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Tumour Review

Gaining momentum: New options and opportunities for the treatment of advanced melanoma

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ABSTRACT

Before 2011, patients with advanced or metastatic melanoma had a particularly poor long-term prognosis. Since traditional treatments failed to confer a survival benefit, patients were preferentially entered into clinical trials of investigational agents. A greater understanding of the epidemiology and biology of disease has underpinned the development of newer therapies, including six agents that have been approved in the EU, US and/or Japan: a cytotoxic T-lymphocyte antigen-4 inhibitor (ipilimumab), two programmed cell death-1 receptor inhibitors (nivolumab and pembrolizumab), two BRAF inhibitors (vemurafenib and dabrafenib) and a MEK inhibitor (trametinib). The availability of these treatments has greatly improved the outlook for patients with advanced melanoma; however, a major consideration for physicians is now to determine how best to integrate these agents into clinical practice. Therapeutic decisions are complicated by the need to consider patient and disease characteristics, and individual treatment goals, alongside the different efficacy and safety profiles of agents with varying mechanisms of action. Long-term survival, an outcome largely out of reach with traditional systemic therapies, is now a realistic goal, creating the additional need to re-establish how clinical benefit is evaluated. In this review we summarise the current treatment landscape in advanced melanoma and discuss the promise of agents still in development. We also speculate on the future of melanoma treatment and discuss how combination and sequencing approaches may be used to optimise patient care in the future.

Introduction

Despite an increase in the incidence of advanced melanoma [1,2], little progress has been made over recent decades in addressing the poor prognosis of patients or the limited treatment options available [3]. Historically, the primary aims of treatment were to reduce tumour burden and palliate symptoms, with little hope for prolonged survival. Chemotherapy remained the standard of care for advanced melanoma; objective response rates (ORRs) range from 5% to 25% for dacarbazine monotherapy and up to 45% for polychemotherapies, but none of these treatments have demonstrated improved overall survival (OS) [4,5].

More recently, extensive research has yielded a greater understanding of the epidemiology and biology of advanced melanoma, leading to the development of several new treatments with different mechanisms of action (MoAs). Six new agents have been approved in the EU, US and Japan for advanced melanoma in recent years: ipilimumab, nivolumab and pembrolizumab (immunotherapies), and vemurafenib, dabrafenib and trametinib (targeted therapies) [6–8]. These agents have dramatically improved the outlook for metastatic melanoma but have also increased the complexity of the treatment algorithm. As well as patient and disease characteristics, treatment decisions must now consider the different activity profiles of agents, balancing the desire for an immediate tumour response with symptom management and quality of life (QoL) [9]. In addition, as long-term survival has become an achievable treatment goal, the optimal measurement of clinical efficacy must be reconsidered. To this end, recommendations for how best to integrate these new agents into clinical practice are only included in more recent treatment guidelines [10–14].

This article reviews the approved treatment options for advanced and metastatic melanoma and recent data from clinical

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trials with novel regimens. It also addresses how future treatment strategies might be improved through sequencing and/or combination approaches.

Systemic treatment approaches

Approved and investigational therapies in metastatic melanoma differ in their MoAs (Fig. 1). Table 1 summarises the key properties of agents developed beyond phase I clinical trials.

Chemotherapy

Historically, systemic treatment of patients with advanced melanoma centred on cytostatic chemotherapy with dacarbazine or other alkylating agents such as temozolomide, fotemustine or taxanes [15]. Dacarbazine induces response rates (RRs) of up to 25% with no OS benefit over supportive care (median OS, 5–11 months) [5,16]. However, in comparator arms of controlled phase III trials of BRAF inhibitors, RRs for dacarbazine were only 6–9% and median OS was 9.7 months [17,18]. The most common treatment-related adverse events (AEs) with dacarbazine are nausea and vomiting, which are manageable with antiemetics in most patients [16].

Biochemotherapy combinations such as dacarbazine plus cytokines (interleukin-2 [IL-2] or interferons [IFNs]), or cisplatin/vinblastine/dacarbazine/tamoxifen (known as the Dartmouth regimen) have demonstrated superior RRs over chemotherapy alone without improved survival [19]. Furthermore, adding IL-2 to chemotherapy increases toxicity [20,21]. Polychemotherapy regimens include carboplatin/paclitaxel, CVD (cisplatin, vincristine and dacarbazine) and the BOLD regimen (bleomycin, vincristine, lomustine and dacarbazine); gemcitabine plus theosulfan is sometimes used in patients with primary ocular melanoma. Again, these combinations fail to significantly improve survival versus monochemotherapy and are therefore not considered appropriate first-line therapies [11], unless a high RR is required.

In a phase III trial, treatment with temozolomide, an oral alternative to dacarbazine, did not improve median OS in newly diagnosed patients with metastatic melanoma versus dacarbazine [22]. However, temozolomide can cross the blood–brain barrier and is widely used in patients with brain metastases [23]. Fotemustine also showed substantial activity in patients with symptomatic or asymptomatic brain metastases in a phase II trial and demonstrated superior RRs and a trend towards improved OS over dacarbazine in a phase III study [24]. Although used in

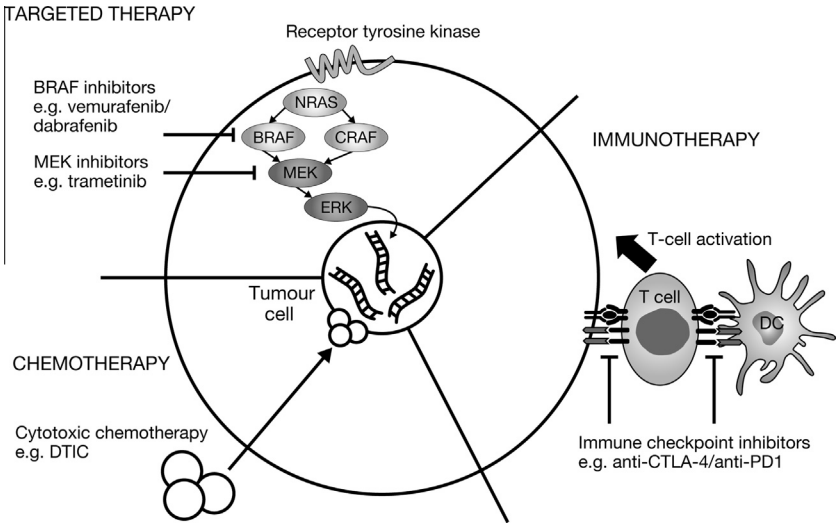

Fig. 1. Systemic therapies in advanced melanoma. *Abbreviations:* CTLA-4 – cytotoxic T-lymphocyte-associated antigen-4; DC – dendritic cell; DTIC – dacarbazine; PD-1 – programmed death 1.

Table 1
Types of antimelanoma therapy.

	Chemotherapy	Targeted therapy	Immunotherapy
MoA[a]	Direct cytotoxicity	Inhibition of MAPK signalling	Immune-related
OS advantage[a]	No	Yes	Yes
PFS advantage[a]	Yes	Yes	Small
Long-term (>2 years) survival[a]	Unknown	Unknown	Yes[b]
Common side effects[a]	Nausea, myelotoxicity	SCCs, ash, arthralgia, pyrexia, photosensitivity	irAEs[b]: colitis, endocrinopathies
Patient population[a]	All	$BRAF^{V600}$-mutation-positive	All[b]
Agents developed beyond phase I trials (highest phase)	DTIC (3)	Vemurafenib (3)	Ipilimumab (3)
	Temozolomide (3)	Dabrafenib (3)	Nivolumab (1)
	Fotemustine (3)	Trametinib (3)	Pembrolizumab (1)
	Nab-P (3)	LGX818 (1)	MPDL3280A (1)
		MEK162 (2)	BMS-936559 (1)
		Selumetinib (2)	T-VEC (3)
		Imatinib mesylate (2)	IL-2 (3)

Abbreviations: DTIC – dacarbazine; IL-2 – interleukin-2; irAE – immune-related adverse event; MAPK – mitogen-activated protein kinase; MoA – mechanism of action; Nab-P – nanoparticle albumin-bound paclitaxel; OS – overall survival; PFS – progression-free survival; SCC – squamous cell carcinoma; T-VEC – talimogene laherparepvec.

[a] Approved treatments (DTIC/vemurafenib/dabrafenib/ipilimumab).

[b] Effects are consistent with expected outcomes generally associated with immunological agents.