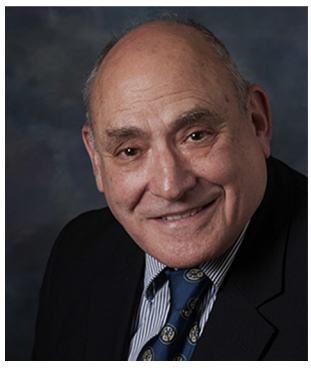
Editor-in-Chief's Note

Musings on Melanoma



Richard I. Shader, MD

Thirty-five years ago this month, a friend and colleague of mine tragically died from a primary orbital melanoma. It was also 35 years ago that the American Academy of Dermatology (AAD) decided to raise awareness of the prevalence and dangers of melanoma by establishing National Melanoma Monday on the first Monday in May.[1] One year later, in 1985, members of the AAD began to offer skin cancer screenings throughout the United States.[2] Curiously, the Canadian Dermatology Association and many like groups around the world recognize the second Monday in May as World Melanoma Day.[3] I also recently learned that another friend and colleague from another country died from metastatic melanoma. I decided to focus my Note this month on melanoma as our way of supporting melanoma patients and research, and I dedicate it to my deceased friends and to others who did not survive this disease. I also dedicate this Note to a dear friend who soldiers on in her continuing battle against her metastatic disease. In her particular case, no primary lesion has ever been identified.

For our nonclinician readers, let's begin with a brief understanding of what a melanoma is. Melanomas start in cells (melanocytes) within moles that have DNA damage from exposure to UV radiation from the sun. Unrepaired DNA damage within melanocytes leads to tumor-promoting genetic mutations. Most melanomas begin in the skin, although as was the case with my friend, they can start elsewhere. Aggressive melanomas spread via the lymph system and typically take hold in the liver, lungs, bones, and brain. One way to recognize a mole that has transformed into a melanoma is to use the mnemonic ABCDE: A = asymmetry; B = irregular border; C = irregular color; D = diameter larger than about a quarter of an inch; and E = evolving/changing in color or size.[4] Some melanomas are not detected until they have metastasized to other locations.

Melanomas are found most commonly in non-Hispanic Caucasians at rates that are over five times those seen in Hispanics, persons of African descent, or Asian/Pacific Islanders. The lifetime risks for developing melanoma in the United States are about 2.5%, 0.58%, and 0.1%, respectively, in non-Hispanic Caucasians, Hispanics, and persons of African descent.[5,6] One worrisome fact is that women under age 30 years who use tanning booths are six times more likely to develop a melanoma than those who do not use them.[7] A family history positive for melanoma is found in about 8% of persons with melanoma, suggesting that, while relevant, genetics are not a powerful risk factor compared to sun exposure and skin color.[8] As of the present time, if melanoma is familial, mutations in two genes have been implicated, *CDKN2A* and *CDK4*.

Like other cells, melanocytes have a cell membrane–spanning receptor for epidermal growth factor (EGFR). EGFR is a receptor tyrosine kinase; once activated it initiates an intracellular signaling cascade that enables cell growth, proliferation, migration, and survival. Overactivation or damage of steps within this cascade can promote tumor growth. One intracellular chain of events activated by EGFR is referred to by cell biologists as the *mitogen-activated protein kinase* (MAPK) pathway. In order, the enzymatic steps in the pathway are called Ras-Raf-MEK-ERK. The MAPK signaling pathway is essential for the normal transcription of genes which in turn are essential for normal cell homeostasis, including proliferation, differentiation, turnover, and survival. In melanocytes, dysregulation of certain steps in this pathway can lead to tumorigenesis.

A total of 422 protein-encoding genes within melanomas have been identified.[9] The most common UV-related damaged gene in melanomas is called *BRAF*, which encodes the protein B-Raf. B-Raf is a serine/threonine protein kinase in the MAPK pathway. Activating mutations of *BRAF* trigger excessive cell proliferation and survival.

The most frequent *BRAF* mutation is *BRAF* V600E, which, along with the *BRAF* mutations 600K, 600R, and 600D, account for about 65% of all melanomas. Another, less commonly mutated gene is *NRAS*—one step earlier in the MAPK pathway. Most of the time these mutations do not co-occur, but some melanomas do have mutations in both genes. Readers interested in more literature on these mutations may wish to consult references 10–12.

Prevention is the most obvious way to avoid melanomas. Common-sense steps include wearing protective clothing and using sunscreen with an SPF rating between 30 and 50. Limiting sun exposure when feasible also helps and avoiding sunburns is especially important. Given the information provided earlier in this Note, the use of tanning booths should be a "no–no." Having grown up in Florida and spending much time outdoors, I can remember my mother's cautionary advice about sun exposure. My most vivid memory, though, is when we went to a beach. My blue-eyed, blond-haired mother would slather her face and shoulders with zinc oxide and wear a very broad-brimmed hat. Years later, we were all taught in medical school that having light or fair skin (especially with freckles), blue or green eyes, and blond or red hair were all risk factors for melanoma.

For small lesions, surgical excision is the most common treatment. The Mohs procedure is usually employed when deeper penetration is suspected. The Mohs procedure involves the successive removal of thin layers until clear margins are detected. When surgery is not successful or when metastases are present, immunotherapy with checkpoint inhibitors that allow T cells to attack the tumors is now fairly commonly tried, either singly or in combination.[13,14]

Recently, antibodies directed at EGFR or intermediaries in the MAPK pathway have been used for metastatic disease.[14,15] Examples of EGFR antibodies are cetuximab* and panitumumab.† Examples of B-Raf inhibitors are vemurafenib,‡ dabrafenib,§ and encorafenib.‖ Examples of MEK inhibitors are trametinib,¶ cobimetinib,# and binimetinib.** From their suffixes *-mab* or *-nib* it should be clear which drugs are monoclonal antibodies and which are protein kinase inhibitors. Several combinations of these drugs were approved in 2018 by the US Food and Drug Administration for use in the treatment of metastatic or unresectable melanoma: (1) encorafenib and binimetinib, along with a companion diagnostic (THxID BRAF Kit; bioMérieux, Durham, North Carolina); and (2) dabrafenib and trametinib.[16]

Studies that compare various combinations of the available checkpoint inhibitors, inhibitors of EGFR and the MAPK pathway, and possibly the cytokine interleukin-2 may yield even more hopeful results. Nonetheless, much progress has been made since 1984. Remember George Orwell's *1984*?

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* Trademarks:Erbitux® (Eli Lilly and Co, Indianapolis, Indiana)

† Vectibix® (Amgen, Thousand Oaks, California)

‡ Zelboraf® (Genentech, South San Francisco, California)

§ Tafinlar® (Novartis Pharmaceuticals Corp, Cambridge, Massachusetts)

‖ Braftovi® (Array BioPharma, Boulder, Colorado)

¶ Mekinist® (Novartis)

Cotellic® (Genentech)

** Mektovi® (Array)

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