a3). Patient B: target lesion in the left axilla (b1), treated for 8.8 months (b2). Post-treatment lymph node excision shows multiple geographic areas of necrosis, rimmed by fibrosis and a lymphocytic infiltrate, demonstrating no viable melanoma cells. Other areas of this lymph node showed rare viable tumor cells, indicating a partial response (b3). Patient C: target lesion in the pelvis (c1), treated for 1.2 months (c2), resulting in a complete pathologic response. Lymph node with complete tumor necrosis, showing a viable remaining lymph node (top left) and necrotic material rimmed by melanin-laden macrophages but no viable tumor cells (c3).

Patients were able to undergo resection of their disease with curative intent after substantial cytoreduction, which further supports the use of neoadjuvant BRAF-targeted therapy. Interestingly, pathologic specimens from patients with radiographic evidence of a partial response demonstrated both partial and complete pathologic responses. This suggests that patients who experience partial radiographic responses using standard RECIST criteria on BRAF-targeted therapy may actually have minimal to no viable malignant cells in measurable lymph nodes. Although not examined in this report, alternative methods of assessing BRAF-targeted therapy response, such as serial PET scanning and monitoring circulating free DNA BRAF V600E levels may more accurately correlate to pathologic findings.

It remains to be seen whether improved survival will be achieved in unresectable locoregional BRAF-mutant melanoma patients undergoing neoadjuvant BRAF-targeted therapy followed by surgery as compared with BRAF-targeted therapy alone. There are limited data on the overall survival of unresectable BRAF-mutant stage III patients, but one would expect this to be less than the median of 2.5 years seen for all N3 patients (American Joint Committee on Cancer; ≥4 lymph nodes or matted lymph nodes involved by metastatic melanoma, or in-transit + lymph node disease metastases) among whom many are surgical candidates at presentation. In our cohort of advanced locoregional BRAF V600E mutant melanoma patients, the median overall survival was not reached after more than two years of follow-up. Whereas four of six patients alive past two years underwent surgery, direct survival comparisons are not feasible because of the small sample size and retrospective nature of the study. However, the ability to remain disease-free off therapy is highly encouraging.

Conclusion

Our findings support the potential benefit of BRAF-targeted therapy in advanced locoregional BRAF V600E mutant melanoma patients, which can increase resectability and lead to pathologic partial and complete responses. Although toxicities and dose reductions/discontinuations were observed, these were similar to those in previous investigations and did not preclude surgical consideration. However, it should be acknowledged that definitive conclusions cannot be drawn from this study because of the small sample size and retrospective design. Multiple prospective clinical trials with neoadjuvant BRAFi plus MEKi strategies or actively enrolling BRAF-mutant melanoma patients with advanced locoregional disease have been planned (clinicaltrials.gov: NCT01972347, NCT02036086, NCT02303951, and NCT02231775). These studies will be valuable for confirmation of the clinical benefit of using a neoadjuvant BRAF-targeted approach. Furthermore, pathologic evaluation of tumors post treatment may provide prognostic information and an opportunity for molecular evaluation of patient-specific tumor responses.
References
