Checkpoint inhibitors in treatment of metastatic mucosal melanoma

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Abstract: Mucosal melanoma (MM) is rare and of extremely poor prognosis. Although significant progress has been made in developing new therapies for patients with metastatic melanoma arising from the cutaneous, knowledge about the effects of treatments for patients with MM is limited. In this review we aim to summarize and evaluate related trials.

Keywords: Anti-programmed cell death 1; checkpoint; mucosal melanoma (MM); ipilimumab; immunotherapy

Introduction

Mucosal melanoma (MM) is an extremely rare and aggressive malignancy which is clinically and biologically distinct from cutaneous melanoma. Most MMs are tending to be diagnosed at a late stage because of their often obscured anatomic site of origin (1). There is a rich vascular and lymphatic supply of mucosal sites, leading to a greater inclination of local, regional, and distal recurrence, as well as regional and distant metastasis (2,3). Furthermore, with the limited number of cases and lack of enough prospective randomized clinical trials, there is no standard of care for treatment in MM. Given these factors, MM commonly presents at a more advanced stage with a very poor prognosis and significantly worse outcomes than cutaneous melanoma (1,4-6).

Based on less cases and randomized trials, patients are commonly treated with the same regimens used for cutaneous melanoma. Nowadays, with the advancement in molecular targeted therapy and immunotherapy, outcomes have been improved in patients with metastatic melanoma. As compared to targeted therapy, immunotherapy can induce durable disease control and long-term survival in patients with metastatic disease, which has dramatically shaped the treatment landscape for metastatic melanoma. Ipilimumab, an antibody that blocks the cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint,

is approved by the United States Food and Drug Administration (FDA) based on an overall survival (OS) advantage in patients with metastatic melanoma (7,8). Additionally, targeting the inhibitory receptor/ligand axis PD-1/PD-L1 with monoclonal antibodies has shown remarkable antitumor activity in patients with melanoma in large phase I studies (9,10). However, very few patients with MM were treated in the clinical trials with treatment of checkpoint blockade (include Ipilimumab and PD-1/PD-L1 antibodies). Therefore it is unknown whether patients with MM can benefit from these agents. As the clinical use of checkpoint blockade continues expanding, identifying its efficacy in MM patients is essential. This review summarizes the important updates on checkpoint blockade in the treatment of MM.

CTLA-4 blockade

Ipilimumab, was the first therapy demonstrated to improve OS in melanoma and was approved as a new therapy for melanoma by U.S. Food and Drug Administration in 2011. Phase III studies show an OS benefit for patients with advanced melanoma (7,8). However, the efficacy of ipilimumab in MM is not clear yet. In a multicenter, retrospective analysis of unresectable or metastatic MM treated

with ipilimumab, 30 patients who underwent radiographic assessment after ipilimumab at approximately week 12 were evaluated by the immune related response criteria. There was one immune-related complete response (irCR), one immune-related partial response (irPR), six immune-related stable diseases (irSD) and 22 immune-related progressive disease. Immune-related adverse events consisted of six patients with grades 1-2 rash, three patients with grades 1-3 diarrhea, one patient with grade 1 thyroiditis, one patient with grade 3 hepatitis, and one patient with grade 2 hypophysitis. The median OS from the time of the first dose of ipilimumab was 6.4 months (11). In 2014, an Italy study reported efficacy and safety of ipilimumab 3 mg/kg in 71 patients with pretreated, metastatic, MM. One (1%) had an irCR and seven had (10%) irPR, with an immune-related best overall response rate (irBORR) of 12%. Seventeen patients had irSD; the immune-related disease control rate (irDCR) was 25/69. Median duration of irSD was 6.7 months with a median follow-up of 21.8 months. Median OS was 6.4 months. The 1-year OS rate was 35%. Median PFS was 4.3 months, and the 1-year PFS rate was 15%. A total of 33 (48%) reported AEs of any grade, Severe (grade 3 or 4) adverse events (AEs) were reported in 11 patients (16%) and considered treatment-related in six patients (9%), comprising diarrhoea (n=3), rash (n=1), liver toxicity (n=1) and asthenia (n=1). Treatment-related AEs were generally reversible with management of per protocol-specific guidelines, with a median time to resolution of 2.6 weeks (range, 0.7-8.7 weeks) (12). Another trial assessing Ipilimumab and radiation therapy for melanoma brain metastases, the survival of the SRS and ipilimumab group was than SRS alone median of 19.9 *vs*. 4.0 months; P=0.009). Four of 10 evaluable patients (40.0%) who received ipilimumab prior to radiotherapy demonstrated a partial response (PR) to radiotherapy, compared with 2 of 22 evaluable patients (9.1%) who did not receive ipilimumab. Ipilimumab was associated with a significantly reduced risk of death in patients with melanoma brain metastases who previously received radiotherapy, supporting the need for multimodality therapy to optimize patient outcomes (13). Limitations of this study included small sample sizes, retrospective, and only three patients were enrolled (two for Ipilimumab + SRS, one for SRS). These trials suggest that ipilimumab treatment is beneficial and well tolerated in patients with metastatic MM. However, all these studies were retrospective and small sample-sized, thus more randomized studies need to be performed in the future.

Tremelimumab, another human antagonist antibodies targeting human CTLA-4, has been being investigated in clinical trials. A phase II trial of tremelimumab monotherapy in 251 melanoma patients demonstrated an ORR of 6.6%, with prolonged duration of response among responders ranging from 8.9 to 29.8 months (14). However, a phase III study of tremelimumab was halted after an interim analysis failed to demonstrate benefit in OS compared with standard chemotherapy, although the median duration of response was longer in patients responding to tremelimumab (15). A phase II trial combining tremelimumab with interferon alfa-2b demonstrated a best ORR of 24%, with an additional 38% of subjects experiencing stable disease (SD). OS was 21 months, significantly longer than reported with ipilimumab or tremelimumab monotherapy (16). However, the efficacy and safety of tremelimumab in patients with resected MM has not been evaluated.

PD-1/PD-L1 blockade

Programmed cell death-1 (PD-1), an immunoinhibitory receptor of the CD28 family, plays a major role in tumor immune escape (17,18). The interaction of PD-1 with its two ligands, B7-H1 and B7-DC (PD-L1 and PD-L2), occurs predominantly in peripheral tissues including the tumor microenvironment and leads to apoptosis and downregulation of T-cell effector function (19). Monoclonal antibodies against PD1 and its ligand (PD-L1), the second generation immunomodulatory antibodies, displayed significant durable benefits in patients with MM (10,20,21).

In the first-in-human study of the PD-1 immune checkpoint inhibitor nivolumab, an acceptable safety profile and durable objective tumor regressions were observed in patients with advanced solid tumors, including 26 of 94 melanoma patients (9). In another phase I study, 9 of 55 patients with advanced, previously treated melanoma had objective responses [three complete responses (CR) and six PR] after being treated with the anti-PD-L1 monoclonal antibody. Five of these patients had response for at least 1 year and five were ongoing at the time of data analysis. Furthermore, fourteen of 55 patients had SD that lasted more than 24 weeks (10). Objective responses with another PD-1-directed inhibitory antibody, lambrolizumab, were recently reported in 44 of 117 (38%) patients with advanced melanoma treated in a phase I study (21). A study of 107 patients with advanced melanoma reported that median OS in nivolumab-treated patients (62% with two to five prior systemic therapies) was 16.8 months, and 1- and 2-year survival rates were 62% and 43%, respectively. Among 33 patients with objective tumor regressions (31%), the

median response duration was 2 years. Seventeen patients discontinued therapy for other reasons rather than disease progression, and 12 (71%) of 17 maintained responses off-therapy for at least 16 weeks. Objective response and toxicity rates were similar to those reported previously (22). However, most of these trials focus on cutaneous melanomas and the efficacy of anti-PD1 therapy for this MM is still unknown. Recently, a case report indicated that a patient with advanced MM responded to anti-PD1 therapy. This patient had an initial nearly CR and remained in remission for 14 months after discontinuing treatment (23). These results suggest that nivolumab may have an impact on survival in patients with advanced melanoma with an acceptable long-term safety profile. Nevertheless, randomized clinical trials on anti-PD-1 antibody in patients with MM are lacking and need to be verified.

For PD-L1 antibody, a multicenter phase I trial provides the first clinical evidence in efficacy. Fifty of 207 patients were melanoma patients. Objective responses were observed in 17% of patients (9 of 52) with melanoma, including three CRs. Many responses were durable, with five responses lasting for more than 1 year. In addition, 27% of patients achieved SD, lasting for more than 24 weeks. Grade 3/4 adverse effects were observed in 9% of patient treated with the drug, including fatigue, emesis, infusion reaction and lymphopenia. No treatment-related death was reported (24). Whether anti-PD-L1 antibody can be used for therapy for metastatic MM will need to be confirmed.

Conclusions

Although monoclonal antibodies targeting immune checkpoint proteins (include Ipilimumab and PD-1/PD-L1 antibodies) have elicited long-lasting anti-cancer response in metastatic melanoma, randomized clinical trials on checkpoint inhibitors in patients with metastatic MM are limited. It is expected that the role of checkpoint inhibitors in patients with metastatic MM will be further clarified after results of more prospective studies are ultimately available in future.

Acknowledgements

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