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The rapidly evolving therapies for advanced melanoma—Towards immunotherapy, molecular targeted therapy, and beyond

Ziqiang Zhu [a,*], Wei Liu [b], Vladimir Gotlieb [c]

[a] Department of Internal Medicine, Brookdale University Hospital and Medical Center, One Brookdale Plaza, Brooklyn, NY 11212, USA
[b] Metabolism and Cancer Susceptibility Section, National Cancer Institute, National Institutes of Health, Frederick, MD 21702, USA
[c] Division of Hematology/Oncology, Brookdale University Hospital and Medical Center, One Brookdale Plaza, Brooklyn, NY 11212, USA

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ABSTRACT

The incidence of melanoma in both males and females continues to rise during the past 40 years despite the stable or declining trends for most cancer types. Due to the tremendous advance in immunobiology and molecular biology, breakthroughs in both immunotherapies and molecular targeted therapies have recently revolutionized the standard of care for patients with advanced melanoma. In 2011, US Food and Drug Administration (FDA) approved ipilimumab, an anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody for metastatic melanoma therapy. Since then, novel drugs including antibodies to programmed cell death 1 (PD-1) such as pembrolizumab and nivolumab (both approved in 2014), selective BRAF inhibitors such as vemurafenib (approved in 2011), dabrafenib (approved in 2013); and MEK inhibitor trametinib (approved in 2013), have greatly extended the potential of immunotherapy and molecular targeted therapy for advanced melanoma. All of which have been demonstrated a significant increase in overall survival rate, and long-term benefits in multiple large clinical trials. Several new agents and novel therapies are currently under phase III clinical trials with the hope of being approved in the near future. We already entered a golden era in oncology that are providing significant survival improvement. In the meantime, new challenges for clinicians also started to emerge. In this review, we presented the existing

* Corresponding author.
E-mail address: zhuz2013@gmail.com (Z. Zhu).

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evidence for the newest treatments for advanced melanoma, including CTLA-4, PD-1/PD-L1 checkpoint inhibitors and BRAF, MEK inhibitors. We also discussed the strengths, limitations and challenges of using these novel therapies, and potential solutions as well as highlighted the areas requiring further research.
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1. Introduction

The incidence of melanoma in both males and females continues to rise during the past 40 years despite the stable or declining trends for most cancer types (Siegel et al., 2014). The main cause of death in melanoma patients is widespread metastases to the lymphatic system and other organs such as lung, liver, bone, and brain. The average survival time with metastatic melanoma was 6–12 months and a 5-year survival rate under 10% with traditional therapies (Agarwala, 2009; Balch et al., 2009). According to the most recent data from 2005 to 2011, the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) program database showed a 5-year survival rate of 16% for metastatic melanoma (Overview of the SEER program, 2015). Due to its aggressive nature and resistance to treatment, significant efforts have been emphasized on prevention by educating the public about the dangers of excess UV exposure from both the sun and tanning beds (Curiel-Lewandrowski et al., 2012). However, the treatment of this devastating skin cancer had little to no advancement for the past 4 decades until recently. Dacarbazine remained to be the only first-line treatment for advanced melanoma since its approval by US Food and Drug Administration (FDA) in 1976. It showed a 10–20% of overall response rate in phase I and II trials with no clear overall survival (OS) benefits (Falkson et al., 1998; Middleton et al., 2000; Avril et al., 2004). High-dose interleukin-2 (HD IL-2), which was approved by US FDA in 1998 on the basis of durable overall response rate of 13–16%, is not considered a standard-of-care due to its toxicity and lack of phase III data (Schwartzentruber et al., 2011). Thanks to the tremendous progress in understanding of immunobiology and the molecular signaling pathway of melanoma development, breakthroughs in both immunotherapies and molecular targeted therapies have revolutionized the standard of care for patients with advanced melanoma. A golden era for advanced melanoma treatment has already began. The approval of anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody ipilimumab by US FDA in 2011, as well as the new drugs including antibodies to programmed cell death 1 (PD-1) such as pembrolizumab and nivolumab (both approved in 2014) and selective BRAF inhibitors such as vemurafenib (approved in 2011), dabrafenib (approved in 2013); and MEK inhibitor trametinib (approved in 2013), have greatly extended the potential of immunotherapy and molecular targeted therapy for advanced melanoma. All of which have shown a significant increase in progression free and overall survival rate with long-term benefits in a proportion of patients compared with chemotherapy in multiple large clinical trials. In addition, several novel modalities such as adoptive T cell therapy (ACT), chimeric antigen receptors (CARs) T cell therapy, oncolytic virotherapy and therapeutic vaccines for advanced melanoma are currently under investigation with the hope of providing us with more exciting results in the near future. Advances in these novel therapies have brought us an opportunity to cure this devastating disease. Meantime, they also raised new challenging for clinicians. In this review, we will discuss the strengths, limitations and challenges of using the current standard of care with these novel drugs for patients with advanced melanoma, and potential solutions as well as areas requiring further research.

2. Immunotherapy

Melanoma study has been at the cutting edge of immuno-oncology research for the past three decades due to the high rate of spontaneous regression of the primary melanoma as well as vitiligo associated with melanoma regression (Sumner, 1953; Printz, 2001). Dr. Steven Rosenberg (NCI/NIH, USA) is one of the pioneers to show solid evidence of immune-induced tumor regression. Along with his efforts, high dose (HD) IL-2 became the first immunotherapy drug approved by US FDA for advanced melanoma in 1998 (Kammula et al., 1998). Despite its toxicity (life-threatening capillary leak syndrome, arrhythmias, and renal toxicity) (Schwartz et al., 2002) as well as lack of randomized phase III clinical trial data which limits its application as a standard therapy, HD IL-2 showed sustained tumor regression in earlier clinical trials (Petrella et al., 2007; Rosenberg et al., 1985). These studies made the first advance and later firmly established the importance of immunotherapy in the treatment of advanced melanoma.

T cell plays a central role in cell-mediated immunity and cancer immunotherapy. The classic two-signal activation model includes signal one, provided by the interaction of T cell receptor (TCR) with its antigen, and signal two, provided by the co-stimulatory interaction between CD28 on T cell surface and its ligand B7-1 on antigen presenting cells (APC) (Chen and Flies, 2013). Subsequently identified co-inhibitory receptors (also known as "immune checkpoints") including CTLA-4 and PD-1 are able to down-regulate the immune system by preventing T cell over-activation, promoting self-tolerance and avoiding autoimmunity (Freeman et al., 2000). CTLA-4, expressed approximately 48 h after T cell activation, binds to B7-1 with greater affinity and serves as a negative regulator ("brake") in limiting T cell activation (Walunas et al., 1994). Once entering tumor microenvironment, activated T cells become "tolerated" (functionally inactivated) by engagement of PD-1 with its ligand PD-L1, which is expressed by the tumor cells (Blank et al., 2004). Therefore, these negative regulation mechanisms become one of the major hurdles that impair T cell anti-tumor activity in cancer immunotherapy. The newly developed monoclonal antibodies targeting the negative regulators (referred to as "immune checkpoint inhibitors") are able to break down T cell tolerance and to restore or augment anti-tumor immune response. Beginning with CTLA-4 blocking antibody ipilimumab, a paradigm shift in the acceptance of immunotherapy for advanced melanoma across the field of oncology is undergoing.

2.1. Anti-CTLA-4: ipilimumab

Ipilimumab is a fully humanized IgG1 monoclonal antibody (Bristol-Myers Squibb) that binds to CTLA-4, thereby enhances T cell activation, proliferation and effector functions. Ipilimumab provided encouraging clinical benefit by prolonging overall survival (OS) among previously treated (MDX010-20 trial) as well as untreated (CA184-024 trial) patients with advanced melanoma, which led to US FDA approval in 2011. In MDX010-20 trial (Hodi et al., 2010), 676 patients with unresectable stage III or IV melanoma who had received chemotherapy were randomized to compare ipilimumab with gp100 peptide vaccine. Gp100 vaccine alone has been shown to induce immune response but has

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