

Chemotherapy, biochemotherapy and anti-VEGF therapy in metastatic mucosal melanoma

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Abstract: Mucosal melanomas arise from melanocytes located at various mucosal membranes, which demonstrate a clear demographic and ethnic disparity. This subtype of melanoma has more aggressive course and poorer prognosis than other subsets of melanomas. Due to their rarity, there is no well-established protocol of staging and treatment of mucosal melanomas. Significant advances have been achieved in novel immunotherapeutic and specific targeted agents for metastatic melanomas. For mucosal melanoma patients especially without known gene mutation, anti-angiogenic therapy combined with chemotherapy or other targeted drugs has shown promising efficacy, either as first- or second-line treatment. In some subset analysis, patients with mucosal melanoma, harboring wild type *BRAF*, might get more clinical and survival benefits than cutaneous ones. Therefore it is rational to further study these therapeutic strategies in the group of mucosal melanoma. Chemotherapy or biochemotherapy only showed limited efficacy without significant survival improvement, but larger sample size study is still required. Herein we presented a comprehensive review of chemotherapy/biochemotherapy and anti-vascular endothelial growth factor (anti-VEGF) therapy in metastatic mucosal melanoma.

Keywords: Mucosal melanoma; chemotherapy; anti-vascular endothelial growth factor therapy (anti-VEGF)

Submitted Apr 30, 2014. Accepted for publication Jul 21, 2014.

doi: 10.3978/j.issn.2304-3865.2014.07.02

View this article at: <http://dx.doi.org/10.3978/j.issn.2304-3865.2014.07.02>

Melanomas are originated from melanocytes, located in skin epidermis, eye, and epithelia of various mucosal sites including nasal cavity/nasopharynx, oropharynx, rectum, anus, and genitourinary tract. Compared to cutaneous melanomas, mucosal melanomas are relatively rare and demonstrate a clear demographic and ethnic disparity. According to a report of the National Cancer Data Base (NCDB), only 1.3% of 82,943 cases with a known primary site occurred at mucosal sites in the year from 1985-1994 (1). Yet a study of 522 consecutive cases in ethnic Chinese reported that 22.6% of cases occurred at mucosal sites (2).

Mucosal melanomas pursue more aggressive natural course and poorer prognosis than other subsets of melanoma (5-year survival rate: 26.8% *vs.* 53.9%) (2). But because of their rarity, there have been few studies of mucosal melanomas. Current available literatures on this

disease are limited and large-scale clinical evidences are absent. As a result, there is no well-established protocol for staging and treatment of mucosal melanomas.

Significant advances in the treatment of metastatic melanoma have been achieved with novel immunotherapeutic agents (3) and targeted agents, which have potential in inhibiting *CKIT* and *BRAF* oncogenic pathways (4,5). And the results of gene detection suggested that mucosal melanoma patients had their unique genetic variation in comparison with cutaneous ones (6). For mucosal melanoma patients with specific gene mutation, targeted agents were also preferred according to the guidelines. Yet for those without known gene mutation, chemotherapy/biochemotherapy and anti-vascular endothelial growth factor (anti-VEGF) therapy remain important treatment options.

Dacarbazine is still the most commonly used cytotoxic

chemotherapeutic agent for cutaneous and noncutaneous metastatic melanomas. Phase III studies showed that dacarbazine was associated with median progression-free survival (PFS) of 1.5 to 1.9 months, and overall survival (OS) of 5.6 to 7.8 months (7-9). However, the majority of dacarbazine-based therapies yielded poor improvements in terms of either PFS or OS, as compared to dacarbazine alone (10). Due to the rarity of mucosal melanomas in the West, most of the patients involved in these studies were cutaneous. Thus systemic chemotherapy for metastatic mucosal melanoma has not been actively pursued. Current available literatures concerning mucosal melanomas were limited to a small retrospective series mainly in Asia. The dacarbazine-based chemotherapy as first-line treatment in noncutaneous metastatic melanomas was analyzed in a multicenter, retrospective study in South Korea (11). From January 1997 to June 2010, 95 patients with metastatic melanoma (7.4% in mucosa of head and neck, 22.1% in the mucosa of the gastrointestinal tract or genitourinary tract), who had received dacarbazine-based chemotherapy (including 54 Dartmouth regimen, 56.8%; dacarbazine, carmustine, and cisplatin, 13.7%; dacarbazine, cisplatin, and tamoxifen, 12.6%; dacarbazine and cytokines 15.8%; dacarbazine alone 1%). After a median follow-up duration of 41 months (range, 2-191 months), median survival time from the start of treatment was 12.1 months [95% confidence interval (CI), 10.9-13.5]. The overall response rate (RR) was 26.3% (95% CI, 17.8-36.4). The multivariate analysis indicated that mucosal melanoma was an independent poor prognostic factor [P=0.001; hazard ratio (HR), 2.988; 95% CI, 1.534-5.821]. The results were comparable with historical series (12). And there was no difference in RR between cutaneous and noncutaneous melanoma (30% *vs.* 20%, respectively; P=0.206). In Caucasian mucosal melanoma patients, dacarbazine-based chemotherapy or biochemotherapy led to similar outcome (objective RR 20% to 36%, median PFS 3 to 10 months) (13,14). In conclusion, though limited efficacy, dacarbazine-based chemotherapy is still a first line treatment option in Asia where mucosal melanomas are more prevalent than in the West.

At present the combination of paclitaxel/carboplatin (PC) has shown efficacy in metastatic melanomas with an objective RR of 20-25% (15-19). Another retrospective study showed that first-line or second-line PC regimen improved objective RR and OS in patients with advanced metastatic cutaneous melanoma (20). In Asia, the efficacy and survival benefit of PC regimen were analyzed in

noncutaneous melanoma in a retrospective study (21). From February 2009 to February 2012, 32 patients with metastatic melanoma were retrospectively analyzed. These patients received intravenous paclitaxel (175 mg/m²) plus intravenous carboplatin [area under the curve 5 (AUC5)] on day 1 of a 21-day cycle as salvage chemotherapy. Of the 32 patients, 10 (31.3%) had mucosal melanoma. The objective RR, PFS, and OS were evaluated. All patients had been pretreated with a median of three systemic chemotherapies. There were no significant differences in response to PC chemotherapy between patients with cutaneous and noncutaneous metastatic melanoma after PC chemotherapy (20% *vs.* 22.7%; P=1.0). The median PFS and OS were 2.53 and 5.2 months for all patients respectively. There was no significant difference in OS between patients with cutaneous and noncutaneous metastatic melanoma (5.2 *vs.* 2.1 months; P=0.75), but a 3-month difference might be considered clinically significant. PC salvage chemotherapy might be a reasonable therapeutic option for heavily pretreated metastatic melanoma patients, including those with noncutaneous melanoma.

Given the modest clinical efficacy of the combination of PC in metastatic melanomas and the development of ABI-007 (Abraxane™, nabpaclitaxel), which is a solvent free, albumin bound formulation of paclitaxel, designed to reduce the Cremophor vehicle associated toxicity of paclitaxel, both suggested examining the anti-tumor of combination of nabpaclitaxel and carboplatin. In a phase II study, the nabpaclitaxel arm demonstrated significantly higher RR and time to progression, as well as a significantly lower incidence of grade 3 or 4 neutropenia, despite the increased dose of paclitaxel being administered in the nabpaclitaxel arm (22).

The weekly combination of nabpaclitaxel and carboplatin appeared to be well tolerated and showed promising clinical activity. The results of randomized phase III trial were also promising and waiting for publication. But the majority of patients involved in these studies were with cutaneous melanoma. The efficacy and survival of nabpaclitaxel plus carboplatin in mucosal melanoma are still required to be further investigated.

Melanoma is a highly angiogenic tumor type, and anti-angiogenesis has been proved to be a potential strategy in melanoma treatment (23). VEGF is highly expressed in melanoma and seems to play an important role in disease progression (10,23,24). Current anti-angiogenic therapies focus on VEGF-VEGF receptor (VEGFR). Among

them, bevacizumab (Avastin), a monoclonal antibody that selectively binds to VEGF and blocks receptor binding, has been most extensively tested in metastatic melanoma patients (19,25-27).

BEAM study was a randomized double blinded Phase II trial, 214 metastatic melanoma patients (73% staging M1c) were randomly assigned in a two-to-one ratio to carboplatin (AUC =5, ≤ 10 cycles) plus paclitaxel (175 mg/m²) and bevacizumab (15 mg/kg, CPB) or placebo (CP) administered intravenously once every 3 weeks (19). The primary end point was PFS. Secondary end points included OS, objective RR and safety. With a median follow-up of 13 months, median PFS was 4.2 months for the CP arm and 5.6 months for the CPB arm (HR, 0.78; P=0.1414). Objective RR were 16.4% and 25.5%, respectively (P=0.1577). Median OS was 8.6 months in the CP arm versus 12.3 months in the CPB arm (HR, 0.67; P=0.0366). A later exploratory analysis showed that OS was 9.2 *vs.* 12.3 months, respectively (HR, 0.79; P=0.1916). Although the later exploratory analysis of OS demonstrated a 21% reduction in hazard of death (HR, 0.79; 95% CI, 0.55-1.13), it was not significantly different. But for the subgroup of mucosal melanoma patients, CPB arm demonstrated a 76% reduction in hazard of death (HR, 0.24; 95% CI, 0.05-1.27). Now a controlled trial of paclitaxel, carboplatin combined with bevacizumab as first line therapy for advanced mucosal melanoma patients, initiated by Chinese investigator, is currently ongoing.

Temozolomide (TMZ) is another optional drug as first-line chemotherapy treatment for melanoma. A multicenter phase II trial of TMZ combined with bevacizumab as first-line regimen for metastatic melanoma demonstrated that better efficacy and survival were achieved in patients, especially those with wild-type *BRAF* (26). Sixty two treat-naïve stage IV patients with *BRAF* mutation status (22 wild-type, 22 mutant, 18 no amplification), were given TMZ 150 mg/m² on days 1-7 orally, and bevacizumab 10 mg/kg every 14 days. The primary endpoint was disease control rate at 12 weeks (DCR12), secondary endpoint was objective RR, PFS, OS and safety. The results showed that DCR12 was 52% and objective RR was 16.1%. The median PFS and OS were respectively 4.2, 9.6 months in the median follow-up of 20.1 months. The OS of *BRAF* wild-type patients was significantly longer than that of the mutants (12.0 *vs.* 9.2 months, P=0.014), suggesting that anti-angiogenic therapy in combination with chemotherapy may be a promising therapy for patients without specific mutations.

In 2010 ASCO meeting, Professor Si reported a phase II

study of a combination of TMZ, bevacizumab and sorafenib for metastatic melanoma patients (28). Thirty seven Chinese metastatic acral melanoma patients were given TMZ 200 mg/m² days 1-5, bevacizumab 5 mg/kg days 1, 15, sorafenib 400 mg bid days 1-28, repeated every 4 weeks. The DCR was 75.7% (28/37), with median PFS 6 months (95% CI, 4.3-7.7), and median OS 12.0 months (95% CI, 9.5-14.5). This study suggested that the efficacy of the combination of TMZ, bevacizumab and small molecule tyrosine kinase inhibitor (TKI) was superior to traditional chemotherapy. However, the mechanism needed to be further studied.

Other small molecule TKI, such as pazopanib and sunitinib, can also inhibit corresponding signaling pathway of VEGFR, platelet-derived growth factor receptor (PDGFR), and so on. Ein-Gal *et al.* reported the latest results of UCI 09-53 study in 2013 (29). It was a single-arm phase II study, which applied pazopanib plus paclitaxel for inoperable stage III or stage IV melanoma patients as first-line treatment. The objective RR was found to be up to 40%, regardless of the status of *BRAF*. The study is expected to continue enrolling 60 more patients in order to further validate the efficacy and survival benefits. Preliminary results of this study suggested that it might be promising to combine multi-targeted small molecule TKI with chemotherapy in metastatic melanoma.

The phosphoinositide 3-kinase (PI3K)-AKT-mTOR pathway is constitutively activated in melanomas, leading to increased cell growth, proliferation, and survival (30,31). In 2013, a study of mammalian target of rapamycin (mTOR) inhibitor combined with anti-angiogenesis drugs for metastatic melanomas was reported (32). A total of 17 treat-naïve patients with inoperable or stage IV melanoma were enrolled and treated intravenously with temsirolimus 25 mg for 1 week and bevacizumab 10 mg/kg every 2 weeks till disease progression. The objective RR was 19%, which was up to 30% in the group with *BRAF* wild-type. At the cut-off date, DCR was 100% in the group with *BRAF* wild-type, and the median PFS was significantly better than patients with mutant. The maximum response duration was up to 35 months. The study suggested that mTOR inhibitor combined with bevacizumab was well tolerated and effective, especially for patients with wild-type *BRAF*.

Endostatin, a representative of endogenous angiogenesis inhibitors, is the 20 kDa internal fragment of the c-terminus of collagen XVIII (33). Genetic evidence has been provided for endostatin, showing that endostatin is an endogenous angiogenesis inhibitor and a tumor suppressor (34).

Endostar is a novel form of recombinant endostatin (rh-ES) purified from *Escherichia coli* with an additional nine-amino acid sequence and forming another histidine tag structure for the convenience of solubility and purification (35). Despite the reasons for the contrasting activity of Endostar in China versus recombinant endostatin in US and Europe have not been clarified, further trials of Endostar in melanoma are worthy of being expected and conducted. A randomized, doubled-blind, placebo-controlled, multicenter phase II study in patients with previously untreated metastatic melanoma were conducted to characterize the efficacy and safety of endostar combined with dacarbazine (36). Patients were randomly assigned in allocation ratio of 1:1 to the placebo plus dacarbazine arm or the endostar plus dacarbazine arm. Patients in both arms received dacarbazine 250 mg/m² by intravenous infusion on days 1-5 of a 21-day treatment cycle for up to maximum of 12 cycles. Endostar (7.5 mg/m²) or placebo was administered intravenously once daily on days 1-14 of a 21-day cycle for up to a maximum of 12 cycles. Response assessments were conducted every 2 cycles. The primary end points were PFS and OS. Secondary end points included RR, DCR and safety. A total of 110 metastatic melanoma patients with wild type *CKIT* and *BRAF* were enrolled, with M1a 39.1%, M1b 39.1%, M1c 29.1%. Median PFS in the Endostar plus dacarbazine arm was 4.5 *vs.* 1.5 months in the placebo plus dacarbazine arm (HR, 0.578; P=0.013). There were also statistically significant improvements in median OS (12.0 *vs.* 8.0 months; HR, 0.522; P=0.005) in favor of the Endostar plus dacarbazine arm. No differences in RR (8.9% in Endostar plus dacarbazine arm versus 3.7% in placebo plus dacarbazine arm, P=0.464) and DCR (53.6% in Endostar plus dacarbazine arm versus 33.3% in placebo plus dacarbazine arm, P=0.051) were observed. The regimen was generally well tolerated and had a manageable toxicity profile. Further subgroup analysis showed that among patients with mucosal melanoma (n=16), combination of endostar and dacarbazine led to 93% (HR, 0.07; 95% CI, 0.009-0.632) reduction in risk of death. However, risk of death (HR, 1.02; 95% CI, 0.305-3.434) and progression (HR, 1.15; 95% CI, 0.394-3.484) were both increased in patients with melanoma on skin with chronic sun-induced damage in Endostar plus dacarbazine arm (n=17).

In summary, chemotherapy or biochemotherapy have shown limited efficacy in mucosal melanoma patients as in cutaneous ones, but further investigation in larger sample size study is needed. Anti-angiogenic therapy combined with chemotherapy or other targeted drugs, either as first-

line or second-line, have shown their efficacy. Nevertheless, given only few mucosal patients were enrolled in these studies owing to its rarity, in subset analysis of some studies, mucosal melanoma patients and *BRAF* wild type patient might get more clinical and survival benefits than cutaneous ones. It is worthy to conduct further study in the group of mucosal melanoma patients.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Cui C, Tang B, Guo J. Chemotherapy, biochemotherapy and anti-VEGF therapy in metastatic mucosal melanoma. *Chin Clin Oncol* 2014;3(3):36. doi: 10.3978/j.issn.2304-3865.2014.07.02