Review of Melanoma Cases Treated at Lehigh Valley Health Network in 2013

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Abstract

Melanoma of the skin, a cancer originating in the pigment producing cells of the skin, is estimated to be the 5th most common type of cancer diagnosed in the United States in 2014(SEER, 2014) (Chabner, Lynch, & Longo, 2008). Prognosis is considerably higher in melanoma that is diagnosed early, thus emphasizing the need for proper and timely treatment (SEER, 2014). Late stage melanoma is also one of the most common neoplasms to metastasize to the brain, a condition believed to be more likely when patients possess a mutated BRAF gene which causes improper regulation of cell growth and division, thus allowing for proliferation of tumor cells (Mittapalli et al, 2012). If discovered, a clearly delineated link between BRAF mutation and melanoma metastasized to the brain would indicate that BRAF testing may serve as a strong prognostic tool and a treatment determining test in the future. By reviewing all of the melanoma cases treated at Lehigh Valley Health Network in 2013, we show that treatment offered to skin and scalp melanoma patients at LVHN in 2013 was in accordance with the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Melanoma Version 4.2014 and that 75% of stage IV melanoma patients with brain metastasis tested positive for the BRAF mutation.

Introduction

According to the CDC, cancer is the second largest cause of death in the United States with an estimated five hundred seventy four thousand seven hundred and forty three deaths per year (CDC, 2011). Melanoma of the skin is estimated to be the 5th most common type of cancer diagnosed in the United States in 2014(SEER, 2014). Melanoma originates in the pigment producing cells of the skin and can arise de-novo, from an atypical nevus, or from melanoma in-situ (Mittapalli et al, 2012) (Chabner, Lynch, & Longo, 2008). Most melanomas are asymmetrical, have irregular borders, are variegated in color, have a diameter greater than six millimeters, or have changed size or shape over time (Chabner et al, 2008). Melanomas can be described by their growth patterns which include superficial spreading melanomas, nodular melanomas, lentigo maligna melanomas, and acral lentiginous melanomas (Chabner et al, 2008).

It is estimated that by the end of 2014 there will have been seventy six thousand one hundred patients diagnosed with melanoma and nine thousand seven hundred and ten melanoma related deaths (SEER, 2014). Melanoma is most common in fair skinned individuals who have experienced intense and intermittent sun exposure, thus exposing them to UVA and UVB radiation (Chabner et al, 2008). The earlier melanoma is diagnosed, the better the prognosis. Localized melanoma has a patient survival rate of ninety eight percent and can be treated rather

successfully with excision of the lesion (SEER, 2014). However, regional melanoma that has spread to the lymph nodes has a survival rate of only sixty two percent and may require not only surgical excision, but also lymph node dissection and potentially a systemic therapy such as chemotherapy or immunotherapy (SEER, 2014). Late stage distant melanoma with metastasis has a survival rate of only sixteen percent and requires excision of the primary legion, systemic therapy and perhaps even a debulking of the metastatic masses (SEER, 2014).

Late stage melanoma is one of the most common neoplasms to metastasize to the brain, preceded only by lung and breast cancers (Mittapalli et al, 2012). Once melanoma has spread to the brain, median prognosis is less than 6 months (Mittapalli et al, 2012). Previously treatments were limited to radiation, surgery, immunotherapy, and chemotherapy (Mittapalli et al, 2012). However, recently research has given rise to a new kind of therapy—BRAF inhibitors. BRAF inhibitors, which target the BRAF mutation, provide another treatment option for patients with melanoma metastasized to the brain and are improving patient prognosis (Lemech et al, 2011). BRAF mutations are a common feature of many aggressive, late stage melanomas and are typically seen in people who are younger at the time of diagnosis (Long et al, 2011). BRAF is a proto-onco gene that encodes a serine-threonine protein kinase which acts in pathways that regulate cell proliferation and growth (Mittapalli et al, 2012). When the BRAF gene is mutated, the cell growth is no longer regulated properly which leads to tumor cell proliferation, invasion, and resistance (Mittapalli et al, 2012). The most common form of this mutation is the V600E mutation which turns kinase activity in the pathway constitutively on and accounts for approximately 80% of BRAF mutations (Mittapalli et al, 2012). Patients with the BRAF mutation tend to have more aggressive disease and a poorer prognosis than their wild type counterparts. Right now BRAF testing is used to give physicians some information about prognosis and determine whether patients are candidates for treatments involving BRAF inhibitors. If the link between BRAF mutation and melanoma metastasized to the brain can be clearly delineated, then BRAF testing may serve as a stronger prognostic tool and treatment determining test in the future.

Melanoma was among the top five cancers diagnosed and treated at Lehigh Valley Health Network (LVHN) in 2013. The goal of this study was to determine if treatments offered to patients with skin and scalp melanoma at LVHN in 2013 were in accordance with the treatments recommended by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Melanoma Version 4.2014 (NCCN Guidelines), which serve as a national standard for diagnosis and treatment of cancer. In addition, some stage III and stage IV patients with aggressive disease or brain metastasis were tested for the BRAF mutation (V600E) in an effort to contribute data to ongoing research to determine if there is a link between BRAF positive mutation and brain metastasis. Herein we show that treatment offered to skin and scalp melanoma patients at LVHN in 2013 was in accordance with the NCCN guidelines and that 75% of stage IV melanoma patients with brain metastasis tested positive for the BRAF mutation.

Methods

All of the charts of patients treated in Lehigh Valley Health Network (LVHN) for melanoma during 2013 were reviewed. Of the 137 charts from 2013, 5 were excluded because of unknown staging, 2 were excluded because they were mucosal melanomas, 1 was excluded because pathology of their resected tissue was not indicative of melanoma, and 1 was excluded because there was no patient follow-up after the initial diagnosis, leaving 128 to be reviewed. Age, gender, stage, treatment, presence of brain metastasis, presence of BRAF mutation (V600E), and patient mortality were determined by reviewing all patient records including radiology and pathology results done during 2013. Accordance with the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Melanoma Version 4.2014 (NCCN Guidelines) was determined by comparing the treatments the patients received at LVHN to the treatments outlined in the NCCN Guidelines. All data analysis was done using Microsoft Excel.

Results and Discussion

Staging of Skin and Scalp Melanoma Patients at LVHN in 2013

Stage	Number of Patients
0	24
1	62
2	21
3	9
4	12

Table 1: Staging of 128 skin and scalp melanoma patients diagnosed and treated at Lehigh Valley Health Network in 2013.

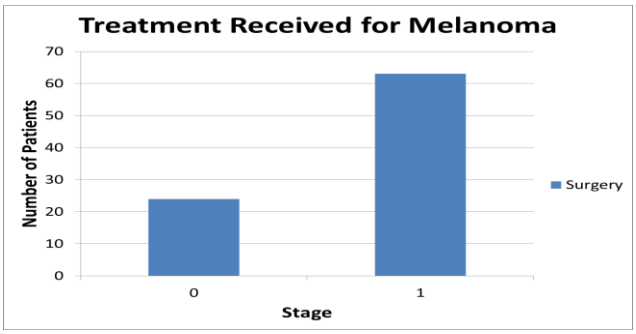

Figure 1: Treatment received for stage 0 melanoma in situ and stage 1 melanoma at Lehigh Valley Health Network in 2013. Surgery can include wide excision, reexcision, and sentinel lymph node biopsy.

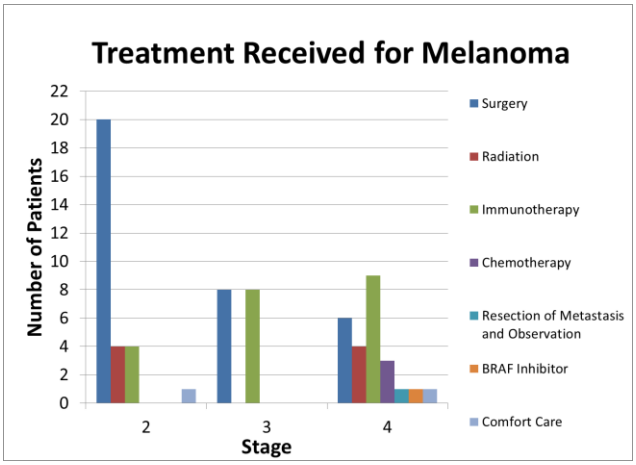

Figure 2: Treatment received for stage 2, 3, and 4 melanoma at Lehigh Valley Health Network in 2013. Surgery can include wide excision, reexcision, sentinel lymph node biopsy, and lymphadenectomy. Radiation includes gamma knife radiation and electron beam radiation. Immunotherapy includes Ipilimumab, interferon alpha (high dose and peggylated), Nivolumab, and immunotherapy combination clinical trials BMS CA209-067, E1609, and BMS CA209-064. Chemotherapy includes carboplatin, paclitaxel, and avastin. Resection of metastasis and observation involved removing the metastatic tissue and observing the patient. Comfort care included hospice and pain medications.

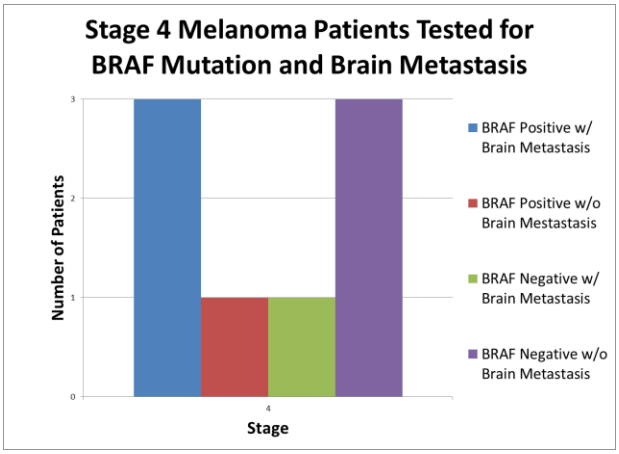

Figure 3: Stage 4 melanoma patients treated at LVHN in 2013 that were tested for BRAF mutation(V600E) and brain metastasis. Excluded from this figure is one stage 3 melanoma patient that tested positive for the BRAF mutation, 2 cases where stage 4 patients were not tested for brain metastasis or the BRAF mutation, and 3 cases where patients were negative for brain metastasis and were not tested for the BRAF mutation.

One goal of our study was to access if treatments offered to skin and scalp melanoma patients treated at LVHN in 2013 were in accordance with the treatments suggested by the NCCN Guidelines. There were one hundred and twenty eight skin and scalp melanoma cases reviewed in total (Table 1). All twenty four of the stage 0 melanoma patients were treated with

surgical resection of the melanoma in situ and then observation (Table 1) (Figure 1). The surgery was first a wide excision of the lesion and then a reexcision if the margins were positive. Patients were encouraged to conduct self-skin exams and follow up regularly with dermatology. This treatment is in accordance with the recommended NCCN Guidelines for melanoma in situ which state that the proper treatment is wide excision, self-skin exams, and a yearly skin exam for life (NCCN Guidelines).

There were sixty two patients diagnosed with stage 1 melanoma (Table 1). Of these patients, twenty four were stage 1A, meaning that their melanoma was not ulcerated or mitotically active and thirty eight were stage 1B meaning that their melanoma was less than one millimeter in thickness and either ulcerated or mitotically active, or between one and two millimeters in thickness and not mitotically active (Edge et al, 2010). All sixty two of the stage 1 patients received surgery (Figure 1). Patients were also offered a sentinel node biopsy. Surgery entailed wide excision, reexcision if necessary, and a sentinel node biopsy if the patient elected for one, followed by observation. Patients were encouraged to perform self-skin exams, follow up with dermatology, and follow up with oncology if necessary. All of the stage IA treatments are in accordance with the NCCN guidelines which suggest that the treatment for stage 1A melanoma is wide excision, discussing a sentinel node biopsy with the patient, self-skin exams, and yearly skin exams for life (NCCN Guidelines). The Stage 1B treatments are also in accordance with the NCCN guidelines which suggest that treatment is wide excision, discussing a sentinel node biopsy, and offering either participation in a clinical trial, interferon alpha therapy, or observation (NCCN Guidelines). The NCCN Guidelines also suggest that stage 1B patients perform self-skin exams, and have yearly skin exams for life (NCCN Guidelines).

There were twenty one patients diagnosed with stage II melanoma (Table 1). Of the twenty one patients, nine were stage IIA meaning that their melanoma was either ulcerated and between one and two millimeters in thickness or not ulcerated and between two and four millimeters in thickness, six were stage IIB meaning that their melanoma was ulcerated and between two and four millimeters in thickness or not ulcerated and greater than four millimeters in thickness, and six were stage IIC melanoma meaning that their melanoma was ulcerated and greater than four millimeters in thickness (Edge et al, 2010). Of the twenty one patients, twenty were offered surgery which involved wide excision, reexcision if necessary, and possibly a sentinel node biopsy (Figure 2). There were also four patients who received electron beam radiation in the adjuvant setting to the primary site (Figure 2). Four patients were offered immunotherapy including interferon alpha (Figure 2). All patients were told to follow up with dermatology, do yearly self-skin exams and if stage IIB or higher, to follow with oncology. All of the treatments offered to stage II melanoma patients at Lehigh Valley Health Network in 2013 are in accordance with the NCCN Guidelines which suggest that treatment would include offering a sentinel node biopsy, wide excision, and either observation or clinical trial for stages IIA, IIB, and IIC and an additional option of interferon alpha for stage IIB and IIC (NCCN Guidelines). In addition, patients are encouraged to do self-skin exams and have yearly skin

exams for life and patients with melanoma of stage IIB or higher are encouraged to follow up regularly with oncology (NCCN Guidelines). One patient elected comfort care due to age and comorbid conditions, which is consistent with the NCNN guidelines as well (Figure 2) (NCCN Guidelines).

There were nine patients diagnosed with stage III melanoma meaning that in addition to having a lesion on the skin, the melanoma had also spread to the lymph nodes (Table 1) (Edge et al, 2010). Of those nine patients, four had stage IIIA meaning that the patient had between one and three lymph nodes affected, two had stage IIIB meaning that the patient had anywhere between one and three lymph nodes affected and possibly evidence of in transit metastases without metastatic nodes, two had stage IIIC meaning that they had greater than four lymph nodes affected or in transit metastases with metastatic nodes, and one had stage IIINOS meaning that it was not otherwise specified (Edge et al, 2010). Of the nine stage III patients, eight had surgery meaning wide excision, reexcision if necessary, sentinel node biopsy if possible, and lymphadenectomy if possible (Figure 2). Those same eight patients also received immunotherapy in the form of Ipilimumab, interferon alpha (high dose and peggylated), Nivolumab, or an immunotherapy combination clinical trial BMS CA209-067, E1609, or BMS CA209-064 (Figure 2). There was one patient who elected for only observation due to age and comorbid conditions. All treatments were determined to be in accordance with the NCCN Guidelines which suggest that treatment can include wide excision of primary tumor, lymphadenectomy, clinical trial, observation, interferon alpha, or radiation to the nodal basin (NCCN Guidelines). In addition patients are encouraged to do self-skin exams, have yearly skin exams for life, and follow up regularly with oncology (NCCN Guidelines).

There were twelve patients diagnosed with stage IV melanoma, meaning that their melanoma had metastasized to another site on the skin, vital organ, or visceral area (Table 1) (Edge et al, 2010). Four of these patients had metastasis to the brain (Figure 3). Stage IV disease is not curable, but it is treatable. Patients were offered a variety of treatment combinations. There six were patients who received surgery involving wide excision of the primary lesion, reexcision if necessary, sentinel node biopsy if possible, and lymph node dissection if necessary and possible (Figure 2). Four patients received gamma knife radiation therapy to the primary site and or the metastasis (Figure 2). Nine patients received immunotherapy which was Ipilimumab, interferon alpha (high dose and peggylated), Nivolumab, or an immunotherapy combination clinical trial BMS CA209-067, E1609, or BMS CA209-064 (Figure 2). There were three patients who were offered chemotherapy which included carboplatin, paclitaxel, and avastin (Figure 2). One patient received a BRAF inhibitor, one received comfort care, and one had their metastasis resected and was observed (Figure 2). All of these treatments offered to stage IV melanoma patients are in accordance with the NCCN guidelines. The guidelines suggest that if the metastasis is determined to be resectable to attempt to resect the disease and then put patients on clinical trial or observation (NCCN Guidelines). If the metastasis is unresectable, the guidelines suggest clinical trial, systemic therapy, palliative resection, radiation therapy, or best supportive

care (NCCN Guidelines). In the case of brain metastasis, the guidelines also suggest radiation or resection of the brain metastasis (NCCN Guidelines).

In addition to determining accordance with NCCN Guidelines, our study also aimed to test stage III and IV patients with aggressive melanoma or brain metastasis for the BRAF mutation (V600E) in an effort to contribute data to ongoing research to determine if there is a link between BRAF positive mutation and brain metastasis. Of the nine, stage III melanoma patients treated at LVHN in 2013, three were tested for the BRAF mutation (V600E) and one was positive for the mutation. Of the twelve stage IV melanoma patients, eight were tested for the BRAF mutation (V600E) and four possessed the mutation while the remaining four were wild type (Figure 3). There were a total of four patients with brain metastasis and of those, three were positive for the BRAF mutation (V600E) (Figure 3). This indicates that 75% of stage IV melanoma patients with brain metastasis treated at LVHN in 2013 had a positive BRAF mutation (V600E) with brain metastasis. We also determined that the average age of patients at LVHN diagnosed with melanoma in 2013 was 63 years. However, the average age at diagnosis for BRAF positive patients was 56 years. This is consistent with the literature findings which suggest that BRAF mutations are more common in younger patients diagnosed with aggressive melanoma (Long et all 2011). Determining the correlation between positive BRAF mutation (V600E) is an important step in potentially using BRAF as a screening mechanism for aggressive melanomas.

Conclusion:

The goals of our study were to determine if the treatment offered to melanoma patients treated at LVHN in 2013 was in accordance with the NCCN Guidelines and to test some stage III and IV patients with aggressive melanoma or brain metastasis for the BRAF mutation (V600E) in an effort to contribute data to ongoing research to determine if there is a link between BRAF positive mutation and brain metastasis. Herein we have shown that treatment offered to skin and scalp melanoma patients at LVHN in 2013 was in accordance with the NCCN guidelines. We have also shown that 75% of stage IV melanoma patients with brain metastasis tested positive for the BRAF mutation. In addition, we showed that the average age of 56 years at which stage IV melanoma patients with BRAF positive disease were diagnosed, as compared to the average age of a melanoma page which is 63, is consistent with the literature which states that BRAF mutation is more common in patients who present with melanoma at a younger age (Long et all 2011). In the future we are hopeful that the link between BRAF mutation and melanoma metastasized to the brain can be clearly delineated so that BRAF testing may serve as a prognostic factor in the future.

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