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Mini-review

Research progress in advanced melanoma

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ABSTRACT

Melanoma is a malignant tumor with high rate of metastasis and poor prognosis. How melanoma develops and how to treat it will continue to be a hot topic. This review briefly summarizes the mechanism of melanoma development and the latest progress in its treatment.

The characteristics of malignant melanoma (MM), which is derived from amine precursor uptake and decarboxylation cells in the neural crest, include high rates of mortality, metastasis, and drug resistance. Currently, MM is divided into four main subtypes according to molecular biology characteristics, clinical histologic features, and relationship between genetic mutations; these are acral, mucosal, non-chronic sun damage, and chronic sun damage (CSD).

Melanoma is a tumor of heterogeneity. Different races, different pathogenic sites, and even different histological types may display entirely different genetic mutations, and amplification or abnormal signal transduction in the mitogen-activated protein kinase (MAPK), KIT, phosphoinositide-3 kinase-serine/threonine protein kinase (PI3K-AKT), or other pathways.

The therapeutic landscape has changed rapidly with the development of novel agents in the past decade, bringing hope to patients with MM. Targeted drugs appear on the market one after another including BRAF inhibitors, MEK inhibitors, anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) agents, and anti-programmed cell death protein-1 (PD-1) agents. However, these novel agents are expensive and not widely produced. Although surprising efficacy is achieved in patients with melanoma, patients often still require standard chemotherapy. Which, if any, regimens show not only clinical benefit but are also affordable to most MM patients? Some studies revealed that various vaccination and anti-angiogenesis inhibitors exerted satisfactory efficacy in patients with melanoma, suggesting that these therapies may become a part of the main armentarium in melanoma treatment. However, previous reviews have not thoroughly discussed these regimens in detail. Thus, this review provides a more comprehensive summary of the potential regimens in melanoma.

Pathogenesis

How melanoma develops has not been entirely explained. Previous studies identified some risk factors for melanoma development. The main ones are male sex (especially men aged older than 60 years); phenotypic predisposition [1,2] (people who are sun-sensitive, with red hair and blue eyes, those with atypical moles or a dysplastic nevus pattern etc); medical history and comorbidities [3–5] (sunburn; precancers such as actinic keratosis; non-melanoma skin cancer such as basal cell and squamous cell carcinomas; and immunosuppression such as HIV/AIDS, solid organ transplantation, and hematopoietic cell transplantation); rare genodermatoses (e.g., xeroderma pigmentosum); genetic predisposition [2] (family history of MM, especially multiple melanoma; melanoma susceptibility polymorphisms including *CDKN2A, CDK4, MCR1*, and other undefined germline mutations); and environment [2,6,7] (history of tanning bed use; residence in sunnier climates or latitudes near the equator; intermittent intense sun exposure or chronic sun exposure).

Plenty of studies found that some MM patients had genetic mutations or gene amplifications, and different histological types displayed differentiation in mutated genes. Genomic mutation

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status helps to estimate the prognosis and guide regimen selection. Presently, the mutated genes reported mainly include *BRAF, NRAS, KIT*, et al. (Table 1).

***BRAF* gene**: *BRAF* is located at chromosome 7p34 and is highly expressed in melanoma, colorectal cancer, and hematopoietic cells. Approximately 50% of patients with advanced melanoma have *BRAF* mutations [8,9]. The BRAF protein is continuously activated because of *BRAF* mutations, leading to an activated MAPK pathway that contributes to unlimited cell proliferation. Previous studies showed that *BRAF* mutations were related to exposure to ultraviolet and sunlight. These mutations mainly exist in skin melanoma but are rarely found in mucosal melanoma. Exon 15 is the most frequently mutated site in the *BRAF* gene, with the V600E and V600K mutations being the most common although other rare types include V600R, V600D, G596R, D594N, L597R, and K601E [10–12].

***KIT* gene**: *KIT* maps to chromosome 4q11-12 and encodes the KIT protein (namely, CD117), which is a tyrosine kinase receptor important for regulating the cell cycle in normal melanocytes. It forms a dimer by binding with relevant stem cell factors (SCFs) to activate tyrosine the kinase activity. It then further triggers the MAPK, PI3K/AKT, and JAK/STAT (Janus kinases/signal transducer and activator of transcription) pathways for the transduction of multiple signals by autophosphorylation, and ultimately activates transcription factors in the cytoplasm and regulates gene expression, cell growth, and proliferation. The main abnormalities of the *KIT* gene include mutations and amplifications. *KIT* mutations occur in about 3% of patients with melanoma especially in acral, mucosal, and CSD melanoma. Studies reveal that the most common *KIT* mutations identified in MM are located in exon 11 (approximately 70%), 13 (about 13%), and 17 (about 9%). The most frequent mutations are L576P in exon 11 and K642E in exon 13. Other described mutations include R634W and S628N in exon 13 and D816V in exon 17 [13–19]. Monsel et al. found that mutations in L576P and K642E enhanced the activation of the PI3K pathway, but had a weaker promotion of the MAPK pathway and few impacts on cell proliferation and malignant transformation. However, the MAPK pathway is the only activated transduction pathway in an hypoxic environment or under the activation of hypoxia inducible factor 1α (HIF1α), resulting in proliferation and canceration [20]. Abnormal proliferation in melanocytes is believed to be the product of mutual interactions between *KIT* mutations and the environment.

***NRAS* gene**: Another important oncogene in MM is *NRAS*. The activation of mutated *NRAS* can lead to abnormal signal transduction in the MAPK and PI3K/AKT pathway. The mutation rate of *NRAS* is about 20% and the most common mutations occur in exons 1 (G12C, G12D, and G12A) and 2 (Q61K, Q61R, Q61L, and Q61H) [9,21,22].

***PTEN* gene**: *PTEN*, located at chromosome 10q23, is frequently affected by loss of heterozygosity. It is regarded as a tumor suppressor gene and can inhibit the PI3K pathway. Previous studies showed that the mutation rate of *PTEN* was approximately 30–40% in melanoma cell lines, and about 10% in primary melanomas. The most frequently affected sites of mutations are located in exon 5 [23,24].

Table 1
Gene mutation in melanoma.

Gene	Most frequently mutated sites	Incidence	References
BRAF	V600E and V600K in exon 15	50%	[8–12]
KIT	L576P in exon 11 and K642E in exon 13	3%	[13–20]
NRAS	G12 in exon 1 and Q61 in exon 2	20%	[9,21,22]
PTEN	exon 5	10%	[23,24]
Others[a]	Various	Unknown	[25–32]

[a] *CDKN2A*, *CCND1*, *GNAQ*, *GNA11*, *TERT*, *MITF*, *P53*, et al.

Others: About 5–10% of patients with melanoma have a family history of the disease, and 20–60% of them have *CDKN2A* mutations [25,26]. Mutations in oncogene *CCND1* are also involved in metastasis and ulcerations in melanoma, and expression of the CCND1 protein is related to Breslow thickness, metastasis, and shorter survival time [27,28]. Some studies on uveal melanoma also found mutations in *GNAQ* and *GNA11*, which were related to the MAPK pathway. The most frequently mutated sites are in exon 5 (Q209L) and 4 (R183C) [29]. Mutation of *BAP1*, which maps to 3q21.1, is also detected in uveal melanoma [30]. Additionally, other genes that have been reported include *TERT*, *MITF*, *P53*, and others [31,32]. Further studies are needed to determine how those genes function and whether there are other genomic mutations.

Progress in treatment

The therapeutic landscape has been rapidly changing in the past decade. Targeted therapy shows better efficacy than traditional chemotherapy. As immune checkpoint agents (e.g., anti-CTLA-4, anti-PD-1) and molecularly-targeted drugs (e.g., BRAF inhibitors, MEK inhibitors) have been included into the treatment of MM, they are gradually taking the place of standard chemotherapy with dacarbazine (DTIC).

In 2017, the National Comprehensive Cancer Network (NCCN) recommendations for patients with unresectable stage IIIc or stage IV melanoma, with or without *BRAF* mutations, in the first-line setting include immunotherapy with checkpoint inhibitors such as anti-PD-1 monotherapy with pembrolizumab (category 2A) or nivolumab (category 1), or nivolumab/ipilimumab combination therapy (category 2A). BRAF-targeted therapy is also recommended and shows good efficacy in patients with *BRAF* mutations and metastatic disease. Category 1 recommendations include BRAF/MEK inhibitor combination therapy with dabrafenib/trametinib or vemurafenib/cobimetinib, or BRAF inhibitor monotherapy with dabrafenib or vemurafenib. For those who have not received any treatment previously, participation in clinical trials is also a good choice. For patients who progress on first-line therapy or achieve maximum clinical benefit from BRAF-targeted therapy, second-line therapy options depend on the Eastern Cooperative Oncology Group (ECOG) performance status (PS). Patients with PS 0–2 have multiple options, including anti-PD-1 monotherapy, nivolumab/ipilimumab combination therapy, BRAF/MEK inhibitor combination therapy (if the patient has a *BRAF* mutation), anti-CTLA-4 monotherapy, high dose IL-2, biochemotherapy, chemotherapy, imatinib (if the patient has a *KIT* mutation), or a clinical trial. Patients with poor PS (PS 3–4) should be offered supportive care. Apart from the above-mentioned regimens, vaccines and anti-angiogenesis agents also show promise in the treatment landscape for melanoma. Each regimen has its own merits and demerits. Treatment selection should be informed by considering the patient's overall health, medical history, comorbidities, economic status, and management of adverse events. More details on these regimens in melanoma are discussed below.

Checkpoint immunotherapy

Anti-CTLA-4 inhibitors

CTLA-4 is a member of the immunoglobulin family expressed on the surface of immature cytotoxic T lymphocytes and regulatory T cells. Once the receptor on immature T cell is activated, CTLA-4 competes with CD28 for binding to B7, shutting down the signaling cascade and then inhibiting the immune response. Ipilimumab is a monoclonal antibody against the immune checkpoint receptor CTLA-4. It prevents receptor–ligand interactions,