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Review

No longer an untreatable disease: How targeted and immunotherapies have changed the management of melanoma patients

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ABSTRACT

The discovery that BRAF is a driver oncogene in cancer, and complementary improvements in our understanding of the immune system have resulted in new targeted and immune-therapies for metastatic melanoma. Targeted therapies achieve impressive clinical results in carefully selected patients but the development of resistance seems inevitable in most cases. Conversely, immune-checkpoints inhibitors can achieve long-term remission and cures, but in a smaller proportion of patients, and biomarkers to predict which patients will respond are not available. Nevertheless, melanoma has led the evolution of cancer treatment from relatively nonspecific cytotoxic agents to highly selective therapies and here we review the lessons from this paradigm shift in treatment and the opportunities for further improvements in outcomes for melanoma patients.

1. Introduction

Malignant melanoma is the most deadly form of skin cancer. It is estimated that there were over 230,000 cases of melanoma globally in 2012 (http://www.wcrf.org/cancer_statistics/world_cancer_statistics.php), with over 76,000 cases and 9,000 deaths in the US (Siegel et al., 2014), over 103,000 cases and 22,000 deaths in Europe (Ferlay et al., 2013), and over 12,000 cases and 1,500 deaths in Australia (http://www.melanoma.org.au/about-melanoma/melanoma-skin-cancer-facts.html).

Early stage melanoma (stage I, II and resectable stage III, local lesion, local lymph nodes spread) can be cured by surgery alone, but late stage metastatic disease (unresectable stage III and IV, lesions spread to distant organs) has generally been considered to be incurable (Balch et al., 2009). Left untreated, the advanced disease has extremely poor outcomes with median overall survival of less than a year and 5 year overall survival of less than 10% (Jang and Atkins, 2014). Until 2011, the standard of care for advanced melanoma was the alkylating agent dacarbazine, and in the US, interleukin-2, high-dose IL-2 (HD IL-2) and interferon-α-2b (IFN-α) were also approved, but these drugs do not provide significant increase in patient survival (Figure 1). Thus, more than 40 years of research had not led to any tangible improvement in patient outcome.

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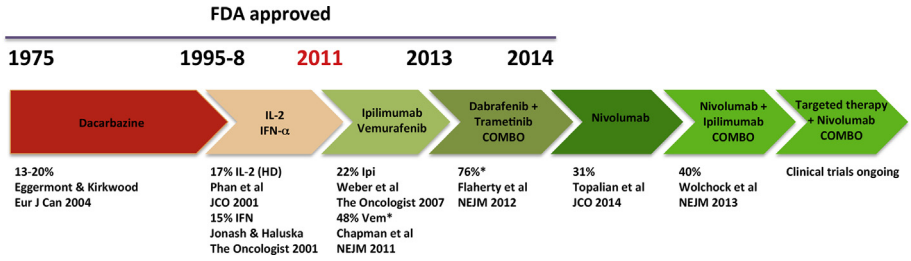

Figure 1 – Progression of advanced melanoma treatment over time. The first FDA approved agent for the treatment of advanced melanoma was the alkylating agent dacarbazine, which was approved in 1975. In 1995 the cytokine IFN-α was approved, then followed by the approval of another cytokine IL-2 in 1998. In 2011 two new agents, the BRAF inhibitor vemurafenib and the CTLA-4 inhibitor ipilimumab were approved, providing a major breakthrough for the treatment of metastatic melanoma. In 2013 the MEK inhibitor trametinib was approved and at the beginning of 2014 a combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib was approved. % = Objective tumour response, *BRAF mutant only.

However, the landscape for melanoma treatment changed in 2011 with the approval of new immune and targeted therapies that extend progression-free and overall survival and could, in some cases, cure the disease. The monoclonal antibody ipilimumab, an immune checkpoint inhibitor, and the small molecule vemurafenib, a BRAF inhibitor, were the first in class of new generations of therapies that achieve life extension and in some cases cures for metastatic melanoma patients in randomised clinical trials. These drugs represent a landmark in the clinical management of melanoma and both received prompt FDA approval in 2011 for first-line treatment in melanoma patients. They were the first new drugs to be approved for melanoma in 13 years. Vemurafenib received European approval 6 months later, but it took almost 2 more years for ipilimumab.

These developments have transformed the clinical management of melanoma and improved patient outcomes and the lessons we learn from melanoma will also impact other cancers. However, despite these advances, not all patients with BRAF mutations respond to BRAF inhibitors and the majority of patients who do respond develop resistance after a relatively short period of disease control. Also, only 15–20% of patients respond to ipilimumab, and it is not currently possible to determine which patients will respond and which will not. Toxicity can also limit use of these drugs in some patients. Thus, there is still work to do, but ipilimumab and vemurafenib are the vanguard of a cadre of exciting new drugs currently undergoing testing in hundreds of clinical trials and in addition to vemurafenib, a second BRAF inhibitor, dabrafenib, and a MEK inhibitor, trametinib, have recently received FDA approval, but have yet to be approved in Europe. On their heels are several other similar drugs, so the revolution in melanoma treatment is ongoing and reflecting the enormous strides recently made, *Science* selected cancer immunotherapy as the 2013 breakthrough of the year (Couzin-Frankel, 2013).

2. Pre-2011 therapies

The development of effective treatments for advanced melanoma has been a long hard road. In 1975 the FDA approved the alkylating agent dacarbazine (5-[3,3-dimethyl-1-triazenyl]-imidazole-4-carboxamide; DTIC) for advanced metastatic melanoma (Figure 1), although objective clinical responses (mostly partial responses) were seen only in 13–20% of patients and durable responses were extremely rare (Eggermont and Kirkwood, 2004). Temozolomide, an orally available DTIC analogue, did little to improve these responses (Middleton et al., 2000) and for the majority of patients durable responses remained elusive even when DTIC or temozolomide were combined with other drugs (Bhatia et al., 2009). A meta-analysis of 48 head-to-head clinical trials with DTIC revealed a weighted average objective response rate (mostly partial responses) of 15.3% for DTIC alone and no increase in survival or response rates with any combination, apart from IFN-α, which gave at best a modest improvement (Lui et al., 2007). A biochemotherapy (BCT) regimen of cisplatin, vinblastine and DTIC (CVD) with IFN-α and high-dose IL-2 did achieve response rates exceeding 50% in phase 2 trials, but at the price of substantial toxicity, preventing this therapy from becoming standard-of-care (Legha et al., 1996). Thus, attempts to improve responses to DTIC were disappointing and for the most part it was used for palliation rather than cure (Figure 1). It would be another 20 years before the FDA approved another treatment for advanced malignant melanoma.

One of the focuses of melanoma research over the years has been immunotherapy. This research strand was sparked by the observation that a small number of patients achieve "spontaneous cures" and these were largely attributed to attack by the patients' immune system on their own tumour. Melanoma became considered to be a highly immunogenic tumour and attempts to modulate the immune system against melanoma became a key challenge, with interleukin-2 (IL-2) leading the way. IL-2 is a cytokine that induces T cell and natural killer cell proliferation and activation, and stimulates production of interferon gamma and tumour necrosis factor by lymphocytes. High-dose IL-2 (HD IL-2) achieved objective tumour responses in 17% of patients and durable responses in ~6% of patients (Atkins et al., 2000). It received FDA approval in 1995 (Figure 1), but is highly toxic and so is reserved for generally fit, high performance status patients (Alwan et al., 2014). The immunomodulatory and anti-tumour cytokine interferon alfa-2b (IFN-α) also achieved response rates of 15–20% and received FDA approval in 1998 (Figure 1), but this treatment is more effective in early disease