Use of the 31-Gene Expression Profile Test to Aid in the Decision of Adjuvant Treatment of Cutaneous Melanoma

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Melanoma is the fifth most common cancer in the United States, with over 7,000 deaths annually. Although most patients diagnosed with early-stage (stage I or II) disease have an excellent prognosis, two out of three patients who die from melanoma were initially diagnosed in early stages. Thus, additional methods to identify which patients are at risk of poor outcomes are needed. DecisionDx-Melanoma is a 31-gene expression profile (31-GEP) molecular risk stratification test that predicts an individual's risk of recurrence or metastasis in patients with cutaneous melanoma (CM). Here, we describe a 61-year-old man who presented with a spot on his upper scalp. A biopsy confirmed malignant melanoma measuring > 3.87 mm, with ulceration and mitotic rate 2 to 3/mm^2. CT, PET, and MRI scans did not reveal metastasis. Following wide local excision and sentinel lymph node biopsy, he was diagnosed with stage IIB CM. Due to the presence of high-risk features, 31-GEP testing was ordered, which revealed Class 2B (high-risk) CM. Due to the high-risk 31-GEP result, the patient was treated off-label with nivolumab for 1 year and received follow-up surveillance scans every 3 months for 3 years. At his last follow-up in April 2022, scans continued to show no recurrent or metastatic disease. The patient continues dermatologic screening every 6 months. The 31-GEP test provides valuable additional information to help clinicians make personalized, risk-based treatment and surveillance plans for patients with CM.

CASE STUDY

A 61-year-old married, White male presented in late 2017 with a spot on his upper scalp. It had existed for approximately 1 year. About 3 to 4 months prior, it started to increase in size and bleed when the patient bumped the lesion, which prompted him to be seen by his dermatology practice. In November 2017, a biopsy was completed, confirming nodular malignant melanoma at level IV measuring at least 3.87 mm in depth. Ulceration was present, the mitotic rate was 2 to 3/mm^2, tumor infiltrating lymphocytes

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were not brisk, and both deep and peripheral margins were positive. The team saw the patient for an initial consult in December 2017 and ordered brain MRI; CT scans of the neck, chest, abdomen, and pelvis; and a PET scan. The patient was instructed to follow up after scans, wide excision, and sentinel lymph node biopsy were completed. Laboratory blood results reported lactate dehydrogenase (LDH) level was 196 U/L in December 2017.

In the United States, melanoma is the fifth most common cancer, representing 5% of all new cancer diagnoses (Surveillance, Epidemiology, and End Results Program, 2023). Melanoma accounts for about 1% of all skin cancers diagnosed in the United States but has the highest mortality rate (American Cancer Society, 2020). In 2024, an estimated 100,640 adults in the United States will be diagnosed with invasive melanoma of the skin, and 8,290 will die from melanoma (American Cancer Society, 2024).

Two out of three patients who develop metastatic disease and die from melanoma were initially classified as stage I or II, according to the American Joint Committee on Cancer (AJCC) melanoma staging guidelines. Many of these patients had a negative sentinel lymph node biopsy (SLNB) result (Howlader et al., 2020). Approximately 88% of patients who undergo SLNB surgery are found to have a negative biopsy result, which categorizes them as being at lower risk for recurrence or metastasis (stage I or II; Chen et al., 2016; Ellis et al., 2010). This data indicates a need to be able to identify patients initially classified as lower risk but who may have a higher-risk tumor biology.

DecisionDx-Melanoma (Castle Bioscience, Inc., Friendswood, Texas) is a 31-gene expression profile (GEP) prognostic test used to predict the individual risk of recurrence or metastasis in patients with stage I, II, and III melanoma based on the biological profile of 31 genes in their tumor tissue (Gerami et al., 2015, 2017; Greenhaw et al., 2020). Prior to the introduction of the 31-GEP, nearly all treatment plan decisions made around the time of melanoma diagnosis relied solely on traditional clinical and pathologic prognostic factors. The 31-GEP uses a validated algorithm to calculate risk and also integrates patient clinicopathologic factors with the 31-GEP score to further individualize test results (Gerami et al., 2015; Hong et al., 2022).

CASE STUDY CONTINUED

The patient returned for follow-up in January 2018. His brain MRI was negative for metastatic disease. CT scans showed multiple pulmonary nodules in the right lung, with the largest in the posterior right middle lobe measuring 9 mm, and mildly enlarged hilar nodes. CT/PET imaging showed small indeterminate lung nodules deemed unlikely to represent metastatic disease because there was no abnormal uptake on the PET scan. The resulting diagnosis was scalp melanoma with no PET findings to indicate metastatic disease.

An ultrasound of the thyroid and neck was ordered by the surgeon due to a mass felt on physical examination suggestive of a lymph node in the left posterior cervical chain; however, the patient stated he had torn a muscle playing football in high school and has had a density in that area ever since. The ultrasound confirmed stable appearance of a level V cervical lymph node with a normal sonographic appearance. An SLNB and wide excision were completed in December 2017 and showed left cervical sentinel lymph node 1 negative for metastatic melanoma, left cervical lymph node 2 showed three benign lymph nodes, and left cervical sentinel lymph node 3 revealed one benign lymph node. Wide local excision of the scalp showed nodular melanoma with negative resection margins. Following SLNB and wide excision, the patient was staged as stage IIB.

Due to the thickness, ulceration, and high mitotic rate, the patient was considered to have a higher-risk tumor biology. The 31-GEP test was ordered to further characterize and help finalize the decision to use adjuvant immunotherapy. *BRAF* testing was also sent; however, the specimen was found to be "quantity not sufficient" for *BRAF* testing. The 31-GEP result was Class 2B (high risk) with a predicted recurrence-free survival of 48% at 5 years and distant metastasis-free survival of 65% at 5 years. In January 2018, due to

the patient's clinicopathologic factors in addition to the high-risk 31-GEP test result (Class 2B), the patient was considered to be at high risk for recurrence and was treated off-label with 1 year of adjuvant immune checkpoint inhibitor therapy with nivolumab (Opdivo), despite the fact that, by traditional staging and guidelines, he was a stage IIB, node-negative melanoma.

During the course of his year of adjuvant treatment with nivolumab (January 2018–February 2019), the patient did not develop severe toxicities related to immunotherapy, but did develop vitiligo to bilateral upper extremities (which has persisted). He completed 1 year of adjuvant treatment and then transitioned to surveillance every 3 months with CT scans of the neck, chest, abdomen, and pelvis, and yearly brain MRI for the first 3 years. The CT scans decreased in frequency to every 4 months starting in year 4 following diagnosis. In April 2022, the patient had an updated PET/CT scan that showed no findings to indicate recurrent or metastatic disease, and the CT scan frequency was reduced to every 6 months. The patient is also to continue routine dermatologic screening every 6 months.

At the time of the patient's diagnosis, only node-positive (stage III) melanoma patients were approved for adjuvant therapy. However, with statistics showing that 60% of patients who die from melanoma had a stage I or II melanoma at the time of diagnosis (Howlader et al., 2020), it was clear that we needed to look deeper to evaluate the true risk for recurrence or metastasis for this patient and determine his treatment plan based on a more complete assessment of his individual risk. Based on clinicopathologic factors plus the results of the 31-GEP test, it was clear that this patient had a much higher risk than indicated by his AJCC staging alone. As a result, the patient was ultimately treated as having higher-risk disease, and he remains disease/recurrence free at 53 months following diagnosis at the time of this writing.

CONCLUSION

Identifying melanoma patients whose cancer genetics reveal higher risk disease than would be indicated by current staging alone continues to be an ongoing issue for clinicians. We continue to see melanoma patients with node-negative disease later develop metastatic disease and die from their melanoma (Thomas et al., 2019). The 31-GEP test provides additional data for clinicians to use to better classify and treat patients. With the 31-GEP, we can now identify melanoma patients who have a higher risk of developing disease recurrence or distant metastatic disease when it is used in combination with standard staging (Greenhaw et al., 2018; Hsueh et al., 2021). Ultimately, the goal would be to have a more personalized approach to staging melanoma patients that provides a better understanding of true individual risk. The use of the 31-GEP in addition to the clinicopathologic features used in standard staging is another step toward achieving a more personalized and focused staging approach.

Disclosure

Ms. Hunt is on the speakers bureau of Castle Biosciences, Inc.

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