

2-28-2014

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## Recommended Citation

Thompson MA. Melanoma: attacking on many fronts. J Patient Cent Res Rev. 2014;1:8-10. doi: 10.17294/2330-0698.1005

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# Melanoma: Attacking on Many Fronts

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It is my honor to be the guest editor of the inaugural issue of the *Journal of Patient-Centered Research and Reviews*. As a hematologist/oncologist and scientist, I am passionate about clinical trials, as well as translational and basic science research. It is an exciting time when access to cutting-edge technology and research may positively impact patients made vulnerable by a cancer diagnosis.

The focus of this issue is melanoma – a skin cancer that is increasing in incidence. A study by Geller et al. looked at the years 1950 to 2007 using the Connecticut Tumor Registry, the original National Cancer Institute Surveillance, Epidemiology, and End Results Program (SEER) site. During this time period, melanoma incidence increased by ~2,000%, while the population of the state increased by 75%.<sup>1</sup> Also, deaths from melanomas tripled for men and doubled for women. They concluded that “Unremitting increases in incidence and mortality of melanoma call for a nationally coordinated effort to encourage and promote innovative prevention and early-detection efforts.”

In this issue, Dennis Baumgardner, MD, reviews melanoma issues in primary care including risk factors, screening for cancer, and why it is so important to recognize the possible early warning signs.<sup>2</sup> One patient, Helen Williams, in “A Rendezvous with an Unexpected Diagnosis,” co-written by Alexandria Rogers, relates her experience with detection and treatment of an early-stage melanoma.<sup>3</sup> The clinical care of patients often starts, for oncologists, after a startling discovery by the patient and family. It is a different experience for every patient, and every patient has a unique story.

Current melanoma treatment strategies include consideration of tumor stage. Stage 0 (in situ) and Stage IA and IIA are typically treated with surgery. Stage IB may include sentinel lymph node biopsy (SLNB) – as described for the head and neck region by surgical oncologists, Martin Corsten, MD, FRCSC, and Stephanie Johnson-Obaseki, MD, FRCSC, from the University of Ottawa.<sup>4</sup> Stage IIB/C

and stage III melanoma may be treated with post-surgical (adjuvant) therapy with high-dose interferon alpha 2 B (IFN). This results in increased relapse-free survival, but does not improve overall survival (OS).<sup>5</sup> As noted below, a long duration form of IFN (pegylated IFN) also does not confer a survival advantage.<sup>6</sup> Dr. Thomé and colleagues developed an online adjuvant high-dose IFN calculator to “facilitate both better physician understanding of prognostic information (baseline and with adjuvant interferon) for individual patients who present with resectable melanomas and more informed patient decisions about whether they should receive adjuvant high-dose interferon therapy after resection of primary melanomas.”<sup>7</sup> This was based on a database of 17,600 patients. They found 5-year survival benefits that ranged up to 13%.

Melanoma care had not significantly changed for many years until recently. The two therapies previously approved by the Food and Drug Administration (FDA), dacarbazine (DTIC; approved in 1975) and high-dose interleukin-2 (IL-2; approved in 1998), are each associated with response rates of only 10 to 20% and

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a small percentage of complete responses; neither is thought to improve OS. In randomized clinical trials, the median survival among patients treated with dacarbazine was less than 8 months. The oral version of dacarbazine, temozolamide, is not FDA approved, but is often used in melanoma treatment since it seems to work as well and is more convenient. To date, adding other drugs to dacarbazine has improved response rate, but not OS, and has not changed the standard of care.<sup>8</sup>

Until recently the National Comprehensive Cancer Network (NCCN) recommended clinical trials, DTIC, or newer cytotoxic agents (carboplatin/paclitaxel) as therapy for advanced unresectable or metastatic melanoma. The management of stage IV melanoma is changing rapidly. From 1998 to 2010, no new systemic therapies were FDA approved, however from 2011 to 2014 five single agents and one combination were approved. In March 2011, ipilimumab was FDA approved for the treatment of metastatic melanoma. Pegylated interferon alfa-2b was also approved that month. Vemurafenib was approved in August 2011, and dabrafenib and trametinib were both approved as single agents in 2013. The combination dabrafenib/trametinib received FDA approval January 10, 2014.

Ipilimumab is given by intravenous (IV) infusion and stimulates the immune system to attack melanoma cells. It is a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4). Ipilimumab has now demonstrated an improvement in OS in two randomized phase III trials, but it has a response rate of less than 10%. Responses are often slow or may even come after initial progression of disease, and the long-term survival benefit seems to be limited to 20-30% of patients.

Peginterferon was approved as adjuvant therapy based on the EORTC 18991 clinical trial.<sup>6</sup> Patients who took the drug delayed cancer recurrence by about 9 additional months compared with patients who did not take the drug. However, there was no improvement in OS. This lack of survival benefit must be considered in light of treatment that can extend up to 5 years at a higher subcutaneous weekly dose for 8 weeks, followed by a lower dose for the remainder of the 5 years. Better melanoma adjuvant therapies are needed.

The next two agents, vemurafenib and dabrafenib, are inhibitors of mutations of *BRAF* (a human gene that results in the production of a “B-Raf” protein). The final agent discussed, trametinib, works on *BRAF* mutation-positive advanced melanoma. Michael Mullane, MD, hematologist and oncologist, Aurora Cancer Care, tackles a clinical case as an illustrative example of our understanding and treatment of melanoma with *BRAF* V600 mutations.<sup>9</sup> Targeting *BRAF* has added a much needed target and chemical armamentarium to our treatment options for patients. These drugs represent molecular targeted agents that may be exploited

as potential future combination therapies. While immunotherapies and *BRAF* inhibitors are exciting developments, Michael Davies, MD, PhD, a melanoma clinician and cancer researcher at the University of Texas M.D. Anderson Cancer Center, looks at “Targeted Therapy for Cutaneous Melanoma: Beyond *BRAF*...” He discusses new molecular targets and the potential of melanoma treatment personalization.<sup>10</sup>

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Vemurafenib is an oral medication, taken twice daily, that inhibits the mutant form of the *BRAF* protein (V600E) that is present in approximately 50% of cutaneous melanomas. Vemurafenib is only effective in patients who have the mutation and it may make tumors grow faster if it is given to a patient who does not have it. Among the appropriate patients, almost all (greater than 90%) achieve some degree of tumor shrinkage and often very rapid onset of symptom relief. However, almost all patients go on to develop resistance to the treatment after an average of 6-7 months.

Dabrafenib is an oral *BRAF* inhibitor, approved as a single agent for treatment of *BRAF* V600E or V600K mutation-positive unresectable or metastatic melanoma. It was approved, as noted, as a combination with trametinib, with the anticipated effect of improving duration of response as well as decreasing secondary skin cancers (i.e. less toxicity with the combination) such as squamous cell carcinomas and keratoacanthomas.

Trametinib is an oral medication for treatment of *BRAF* V600E or V600K mutation-positive unresectable or metastatic melanoma. It is an inhibitor of the mitogen-activated protein kinase (MAPK) enzymes MEK1 and MEK2. It was approved in 2014 with the *BRAF* inhibitor dabrafenib as a combination to target two different tyrosine kinases in the RAS/RAF/MEK/ERK pathway. Approval of the combination was based on durable objective responses.

Thus, stage IV (metastatic) melanoma treatment has seen tremendous recent progress, and that progress – like in other cancers – is now focusing on moving FDA-approved treatments from the metastatic to adjuvant setting. This will need support from patients, physicians, and sponsors for clinical trial accrual, and tumor tissue sampling for translational research, in order to make rapid improvements in patient care. We know that melanoma subtypes have different mutation characteristics. Therapies will increasingly be considered by molecular pathways by both physicians and patients – such as the CollabRx Therapy Finder (<http://therapy.collabrx.com/melanoma>). For instance, melanoma subtypes with associated mutations include: 1) cutaneous without evidence of chronic sun damage (BRAF and NRAS mutations); 2) acral – palms, soles, or mucosal or subungal (nail bed) (c-KIT mutations); and 3) uveal (GNAQ and GNA11 mutations). We can expect that new strategies in melanoma will include elucidating and capitalizing on new targets for melanoma treatment and understanding of resistance. Old and new immunotherapies may be used in sequence, or combinations, with cytotoxic chemotherapies, radiation, surgery, imaging, and newer molecular targeted therapies to continue improving melanoma care. We may also see the increase of patient-centered communities that ignite melanoma research. Social media is using the hashtag #melism (melanoma social media) to identify tweets of interest and Matthew Katz, MD, and others have called for crowdsourcing clinical trials.<sup>11</sup>

We anticipate more cutting-edge articles on melanoma in upcoming issues. Finally, I appreciate the support of Editor-In-Chief, Dennis Baumgardner, MD, who helped establish and manage this inaugural issue, along with Randall Lambrecht, PhD, who founded *JPCRR*. Special thanks to the editorial team of Tyler Curtis and Tonya Limberg for helping pull everything together and making us look good. Thank you for reading the first issue of *JPCRR* focusing on patient-centered research.

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