Review Article



# Adjuvant therapy of mucosal melanoma

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**Abstract:** Mucosal melanoma is a rare subtype of melanoma and associated with extremely poor prognosis. However, standard adjuvant therapy for mucosal melanoma has not been established. Some approaches have been studied to reduce the risk of recurrence in patients. These include adjuvant chemotherapy, immunotherapy, targeted therapy, and radiotherapy (RT). In this review we aim to summarize and evaluate the therapies in development.

**Keywords:** Adjuvant therapy; chemotherapy; immunotherapy; mucosal melanoma; targeted therapy

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## Introduction

As compared to cutaneous melanomas, mucosal melanomas (MM) are extremely rare in Caucasians (1.3% of all melanomas) and relatively rare in Asians based on lower incidence of melanoma, though MM are the secondary predominant subtypes of melanomas in Asians (1-3). MM are generally classified according to primary sites (4). MM have a very poor prognosis and significantly worse outcomes than cutaneous melanomas (4-7). Early diagnosis combined with appropriate surgical therapy is currently the only curative treatment for melanoma (8,9). Despite that systemic adjuvant therapy has been investigated for cutaneous melanoma, it remains expected for MM. Either strategies for early diagnosis of MM or effective adjuvant therapies for MM are urgently needed to be established. Systemic adjuvant treatment for melanoma should be considered when a patient is clinically free of disease following surgical excision of the primary high-risk tumor and is at high risk for recurrence, especially for patients with AJCC stage of IIB, IIC and III (8,10,11). Currently, some approaches have been studied to reduce the risk of recurrence in MM patients. These include adjuvant immunotherapy, chemotherapy, targeted therapy and radiotherapy (RT). In this review we aim to summarize and evaluate these therapies in development.

## Adjuvant treatment

### *Adjuvant treatment with immunotherapy*

#### Interferon

At present the most common adjuvant treatment in high risk cutaneous melanomas is high-dose IFN-α2b (HDI). The randomized trials with HDI suggest that HDI can significantly improve relapse-free survival (RFS) and/or overall survival (OS) of high-risk cutaneous melanoma patients (12-14). In clinical trials of HDI as adjuvant therapy (E1684, E1690 and E1694), only a few mucosal melanoma patients were enrolled, but the efficacy in this subset was not specified (12-14). Trials of adjuvant treatment with HDI are seldom performed for MM. Our randomized study comparing HDI with chemotherapy for resected mucosal melanoma presented an interesting result, the median RFS of HDI group in the trial was only 9 months (15), which was much less than the previously reported RFS in cutaneous melanoma and less than our another trial of HDI in acral melanoma (median RFS: about 22.5 months) (12-14,16). Considering that all the enrolled patients in current trial were in stage II/III (localized and regional), this difference in RFS may be due to the different subtypes of enrolled melanoma patients, with our trial focusing on MM patients who usually had very poor prognosis. However, HDI could

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also improve the RFS and OS of stage II/III MM patients as compared to observation, suggesting that HDI may be a choice of adjuvant therapy for MM patients.

Adjuvant pegylated interferon alfa-2b (PEG-IFN-2b) was approved for treatment of resected stage III melanoma in 2011. Some follow-up data has been published recently from the EORTC 18991 study, showing that PEG-IFN increases the RFS, but no significant differences were observed in OS between the two groups (17). Similarly there was no mucosal melanoma patients be enrolled in this randomized trial.

**Checkpoint inhibitors**

Nowadays, only IFN has shown to be beneficial in RFS and in less degree in OS in high risk cutaneous patients, therefore it is necessary to continue to study on novel therapies. Some new agents against metastatic melanoma may be used as adjuvant therapy in the future, the representative agents are checkpoint inhibitors, including CTLA-4 and PD-1/PD-L1 inhibitor.

Ipilimumab, an anti-cytotoxic T-lymphocyte antigen 4 antibody, was the first compound demonstrated to improve OS in melanoma and was approved as a new therapy for melanoma by U.S. Food and Drug Administration in 2011, as phase III studies shows an OS benefit for patients with advanced melanoma (18,19). However, the efficacy of ipilimumab in mucosal melanoma is still largely unclear. In 2014, a study reported efficacy and safety of ipilimumab 3 mg/kg in 71 patients with pretreated, metastatic, mucosal melanoma. With a median follow-up of 21.8 months, the response rate was 12%. Median progression-free survival (PFS) and OS were 4.3 and 6.4 months, respectively (20). Another multicenter, retrospective analysis of 33 patients with unresectable or metastatic mucosal melanoma treated with ipilimumab reported that the median OS from the time of the first dose of ipilimumab was 6.4 months (range, 1.8-26.7 months). Long-lasting response to ipilimumab were observed, but the overall response rate was low (21). All results above suggested that ipilimumab may be a feasible treatment option in pretreated patients with metastatic mucosal melanoma. So far the benefit of ipilimumab for earlier-stage disease has not been established yet. Ipilimumab in the adjuvant setting has been being evaluated in two ongoing phase III trials (NCT00636168 and NCT01274338). In NCT00636168, ipilimumab is being compared with placebo after resection of high-risk stage III melanoma, with recurrence-free survival as the primary endpoint. Accrual has been completed and results are anticipated. Ipilimumab is also being compared with high-dose recombinant interferon-α-2b in another trial (NCT01274338) (22).

In 2012, preliminary investigations of PD-1 inhibitors came to fruition, demonstrating a strong sign of efficacy and safety. PD-L1 antibodies are being developed in tandem with PD-1 (23). Many tumor responses achieved with PD-1 and PD-L1 inhibition were durable in the phase I trials and were observed in a larger proportion of patients with melanoma than typically observed with ipilimumab antibodies, with an acceptable toxicity profile (24). Whether PD-1/PD-L1 inhibitors can be used for adjuvant therapy for melanoma, especially mucosal melanoma, will need to be confirmed.

***Adjuvant treatment with chemotherapy***

In previous randomized studies, adjuvant chemotherapy has not shown any significant benefit in cutaneous melanoma, even at high doses with the support of autologous bone marrow (25). Retrospective studies on adjuvant chemotherapy for patients with mucosal melanoma have been reported (26,27). However, interpretable data derived from randomized clinical trials on adjuvant chemotherapy in patients with mucosal melanoma are lacking. *In vitro* studies suggest that cisplatin may enhance the antitumor activity of temozolomide by its ability to downregulate alkylgua-nine alkyltransferase (28). Most recently, Flaherty and colleagues reported that biochemotherapy consisting of dacarbazine, cisplatin, vinblastine, interleukin-2 (IL-2), IFN-a, and G-CSF showed significant improvements in RFS (median, 4.0 *vs*. 1.9 years; P=0.034) in high-risk stage III melanoma, but not in OS, which was a co-primary endpoint, as compared with HDI (29). This study indicated that dacarbazine in combination with cisplatin can be used in adjuvant chemotherapy for melanoma. But most of these studies were retrospective, either with small sample sizes or nonrandomized studies. Therefore there is no convincing evidence for adjuvant chemotherapy for patients with mucosal melanoma.

Most recently, we reported a randomized phase II study comparing the activity and safety of temozolomide plus cisplatin with that of HDI in patients with resected mucosal melanoma. In this trial, MM patients in stage II/III after surgery were randomized into three groups: observation group (group A, surgery alone), HDI group (group B, treated with $15\times10^6$ Unit/$m^2$/day IFN-α2b, followed by $9\times10^6$ Unit IFN-α2b), and temozolomide (200 mg/$m^2$/day) plus cisplatin (75 mg/$m^2$) group (group C). The endpoints were RFS OS and toxicity. One hundred and eighty-nine patients were enrolled and finally analyzed. With a median

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follow-up of 26.8 months, the median RFS were 5.4, 9.4 and 20.8 months in group A, B and C, respectively. Estimated median OS in group A, B and C were 21.2, 40.4 and 48.7 months, respectively. Patients treated with temozolomide plus cisplatin demonstrated significant improvement in RFS (P<0.001) and OS (P<0.01) than those treated with either HDI or surgery alone. Toxicity was generally mild to moderate (15). Our trial is the first to suggest that temozolomide based chemotherapy may be better than HDI in terms of both RFS and OS in this specific subtype of patients with mucosal melanoma. However, as a single-center trial, adjuvant therapy using chemotherapy or HDI in patients with mucosal melanoma may require more randomly controlled trials in the future.

### *Adjuvant treatment with targeted therapy*

The finding that melanomas frequently contain driver oncogenes such as *BRAF*, *NRAS*, and *KIT* has revolutionized treatment for advanced melanoma during the past decades. Approximately 40-50% of patients harbor activating mutations of BRAF in Caucasians melanoma patients (30). The frequency of c-kit mutations is 10.8% in Chinese melanoma patients and 9.6% in mucosal melanoma patients (2). Targeted therapies are evolving rapidly in the treatment of melanoma. The c-kit inhibitor imatinib (enrolled 13/28 mucosal melanoma patients) (31), the BRAF inhibitors vemurafenib (32) and dabrafenib (33), and the MEK inhibitor trametinib (34) significantly improve survival in patients with advanced disease. However, these targeted therapies have not been clinically evaluated for melanoma as adjuvant therapy. BRAF inhibitor vemurafenib and the combination of dabarafenib and trametinib are currently being evaluated in the adjuvant setting in patients with stage III and high risk stage II disease. Given results that adjuvant imatinib improves survival in GI stromal tumors (35,36), we conducted a randomized phase II clinical trial in resected melanoma (include MM) patients to compare the efficacy and safety of HDI with imatinib as adjuvant therapy. All the results of these studies are eagerly awaited.

### *Adjuvant treatment with radiotherapy (RT)*

It is an option in melanomas with a high risk of regional recurrence after lymphatic clearance. In a randomized study with 227 patients, considered as having a high risk of recurrence, 109 were included in the adjuvant RT group and 108 were in control group. After a mean follow up of 27 months, 20 patients had recurrences in the RT group and 34 did in the control group (P=0.0410), suggesting a better improvement in the local recurrences with RT but not in the survival rate (37).

As with mucosal melanoma, any clinical benefit derived from adjuvant RT appears to be limited to the primary site. RT is commonly used in the adjuvant treatment of surgically resected head and neck MM, one retrospective analysis of 69 patients with head and neck MM suggested improved local control for patients treated with adjuvant RT (38). With regard to anorectal mucosal melanoma, due to the risk of local recurrence and its associated morbidity, adjuvant RT may be considered after definitive surgical resection. RT delivered in this setting does not appear to alter long-term survival, though some series have suggested it may improve local control following sphincter sparing surgery (39,40). However, most of these studies were retrospective, small sample-sized or non-randomized studies, more randomized studies need to be performed in the future.

## Conclusions

MM has a very poor prognosis and significantly worse outcomes than cutaneous melanoma. Surgical resection remains the most important treatment and can result in cure of tumor. Systemic adjuvant treatment of MM may be considered specially for high-risk patients. Temozolomide based chemotherapy may be better than HDI as adjuvant therapy of MM. Targeted therapy and checkpoint inhibitors could be novel strategies of adjuvant therapy for MM. Adjuvant RT may improve local control but not OS. It is expected to analyze these adjuvant therapies in randomized clinical trials in order to improve prognosis of MM patients.

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