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Mini-review

Advances in targeted therapy for unresectable melanoma: New drugs and combinations

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ABSTRACT

Melanoma is the most deadly cutaneous cancer primarily derived from melanocytes with a poor prognosis in advanced stage. The therapy regimen for early stage melanoma patients is surgical resection with adjuvant IFN-alpha-2b therapy. For metastatic lesions, standard chemotherapy such as dacarbazine (DTIC) has not achieved a satisfying response rate. Therefore, new approaches to manage this deadly disease are highly expected to enhance the cure rate and to extend clinical benefits to patients with unresectable melanoma. Fortunately, the targeted therapeutic drugs and immunotherapy such as vemurafenib, dabrafenib, ipilimumab, and trametinib have shown their special advantage in the treatment of advanced melanoma. This article is to overview the advances in targeted therapy for unresectable melanoma patients.

Introduction

The incidence rate of melanoma reached 5% and 613,000 new cases of melanoma in situ were estimated to be diagnosed in 2013 in the US [1]. The main therapy for early-stage melanoma is surgical resection IFN-alpha-2b with a high five-year survival rate. For patients with stage III/IV melanoma who were not suitable for surgery, an alkylating agent DTIC is the major treatment. However, patients with melanoma easily become resistant to DTIC. In addition, DTIC also has serious side effects with a 10% response rate and only 36% one-year survival rate [2]. Therefore, new therapies are needed to cope with this lethal disease more effectively. Immunotherapies such as Anti-CTLA-4 and anti-PD-1/PDL-1 are making great success in improving the prognosis of melanoma patients. Along with this, mutant genes involved in the melanoma-related signal pathways have been discovered and the targeted therapeutic drugs such as vemurafenib have benefited the unresectable melanoma patients with BRAF mutation. This article will focus on recent progress of molecular targeted therapies for melanoma (Table 1).

BRAF inhibitor

BRAF, a serine/threonine protein kinase, is involved in the RAS–RAF–MEK–ERK cascade signaling pathway, thus regulating a number of important cellular functions, such as cell survival, proliferation and apoptosis resistance [15]. As an oncogenic driver of melanoma, no less than 50% mutated *BRAF* was identified in melanoma and the targeted drugs of BRAF showed a potentially effective therapy for patients with melanoma [16].

Sorafenib is a non-selective inhibitor of tyrosine kinases including RAF kinase. A series of clinical trials on sorafenib have been initiated. Unfortunately, as a single agent, sorafenib has limited antitumor activity in patients with melanoma, and therefore the relationship between mutated *BRAF* and clinical responses of sorafenib cannot be established, although sorafenib is well tolerated with mild and easily manageable adverse events (AEs) in clinic [3,17,18].

Vemurafenib, the first selective and potent inhibitor of oncogenic BRAF kinase, was approved by the Food and Drug Administration (FDA) in 2011 for use in patients with advanced or unresectable melanoma, especially in patients with *BRAF* V600E tumors in which more than 80% *BRAF* mutation was detected [19]. Moreover, vemurafenib has been demonstrated to have great impacts on progression free survival (PFS), overall survival (OS) and median

Abbreviations: BRAF, v-raf murine sarcoma viral oncogene homolog; MEK, MAP kinase-ERK kinase; KIT, V-KIT Hardy–Zuckerman 4 feline sarcoma viral oncogene homolog; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1/PD-L1, programmed death-1/ programmed death-1 ligand; VEGF, vascular endothelial growth factor; mTOR, mammalian target of rapamycin; PR, partial response; CR, complete response; SD, stable disease; PFS, progression-free survival; AEs, adverse events; M, male; F, female; Ipi, ipilimumab.

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Table 1
The comparison of endpoints and adverse events among molecular targeted drugs in recent melanoma clinical trials.

Drugs/anti-molecules	Targets	Stage of clinical trials	Patients enrolled	Object response (CR + PR)	SD	PFS	AEs	Reference
Sorafenib	B-RAF-V600E	Phase II	Total: 36 M: 20 F: 16	CR: none PR:1	3	63 days	Diarrhea (30%) Rash (46%) Alopecia (22%)	[3]
Vemurafenib	B-RAF-V600	Phase II	Total: 29 M: 25 F: 4	CR: none PR:3	None	6 months	Fatigue (52%) Rash (48%) Arthralgia (38%)	[4]
Dabrafenib	B-RAF-val600Glu B-RAF-val600Lys	Phase II	Total: 172 Glu: 139 Lys: 33	No-checked	Total: 78 Glu: 69 Lys: 9	16.1 vs 8.1 weeks	Pyrexia(26) Rash (6%)	[5]
Trametinib	MEK-1/2	Phase II	Total: 97 M: 68 F: 29	CR:1 PR:13	40	1.8 months/4 months	Rash/dermatitis acneiform (84%) Nausea (30%)	[6]
Selumefinib	MEK-1/2	Phase II	Total: 45 M: 22 F: 23	CR:1 PR:17	9	13.9 months	Nausea (66%) Diarrhea (50%) Vomiting (50%)	[7]
Binimetinib (MEK162)	MEK-1/2	Phase II	Total: 71 N-RAS-mutant: 30 B-RAF-mutant: 41	Total: 14 N-RAS-mutant: 6 B-RAF-mutant: 8	Total: 26 N-RAS-mutant: 13 B-RAF-mutant: 13	N-RAS-mutant: 3.7 months B-RAF-mutant: 3.6 months	N-RAS-mutant vs B-RAF-mutant: Acneiform Dermatitis (18 vs 15) Rash (6 vs 16)	[8]
Imatinib	c-KIT	Phase II	Total: 43 M: 20 F: 23	PR:10	13	3.5 months	Edema (100%) Fatigue (69.8%) Anorexia (69.8%)	[9]
Nilotinib	c-KIT	Phase II	Total: 11 M: 5 F: 6	CR: 0 PR: 2	5	2.5 months	Anorexia (11.1%) Nausea/vomiting (33.3%)	[10]
Bevacizumab	VEGF-A	Phase II	Total: 35 M: 19 F: 16	CR:1 PR:5	5	21.4 months	Fatigue (14%) Proteinuria (34%) Hypertension (40%)	[11]
Bevacizumab + everolimus	VEGF mTOR	Phase II	Total: 57 M:39 F:18	CR:1 PR:6	No-checked	4 months	Neutropenia (11%) Anemia (49%) Fatigue (65%)	[12]
Ipilimumab + gp100 ipilimumab	CTLA-4	Phase II	Ipi + gp100: Total: 403 M: 247 F: 156 Ipi: Total: 137 M: 81 F: 59	CR:1 PR:22 CR:2 PR:13	58 vs 24	2.76 vs 2.86 months	Diarrhea (38.4 vs 32.8%) Nausea (33.9 vs 35.1%) Constipation (21.3 vs 20.6%)	[13]
Ipilimumab + dacarbazine	CTLA-4	Phase II	Total: 250 M: 152 F: 98	CR:4 PR:34	45	12 weeks	Diarrhea (40.4%) Rash (25.9%) Pyrexia (36.8%)	[14]