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Do BRAF Inhibitors Improve Survival in Patients with BRAF V600E Mutant Melanoma?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Do BRAF inhibitors improve survival in patients with BRAF V600E mutant melanoma?"

STUDY DESIGN: Review of primary literature sources that examined survival rates in BRAF V600E mutant melanoma patients receiving treatment with a BRAF inhibitor.

DATA SOURCES: Two randomized controlled trials and one cohort study evaluating the use of BRAF inhibitors in patients with BRAF V600E mutant melanoma were found using OVID, Medline, and PubMed.

OUTCOMES MEASURED: Overall survival and progression free survival were the outcomes measured to determine survival rates in patients with BRAF V600E mutant melanoma.

RESULTS: Chapman et al demonstrates an overall survival rate of 84% for Vemurafenib (95% CI, 78-89) compared to 64% for Dacarbazine (95% CI, 56-73). Progression free survival was 5.3 months for Vemurafenib compared to 1.6 months for Dacarbazine.

Sosman et al, a cohort study, demonstrates an overall survival rate of 58% (95% CI, 49-67) after 12 months. Progression free survival was 6.8 months (95% CI, 5.6-8.1).

Hauschild et al demonstrates an overall survival rate of 57% for Dabrafenib compared to 22% for Dacarbazine. Progression free survival was 5.1 months for Dabrafenib compared to 2.7 months for Dacarbazine.

CONCLUSIONS: All studies reported longer periods of progression free survival and an increase in overall response rates. This suggests that BRAF inhibitors improve survival in patients with V600E mutant melanoma.

KEY WORDS: Melanoma; BRAF inhibitor; Survival

INTRODUCTION

Melanoma is a form of skin cancer that affects melanocytes. Melanocytes are found in the epidermis and produce melanin, the major pigment responsible for skin color. Melanoma is sometimes described as the "ugly duckling sign", meaning that it doesn't look like other nevi. Typically nevi suspicious of melanoma are asymmetric, have irregular borders, appear black or brown in color, are larger than 6 mm in diameter, and evolve in size, shape, or color (ABCDE rule). Melanoma most commonly occurs on sun exposed areas of the skin but not exclusively. In addition, the incidence of melanoma increases with age, however younger patients may also be diagnosed with melanoma.[1]

Skin cancer is the most commonly diagnosed cancer. Melanoma accounts for less than 2% of skin cancer but it is the most deadly. The American Cancer Society estimates 76,100 new cases and 9,710 deaths from melanoma in the United States for 2014. In addition, the number of new cases of melanoma in the US has been increasing for the past 30 years.[1] Studies examining all stages of disease, indicate the annual cost of treatment ranges from $44.9 million to $932.5 million.[2] It is estimated that there are 17.4 million visits from 1979 to 2010.[3]

Risk factors of melanoma include UV light exposure, presence of moles, fair skin, freckling, light hair, and positive family history. However, it is not known how these risk factors cause melanoma. It is known that patients with melanoma are at a higher risk of recurrence. However, methods to lower the risk of melanoma progression or recurrence remain unknown.[1]

Early stages of melanoma can be treated with surgery alone but more advanced stages require additional treatment. Surgical treatments includes wide excision, lymph node dissection, and removal of metastatic disease. Common immunotherapy includes Ipilimumab, Pembrolizumab, Interferon-alpha, Interleukin-2, Bacille Calmette-Guerin (BCG) vaccine, and Imiquimod cream. Targeted therapies include BRAF inhibitors (Vemurafenib and Dabrafenib)

and MEK inhibitors (Trametinib). Typical chemotherapies include Dacarbazine, Temozolomide, Nab-paclitaxel, Carmustine, Cisplatin, Carboplatin, and Vinblastine. Radiation is also a common treatment modality.[2] Metastatic melanoma has a poor prognosis with an average 8-18 month survival rate in patients with stage IV melanoma. Until 2011, Dacarbazine was the only monotherapy approved by the FDA for metastatic melanoma.[1,4]

The therapies listed above all play an important role in the treatment of melanoma. 50% of melanoma patients have a mutation of the BRAF gene. BRAF is an oncogene, meaning this mutation increases cell proliferation. Therefore, melanocytes reproduce at an uncontrolled rate, resulting in cancer. BRAF inhibitors are effective in shrinking tumors in half of patients with metastatic melanoma with a mutated BRAF gene.[1] This paper evaluates two randomized controlled trials (RCTs) and one cohort study comparing the efficacy of BRAF inhibitors as a therapy for improving survival in patients with BRAF mutant melanoma.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Do BRAF inhibitors improve survival in patients with BRAF V600E mutant melanoma?"

METHODS

To examine this question, this paper focuses on patients 18 years or older with stage III/IV BRAF V600E mutant melanoma. Interventions that were considered in literature search included BRAF inhibitors, Vemurafenib or Dabrafenib. Types of studies examined include two randomized control trials and one cohort study. Chapman et al is a phase 3 randomized clinical trial comparing Vemurafenib, a BRAF inhibitor, and Dacarbazine, the FDA approved treatment for metastatic melanoma at the time of publication. Overall survival, progression free survival, and tumor response were measured.[4] Sosman et al is a multicenter phase 2 trial cohort study

investigating the efficacy of Vemurafenib with respect to overall response rate, progression free survival, and overall survival.[5] Hauschild et al is a phase 3 randomized controlled trial that compared efficacy of Dabrafenib, a BRAF inhibitor, and Dacarbazine by measuring progression free survival and overall survival.[6]

A detailed search was completed using OVID, Medline, and PubMed with the key words of "Melanoma", "BRAF inhibitors", and "Survival". Articles were English language peer reviewed publications from 2011 and 2012. The criteria used for selection was based on relevance to the proposed clinical question and patient oriented outcomes (POEMS). Inclusion criteria were at least two randomized control trials. Exclusion criteria included patients less than 18 years of age, central nervous system metastasis, and other invasive cancers within five years of enrollment. Statistics that were reported include RBI, ABI, NNT, and 95% Confidence interval. Table 1 provides information regarding inclusion and exclusion criteria and specific study interventions.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yr)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Chapman[4] (2011)	RCT	675	>18	-previously untreated stage IIIC or IV melanoma, positive for BRAF V600E -Life expectancy of 3 months or longer -ECOG performance status of 0 (fully active) or 1 (restricted in physically strenuous activity but ambulatory) -Adequate hematologic, hepatic, renal function	-history of cancer within past 5 yrs (except basal, squamous cell of the skin or cervical cancer) -Metastasis to CNS	3	960 mg of Vemurafenib PO BID

Sosman[5] (2012)	Cohort Study	132	>18	-Stage IV melanoma with BRAF V600 mutation & progressive disease after at least one prior systemic treatment -ECOG performance status of 0 (fully active) or 1 (restricted in physically strenuous activity but ambulatory)	-Brain metastasis uncontrolled after at least 3 months of local therapy -Other invasive cancers within 5 yrs from enrollment -Inadequate hematologic, hepatic, & renal function	0	960 mg of Vemurfenib PO BID
Hauschild [6] (2012)	RCT	250	21-93	-previously untreated stage III or IV BRAF V600E mutant positive melanoma -ECOG performance status of 0 (fully active) or 1 (restricted in physically strenuous activity but ambulatory) -Adequate hematologic, hepatic, renal, & cardiac function	-surgery, radiotherapy, or immunotherapy within 4 wks -History of HIV, G6PD, or previous cancer in last 5 yrs - CNS metastasis - Corrected QT interval >480ms, ACS, stent placement, arrhythmias, heart murmur grade 2 or higher	80	150 mg of Dabrafenib PO BID

OUTCOMES MEASURED

The outcomes measured were overall survival and progression free survival. Both of which are patient oriented evidence that matters (POEMS). These outcomes were measured consistently across the three studies. Chapman et al measured overall survival, progression free survival, and tumor response. Overall survival is reported as a percent of patients living out of the total number of patients that entered a treatment group. Progression free survival was the time from randomization to documented disease progression or death. Tumor response, a decrease in tumor size, was also reported. Two-sided unstratified log-rank test were used to compare survival rates in the two study groups. Event time distribution was estimated using the Kaplan-Meier method.[4] In the Sosman et al study, overall response rate was defined as the

number of patients with complete or partial response divided by the total number of treated patients. Progression free survival, and overall survival were estimated using the Kaplan-Meier method while medians with two-sided 95% confidence intervals were calculated using the Brookmeyer and Crowley method.[5] Hauschild et al progression free survival and overall survival were reported with two-sided 95% confidence intervals.[6]

RESULTS

At 6 months, Chapman et al reported an overall survival rate of 84% (95% CI, 78-89) for Vemurafenib and 64% (95% CI, 56-73) for Dacarbazine. Progression free survival was 5.3 months in the Vemurafenib group and 1.6 months in the Dacarbazine group. 65% of patients could be evaluated for tumor response. In the Vemurafenib group, 48% (95% CI, 42-55) of patients had a detectable decrease in tumor size (2 patients had a complete response and 104 had a partial response) with a median time to response of 1.45 months. In the Dacarbazine group, 5% (95% CI, 3-9) of patients experienced a decrease in tumor size (all partial response) with a median time to response of 2.7 months. Tumor response rates between the two groups were considered highly significant ($P<0.001$ with chi-square test).[4]

Sosman et al reported an overall response rate of 53% (95% CI, 44-62) for patients receiving Vemurafenib. 6% of patients experienced a complete response while 47% received a partial response. The progression free survival was 6.8 months (95% CI, 5.6-8.1). The median overall survival was 15.9 months (95%, 11.6-18.3). The overall survival rates at 6, 12, and 18 months are reported in **Table 2**.[5]

Table 2: Overall Survival Rate of Patients Receiving Vemurafenib

Time	Overall Survival Rate
6 months	77% (95% CI, 70-85)
12 months	58% (95% CI, 49-67)
18 months	43% (95% CI, 33-53)

Hauschild et al reported overall survival rate of 57% for patients receiving Dabrafenib treatment while overall survival rate for Dacarbazine was 22%. The median time on study was 4.9 months. Progression free survival for the Dabrafenib group was 5.1 months and 2.7 months for the Dacarbazine group. Response rates were reported as 50% (95% CI, 42.4-57.1) for Dabrafenib and 6% (95% CI, 1.8-15.5) with a 5.5 month duration of response.[6]

Treatment effects of the three studies are displayed in **Table 3**. Relative Benefit Increase (RBI) represents the increased chance of a positive outcome if treated with a BRAF inhibitor compared to the chance of positive outcomes if treated with the control, Dacarbazine. Absolute Benefit Increase (ABI) represents the actual increase in positive outcomes between the treatment of BRAF inhibitors and Dacarabazine. Number Needed to Treat (NNT) was calculated in order to describe the number of patients that would need to be treated in order for one patient to survive.

Table 3: Treatment Effects of BRAF Inhibitors in Patients with BRAF V600E Mutant Melanoma

STUDY	CER (%)	EER (%)	RBI (%)	ABI (%)	NNT (n)
Chapman et al[4]	0.64	0.84	0.3125	0.2	5
Sosman et al[5]	n/a	n/a	n/a	n/a	n/a
Hauschild et al[6]	0.22	0.57	1.59	0.35	3

CER= Control Event Rate; EER= Experimental Event Rate; RBI= Relative Benefit Increase; ABI= Absolute Benefit Increase; NNT= Number Needed to Treat

Most common side effects of Vemurafenib include cutaneous events, arthralgia, fatigue, photosensitivity skin reactions. Cutaneous squamous cell carcinoma, keratoacanthoma, or both developed in 18% of patients in the Chapman et al study[4] and 26% of patients in the Sosman et al study.[5] Most common side effects of Dacarbazine include fatigue, nausea, vomiting, and neutropenia.[4,5,6] Dabrafenib has a similar side effect profile to Vemurafenib.[6]

DISCUSSION

Treatment options for metastatic melanoma are limited. Once the BRAF mutation was known to be associated with melanoma, BRAF inhibitors appeared to be a promising target for therapy.[5] Nearly 50% of patients with melanoma are positive for the BRAF V600 mutation. BRAF inhibitors induce a clinical response in more than half of patients that are positive for the BRAF V600 mutation.[4,5,6] Vemurafenib was approved by the FDA in 2011 for the treatment of metastatic melanoma. Dabrafenib was later approved in 2013.[1]

One of the more common toxic effects related to the use of BRAF inhibitors involved the skin. Cutaneous squamous cell carcinoma and keratoacanthoma were removed with simple excision. Other side effects such as arthralgia, rash, fatigue, and photosensitive reactions were primarily managed with dose reduction.[4,5,6]

One important consideration is how BRAF V600 mutant melanomas become resistant to BRAF inhibitors. In all three studies, BRAF inhibitors exhibited progression free survival for at least 5 months. During this time melanomas responded to BRAF inhibitor target therapy. As time progressed, tumors gained resistance and progression occurred. At this time no mechanism of resistance has been identified but is an important consideration for further treatment and research.[4,5,6]

CONCLUSION

Based on the analysis of the three studies, this selective EBM review concludes that BRAF inhibitors do indeed improve survival in patients with BRAF V600E mutant melanoma. Studies reported improved survival rates of at least 50% and in one study up to 80%.[4,5,6] The use of BRAF inhibitors for the treatment of BRAF V600E mutant melanoma has shown to decrease tumor size, slow the progression of the disease, and ultimately prolong life in patients with

metastatic disease. Future research should be aimed to minimize side effects and also to determine the mechanism of resistance in order to prolong tumor response to treatment and further improve survival.

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