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Research review paper

Nanotechnology-based strategies for combating toxicity and resistance in melanoma therapy

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ABSTRACT

Drug toxicity and resistance remain formidable challenges in cancer treatment and represent an area of increasing attention in the case of melanoma. Nanotechnology represents a paradigm-shifting field with the potential to mitigate drug resistance while improving drug delivery and minimizing toxicity. Recent clinical and pre-clinical studies have demonstrated how a diverse array of nanoparticles may be harnessed to circumvent known mechanisms of drug resistance in melanoma to improve therapeutic efficacy. In this review, we discuss known mechanisms of resistance to various melanoma therapies and possible nanotechnology-based strategies that could be used to overcome these barriers and improve the pharmacologic arsenal available to combat advanced stage melanoma.

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1. Introduction

The American Cancer Society estimates that more than 1 in 50 Americans will develop melanoma in their lifetime, with about 74,000 new cases and nearly 10,000 deaths from melanoma in 2015 (Siegel et al., 2014). While early stage disease can be extirpated surgically with good outcomes, advanced stage disease is often unresectable – or recurs shortly after resection – and heralds a poor prognosis, with a median survival of less than 1 year and a 5-year-survival of less than 20% (Erickson and Miller, 2010). Further, melanoma is a highly plastic disease with a complex biology that involves cancer cells, immune cells, and stromal cells. While this feature presents numerous obstacles to developing effective therapies, it also provides multiple opportunities for drug development. An overview of recently developed drugs in melanoma pharmacotherapy is included in Table 1.

Until 2011, the only FDA approved systemic treatments for primary treatment of advanced melanoma were the cytokine interleukin-2 (IL-2) and the cytotoxic agent dacarbazine (DTIC) (Atkins et al., 1999, 2000; Eggermont and Kirkwood, 2004; Gogas et al., 2007; Sullivan and Flaherty, 2014). While these have historically been instituted in patients with disseminated disease, the impact of these agents on median survival and progression free survival is marginal, with objective responses generally being observed in only 10–15% of treated patients (Atkins et al., 1999, 2000; Balch et al., 2001; Wong et al., 1993).

More recently, advances in targeted therapy have brought new promise for combating melanoma with enhanced efficacy (Friedlander and Hodi, 2010; Puzanov and Flaherty, 2010; Shtivelman et al., 2014). In 2002, B-RAF was discovered to be the most frequently mutated gene in melanoma, with approximately 50% of patients harboring mutant B-RAF. Shortly thereafter, therapies (vemurafenib, dabrafenib) targeting the most common mutant isoform of B-RAF (V600E) were developed (Bollag et al., 2010; Flaherty et al., 2010b). Tramatenib, an inhibitor of Mitogen-activated protein kinase kinase (MEK) downstream of B-RAF, was also developed as a pharmacotherapeutic option (Chung and Reilly, 2015). Alone, these single targeted therapies have led to significant progression free survival benefit on the order of 5–7 months, with the majority of patients responding to therapy. Unfortunately, drug resistance rapidly develops during this interval, preventing long-term response and ultimately resulting in disease progression, which may be quite rapid (Dummer and Flaherty, 2012; Luke and Hodi, 2013). Clinical trials have shown that multi-targeted therapy involving combinations of targeted agents may produce better results. Combination therapy consisting of dabrafenib and tramatenib, for example, has achieved objective responses in 76% of participants for an average duration of 10.5 months (Johnson et al., 2014; Long et al., 2014; Robert et al., 2015a).

Similarly, advances in immunology and immunotherapy have improved the pharmacologic arsenal available to treat late stage melanoma. The most recent and exciting step has been the development and approval of several antibodies that release the "brake" on cytotoxic T cell activity. The first of these to be approved was ipilimumab, a fully humanized monoclonal antibody that blocks CTLA-4, a negative regulator of T-cell function, thereby augmenting cytotoxic T-cell activation and consequently anti-melanoma immunity (Hodi et al., 2010; Hwu, 2010; Rivere et al., 2011). While the best overall response rate to ipilimumab is only 10% (disease control rate of approximately 25–30%), it may provide long-lasting benefits to those who do respond and has been shown to result in an improvement in overall survival on the order of 3–4 months (Hersh et al., 2011; O'Day et al., 2010; Ott et al., 2013b; Robert et al., 2013; Wolchok et al., 2010). Another checkpoint molecule is PD-1, a signaling receptor often upregulated by melanoma that contributes to T cell anergy by binding to PD-L1 on immune cells. Several anti-PD-1 antibodies have been developed and have been tested in clinical trials (Luke and Ott, 2015; McDermott et al., 2014). Clinical responses to PD-1 inhibitors have been promising, with the first such compounds, nivolimab and pembrolizumab, approved for use in melanoma in the US (Johnson et al., 2015; Long et al., 2015; Robert et al., 2015b). Like targeted therapies, combinations of immune therapies are also promising, with the concurrent administration of ipilimumab and nivolumab producing a recently reported 2-year survival of 79% (Weber et al., 2013; Wolchok et al., 2013). Unfortunately, this benefit is limited by the development of severe immune toxicities, with one study finding the occurrence of grade 3/4 adverse events in 53% of patients treated with this combination, leading 30% of patients to discontinue this therapy (O'Sullivan Coyne et al., 2014; Weber et al., 2013; Wolchok et al., 2013).

Both immunotherapies and targeted therapies are promising for advanced-stage melanoma, but toxicity, limited efficacy, and/or drug resistance remain formidable problems (Eggermont and Robert, 2011; Menaa, 2013; Miller et al., 2014; Olszanski, 2014; Spagnolo and Queirolo, 2012). While combinations of these agents may increase efficacy, this can also be at the expense of a marked increase in toxicity. Consequently, further optimization of these strategies will be required to improve efficacies and overcome undesirable toxicities associated with use (Flaherty et al., 2010a, 2012a; Hodi, 2010; Sullivan and Flaherty, 2014). Taken together, these obstacles have driven researchers to investigate novel methods of drug delivery to improve efficacy, achieve targeting specificity, enhance drug concentration in tumor sites, optimize dosing & pharmacokinetics, reduce toxicity, and provide possible imaging capabilities with the ultimate goal of improving cancer therapy (Chen et al., 2013; Estanqueiro et al., 2015; Farokhzad and Langer, 2009; Felice et al., 2014; Pacheco et al., 2011).

Table 1
Recently developed pharmacotherapeutics options in melanoma. Dabrafenib, Vemurafenib, Trametinib, Cobimetinib, Pembrolizumab, Nivolumab, and Ipilimumab have been approved by the US Federal Drug Administration.

Drug class	Target	Examples
Targeted therapy	RAF	Dabrafenib, Vemurafenib
	MEK	Trametinib, Cobimetinib
	ERK	SCH772984
Immune therapy	PD-1	Nivolumab, Pembrolizumab
	PD-L1	BMS936559 (MDX1105)
	CTLA-4	Ipilimumab

2. General principles involving the use of nanotechnology in cancer treatment

Nanotechnology, which encompasses a broad spectrum of particles from 1 to 200 nm in size, has been applied in medicine to circumvent several therapeutic limitations that are often encountered in melanoma therapy (Bei et al., 2010; Gowda et al., 2013). Several types of nanoparticles have been developed for the treatment of cancer, including

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