Critical Reviews in Oncology/Hematology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Metastatic melanoma treatment: Combining old and new therapies

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ARTICLE INFO

Article history:
Received 2 October 2014
Received in revised form 16 October 2015
Accepted 12 November 2015

Keywords:
Melanoma
Treatment
Targeted therapy
Immunotherapy
Combination therapy

ABSTRACT

Metastatic melanoma is an aggressive form of cancer characterised by poor prognosis and a complex etiology. Until 2010, the treatment options for metastatic melanoma were very limited. Largely ineffective dacarbazine, temozolamide or fotemustine were the only agents in use for 35 years. In recent years, the development of molecularly targeted inhibitors in parallel with the development of checkpoint inhibition immunotherapies has rapidly improved the outcomes for metastatic melanoma patients. Despite these new therapies showing initial promise; resistance and poor duration of response have limited their effectiveness as monotherapies. Here we provide an overview of the history of melanoma treatment, as well as the current treatments in development. We also discuss the future of melanoma treatment as we go beyond monotherapies to a combinatorial approach. Combining older therapies with the new molecular and immunotherapies will be the most promising way forward for treatment of metastatic melanoma.

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http://dx.doi.org/10.1016/j.critrevonc.2015.11.011
1040-8428/

Please cite this article in press as: Davey, R.J., et al., Metastatic melanoma treatment: Combining old and new therapies. Crit Rev Oncol/Hematol (2015), http://dx.doi.org/10.1016/j.critrevonc.2015.11.011

1. Introduction

Treatment of metastatic melanoma has rapidly progressed in recent years. These advancements are a culmination of decades of research investigating the role of the immune system in cancer, and the role of oncogenic driver mutations in melanoma. Melanoma treatment was largely unsuccessful until 2010, as traditional cytotoxic chemotherapies displayed very low levels of efficacy. Since, the implementation of therapies developed to specifically target oncogenic driver mutations or immune system blockade, response rates have increased dramatically. Here, we review the evolution of melanoma treatment over the last 40 years, discuss and evaluate existing and emerging treatments, and highlight the need for new approaches, particularly combinations of old and new therapies.

2. Chemotherapy

From the 1970s to the early 2000s there were very few new treatments approved by the Food and Drug Administration (FDA) for melanoma, which was largely due to the limited understanding of melanoma biology. Initially, several cytotoxic agents were examined for efficacy which lead to the approval of dacarbazine (DTIC) in 1975 (Garbe et al., 2011). The mechanism of action of DTIC is primarily the addition of an alkyl group to the bases in DNA, thereby preventing the cells ability to replicate. As a single agent, DTIC produces partial response in up to 25% melanomas (reviewed in (Eggermont and Kirkwood, 2004; Huncharek et al., 2001)) with complete response reported in approximately 5% (Huncharek et al., 2001). Despite this, DTIC was approved as first-line therapy for metastatic melanoma. Randomised, controlled trials have not shown that DTIC improves survival (Robert et al., 2011), therefore DTIC alternatives and combinations containing DTIC became the focus of further studies. 25 years after DTIC was approved temozolamide, an oral delivery DTIC derivative, showed a similar response rate in metastatic melanoma, but with the advantage of being able to cross the blood–brain barrier, it became first-line therapy for brain metastases (Middleton et al., 2000). In 2004, the chloroethylnitrosourea alkylating agent, fotemustine was shown to have a higher overall response rate (ORR) compared to DTIC in first-line treatment of melanoma. A trend in favour of overall survival was also reported (Avril et al., 2004), therefore fotemustine received approval for use as first-line therapy in Europe and Australia.

The lack of improved survival for melanoma in response to DTIC, fotemustine and temozolamide and the limited alternative treatments became a driving force to develop new therapies. The most heavily studied alternative is immunotherapy.

3. Immunotherapy

Cancer immunotherapy is a general term referring to activation of the immune system to induce objective responses, disease stabilization (Drake et al., 2014; Mellman et al., 2011) and long term survival. Recent advancements in immunotherapy have provided evidence that it remains a valid approach, and potentially the most effective strategy for melanoma treatment. Immunotherapy has been explored via multiple avenues in melanoma, involving the use of cytokines, vaccines and targeted antibodies. This section will discuss some of the more significant advancements in immunotherapy as well as the most promising potential treatment options.

3.1. Cytokine therapy: interleukin-2 (IL-2)

IL-2 is a cytokine that stimulates the generation of lymphokine activated killer (LAK) cells, which detect and lyse tumour cells (Rosenberg et al., 1985). IL-2 therapy is used to treat many different types of cancer with varying results (Jin et al., 2004; Mani et al., 2009; Sivanandham et al., 2002; Marchand et al., 2001). In the 1990s, phase II and III trials for high dose IL-2 reported complete response rates for melanoma of approximately 7%, and partial response rate of 10% (Rosenberg et al., 1994a; Schwartzentruber et al., 2011; Atkins et al., 1999). Long-term survival (>5 years) is seen in approximately 8% of stage IV patients treated with high dose IL-2 irrespective of the site of metastases (Keilholz et al., 2002). The use of high dose IL-2 is restricted by the adverse affects on multiple organ systems (e.g. cardiovascular, respiratory, nervous, renal, digestive, and skin) (McDermott et al., 2014), therefore low dose and IL-2 combination treatments have also been trialled with limited success (Elias et al., 2005; Riley, 2013; Blank et al., 2011; Ott et al., 2013; Curran et al., 2010). A considerable amount of research is now being devoted to identifying predictive biomarkers to maximise the use of high dose IL-2 therapy. Although there has been several possible biomarkers identified including NRAS mutation status and CXCR3/CCR5 expression and polymorphisms (Joseph et al., 2012; Bedognetti et al., 2013), there is still no confirmed predictive factors for response to IL-2 monotherapy in metastatic melanoma (Dudley et al., 2008; Kirkwood and Tarhini, 2009).

Several other cytokines have been explored as possible treatment options, such as IL-7, IL-15, and IL-18 (Le et al., 2009). Although these alternative cytokines rely on slightly different mechanism of actions, such as faster T-cell proliferation or reduced T-cell apoptosis, similar to IL-2, they show limited response as monotherapies (Le et al., 2009; Dong et al., 2010).

3.2. Monoclonal antibody therapy anti-CTLA4

Activated T cells express the receptor CTLA-4 on their surface (Freeman et al., 1993). CD86 binds to this receptor and causes a downregulation of these activated T-cells in order to regulate immune system function. Ipilimumab is an IgG1 monoclonal antibody that binds to the CTLA-4 receptor, blocking CD86 and enhancing T-cell survival and activity (Freeman et al., 1993). These T-cells are then able to identify and initiate the destruction of tumour tissue. Ipilimumab was the first anti-CTLA-4 monoclonal antibody immunotherapy trialled for treatment of melanoma, gaining approval in March 2011. Response rates for Ipilimumab monotherapy range from 5% to 15% across various clinical trials, due to changes in dosage and patient selectivity (Robert et al., 2011; Hersh et al., 2011; Kaplan, 2011; Luke et al., 2013). Long-term (up to 10 years) overall survival (OS) data for monotherapy ipilimumab has provided evidence that durable, long-term survival is achievable. The pooled analysis of 1861 patients representing 12 separate studies found median OS was 11.4 months (95% CI, 10.7–12.1 months), with a plateau of 22% in the survival curve at around year 3 (Schadendorf et al., 2015).

Trials for combination therapy have shown that the ipilimumab and DTIC together exhibit greater effectiveness than DTIC alone (Robert et al., 2011). This synergy is thought to be partially a result of the newly discovered immunomodulatory activity of dacarbazine (Hervieu et al., 2013a,b). Interestingly, ipilimumab-associated adverse effects, particularly gastrointestinal perforations, diarrhoea and colitis were lower with ipilimumab and DTIC combination than ipilimumab monotherapy at the same dose, however elevations in liver function values were reported (Robert et al., 2011). Response rates for the combination therapy have not exceeded 15% in any of the clinical trials (Robert et al., 2011; Hersh et al., 2011; Kaplan, 2011; Luke et al., 2013). Ipilimumab is also being trailed in combination with other new treatments, such as the anti-PD1 receptor antibodies pembrolizumab (formerly lambrolizumab) and nivolumab, as well as several BRAF inhibitors (both described below) (Curran et al., 2010; Sondak et al., 2011; Wolchok et al., 2013). A recent study by Larkin

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