Review Article

Treatment of *KIT*-mutated metastatic mucosal melanoma

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Abstract: Mucosal melanoma is a rare, aggressive histologic subtype of malignant melanoma, and prognosis for patients with metastatic mucosal melanoma is very poor. In general, conventional cytotoxic agents alone or in combination with immunologic drugs have limited clinical benefit. Advances in molecular analytic techniques have helped researchers discover genetic aberrations in KIT, a receptor tyrosine kinase, in nearly 40% of patients with mucosal melanoma. Preclinical studies have demonstrated that hot-spot mutations, mostly substitutions in exons 11 and 13, result in constitutive activation of KIT and its downstream signal transduction pathways, such as the MEK/ERK, PI3K/AKT and JAK/STAT pathways. KIT inhibitors, most notably imatinib, have shown promising clinical activity in *KIT*-mutant advanced melanoma, including mucosal melanoma, with clinical response rates exceeding 35% in patients with hot-spot mutations in exon 11 or 13 and/or a high mutant/wild-type allelic ratio. However, the duration of disease control is rather short in general, and treatment with KIT inhibitors as single agents is not optimal. Well-designed mechanistic studies aimed at assessing molecular differences between various *KIT* mutations or other aberrations and mechanisms of resistance are urgently needed to improve KIT-targeting therapy for melanoma. In addition, with availability of checkpoint inhibitors, such as anti-CTLA4 and/or anti-PD-1 antibodies, immunotherapies using those inhibitors alone or in combinations of such immunotherapies with KIT inhibitors may lead to more effective therapeutic regimens. This review discusses the rationale for KIT inhibitor therapy in patients with metastatic mucosal melanoma and the findings of preclinical and clinical studies of KIT inhibitors in this patient population.

Keywords: Dasatinib; imatinib; *KIT*; melanoma; mutation

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Introduction

Melanoma results from malignant transformation of normal melanocytes and can therefore develop in any organ in which melanocytes are present. Since the vast majority of melanocytes are distributed throughout the epidermal layer of the skin, most malignant melanomas arise from the skin. However, a small subset of melanomas originate from noncutaneous tissues and organs, such as the mucosal surface of the oral cavity; nasal sinus; vagina, urethra and rectum; choroid and even visceral organs. Melanoma arising from the mucosal surface accounts for <2% of all melanomas among the white population, whereas it is the second most common melanoma subtype in Asians after acral lentiginous melanoma (1-5). In Black and Asian populations, nearly 12% and 22% of melanomas, respectively, are of mucosal origin (3,4). The reasons for such differences in the prevalence of distinct histologic subtypes of melanoma among various populations are not well understood. Because of the overall low prevalence of mucosal and subungual melanomas in the general population, research on their biology and on systemic treatment has been substantially more limited than research on typical cutaneous melanomas.

For patients with mucosal melanoma, prognosis is poor, and the median survival is short. A recent population-

based analysis revealed that the 5-year relative survival rate was significantly lower in patients with mucosal melanoma (34%; 95% confidence interval 31.9-36.1) than in those with cutaneous (89%; 95% confidence interval 88.7-89.2) or ocular (78.4%; 95% confidence interval 76.9-79.8) melanoma (6). For patients with anorectal mucosal melanoma, outcomes are particularly bad: the median survival duration ranges from 8 to 23 months, and the 5-year overall survival rate is between 3% and 22% (7-9).

Mucosal melanoma is generally considered an aggressive disease. In addition, its poor prognosis may be explained by late detection of primary disease in many patients and the difficulty of excising the primary lesions with an adequate margin due to their covert locations. In patients with recurrent, unresectable or distant metastatic mucosal melanoma, median overall survival is <10 months (7,10-12).

Traditional systemic therapeutic options have yielded disappointing results. In a series of retrospective studies assessing the clinical efficacy of biochemotherapy, which includes dacarbazine and interleukin-2-based combination regimens, in patients with advanced mucosal melanoma, clinical response rates were between 36% and 47%, and median time to disease progression was 3-10 months (13-15). These data suggest that the responsiveness of mucosal melanoma to biochemotherapy may be similar to that of cutaneous melanoma despite the seemingly worse prognosis in patients with mucosal melanoma. However, the durable clinical responses are rare, and most patients will die of the disease within a year. In fact, the clinical efficacies of cytotoxic chemotherapeutic drugs have not been well studied in prospective clinical trial setting due to the rarity of this disease. Until recently, the majority of the literature on mucosal melanoma consisted of case reports of a few patients who were treated with systemic chemotherapy. Those case reports frequently lacked details of treatment regimens and systematic evaluation of responses, and the activity of cytotoxic drugs appeared to be modest at best.

Fortunately, in the last decade, advances in melanoma molecular biology have increased our understanding of how different kinds of melanoma respond to systemic therapy. As we identify different genetic mutations in various components of the signaling pathways that are critical for melanoma cell proliferation and survival, we are also identifying genetic aberrations that can potentially serve as therapeutic targets. In particular, the recent discovery of frequent somatic *KIT* mutations in patients with mucosal melanoma has shaped new strategies for therapeutic intervention in cases of advanced disease.

KIT signaling in melanoma

The cellular gene c-*KIT*, which is homologous to the transforming gene v-*KIT* from a feline sarcoma retrovirus, encodes the mast/stem cell factor (SCF) receptor, a type III receptor tyrosine kinase. Binding of the membrane-bound form of the SCF to KIT kinase, also known as CD117, results in sustained KIT activation, which leads to activation of a number of downstream signal transduction pathways, including the mitogen-activated protein kinase (MAPK) and PI3K/AKT pathways (16-19). A functional KIT/SCF axis plays an essential role in proliferation, migration and survival of melanocytes and their precursors (17,20,21) and allows melanoblasts to migrate to the epidermis and hair follicles from the neural crest (22,23). Mutations that inactivate KIT during embryonic development can cause a loss of function in melanocytes and depigmentation of skin and hair, as in human piebaldism (24).

KIT is frequently expressed in malignant melanoma to various degrees. According to immunohistochemical staining analyses, KIT is expressed in 23-67% of melanoma specimens, depending on the definition of positive expression in terms of the frequency of stained melanoma cells (25,26). Satzger and colleagues found that 40 (91%) of 44 mucosal melanoma tumor specimens had KIT staining in at least 10% of melanoma cells (27). Interestingly, however, KIT is downregulated as melanomas progress to advanced stages (26,28,29). These findings indicate that the role of the KIT signaling pathway in progression of melanoma is not straightforward and suggest that the expression level of KIT by itself may not be a good predictive marker for KIT-targeting therapy.

The complexities of KIT signaling and their potential importance for treatment strategies became more apparent when Curtin and colleagues demonstrated the presence of genetic KIT aberrations in small subgroups of melanomas (30). Using a comparative genomic hybridization analysis of the DNA content of 102 primary melanoma specimens, those researchers found *KIT* mutations and/or increased copy numbers in 36% of acral lentiginous melanoma specimens and 39% of mucosal melanoma specimens, with 11% and 21% mutation rates for acral lentiginous melanoma and mucosal melanoma specimens, respectively. Subsequent studies reported *KIT* mutations in 12-23% and 16-20% of acral lentiginous and mucosal melanoma specimens, respectively (31-33). The melanoma specimens harboring a *KIT* mutation did not have BRAF mutations, which are the most common mutations in melanoma arising from nonchronically sun-damaged skin.

KIT mutations in melanomas are usually substitutions of a single amino acid in exon 11, 13, or 17, in contrast to *KIT* mutations in gastrointestinal stromal tumors, in which the most common *KIT* mutations are deletions or insertions in exon 11 (18). The majority of *KIT* mutations in melanoma affect the juxtamembrane domain of the KIT protein and lead to constitutive activation of KIT independently of ligand binding (34).

Mutated *KIT* kinases regulate both the MAPK and the PI3K/AKT pathways (30,35). Alexeev and colleagues showed *in vitro* and *in vivo* that melanocytes with the *KIT* mutation *D814Y* were less differentiated, had reduced cell cycle times and migrated at a greater rate than melanocytes with wild-type *KIT* (36). As we discuss in the next section, these characteristics may provide new targets for combinatorial therapies.

Preclinical studies of imatinib

Monsel and colleagues demonstrated the tumorigenic potential of a *KIT* mutation, *Δ576P*, by subjecting mouse melanocytes transfected with induced mutant KIT to hypoxia or coexpression of hypoxia-inducible factor (HIF)-1α (37). In that *in vitro*. model, exposure of the transfected melanocytes to hypoxia or coexpression of HIF-1α was necessary to induce melanoma progression and activate the MAPK pathway in addition to the activation of the PI3K pathway induced by transfection of the *KIT* mutation. Proliferation of transformed melanocytes and activation of the MAPK pathway were inhibited by treatment with imatinib, suggesting that mutant *KIT* plays an oncogenic role in melanoma.

In another study, Bougherara and colleagues tracked *V560G* and *D816V* mutant *KIT* proteins intracellularly by tagging them with green fluorescent protein (38). The mutant *KIT* proteins were unable to reach the cell membrane with high mannose glycosylation and were trapped intracellularly. Treatment with imatinib reversed the abnormal KIT phosphorylation and glycosylation pattern and restored protein localization in the cell membrane in V560G *KIT* mutant cells but not in D816V *KIT* mutant cells, which are known to be resistant to imatinib.

Jiang and colleagues showed that KIT protein with a mutation and/or amplification can behave as an oncogene in mucosal melanoma. The researchers tested the inhibitory effect of imatinib in three metastatic mucosal melanoma cell lines with a low passage number (39). Amplification of the exon 11 *V559A KIT* mutation in cell line M6 was associated with overexpression of KIT phosphorylated KIT. Imatinib induced apoptosis and inhibited the activated KIT, MAPK and PI3K/AKT pathways in M6 cells. In contrast, in the other two cell lines, both of which had the wild-type KIT allele, KIT copy number was not increased and cell growth was not affected by imatinib treatment.

Clinical studies of imatinib

After imatinib therapy was shown to be effective in patients with chronic myelogenous leukemia, imatinib was investigated in patients with metastatic melanoma in the mid-2000's. Expectations were high because of the high prevalence of KIT overexpression and high expression of platelet-derived growth factor receptor in melanoma. However, the results of three phase II studies of unselected, metastatic melanoma patients were disappointing (40-42). In a phase II study by Kim and colleagues, 21 melanoma patients with high expression levels of total KIT, platelet-derived growth factor receptor alpha and/or beta, were treated with 400 mg of imatinib twice a day (42). Although the only patient who had a durable clinical response of more than 12 months had the highest intensity and percentage of KIT expression without a *KIT* mutation, no other patients had a clinical response, and the level of KIT expression did not predict overall clinical benefit. In the two other phase II studies of imatinib, none of 42 patients with advanced melanoma had a clinical response (40,41).

Interest in imatinib treatment for advanced melanoma in unselected patients initially subsided after those disappointing findings. However, the subsequent preclinical finding that KIT mutations are frequent in acral lentiginous and mucosal melanomas (30) rekindled enthusiasm for evaluation of KIT inhibitors in patients with metastatic melanoma, especially in those with a *KIT* aberration. Carvajal and colleagues conducted an open-label single-arm phase II trial of imatinib in patients with metastatic melanoma harboring *KIT* mutations or amplification (32). The patients were treated with 400 mg of imatinib twice a day. Four of 25 evaluable patients had an objective clinical response lasting more than a year, and two of the four responders had a complete response. Five patients had stable disease for at least 3 months, and two other patients responded for the first 6 weeks. The type of *KIT* mutation and the ratio of mutant to wild-type *KIT* alleles were predictive of clinical response to imatinib. Melanoma patients with a *KIT* mutation affecting a recurrent hot spot, such as the *L576* or *K642E* mutation, had better clinical outcomes than those without a hotspot mutation, whereas those with a *V654A* or *D820Y* mutation, which are known

to be associated with imatinib resistance in gastrointestinal stromal tumors, had early disease progression. In addition, melanoma patients with a mutant/wild-type allelic ratio of >1 had a higher response rate. Although the overall response rate for the total 28 patients was 16%, with a median time to progression of 12 weeks, the response rate was 40% in patients with mutations affecting the recurrent hot spots and/or with a mutant/wild-type allelic ratio of >1. These findings indicate that an accurate identification of *KIT* mutation is both practical and necessary to select patients who may benefit from imatinib treatment.

In another phase II study of imatinib, Hodi and colleagues reported an overall response rate of 29% and a confirmed response rate of 21% (according to the Response Evaluation Criteria in Solid Tumors) among 25 patients with advanced melanoma harboring a *KIT* amplification and/or mutation: median time to disease progression was 3.7 months (33). The response rate was notably higher in patients with a KIT mutation than in patients with KIT amplification only (55% versus 0%), although median time to progression did not differ significantly between the two subgroups. Interestingly, all four patients who also had a synchronous NRAS mutation had early disease progression, suggesting a possible NRAS-associated resistance mechanism.

A phase II study of imatinib in patients with metastatic melanoma containing a *KIT* mutation or amplification was also conducted in China by Guo and colleagues (43). Forty-three patients were treated initially with 400 mg of imatinib once a day, with an option to increase to 800 mg a day for patients whose disease progressed while they were receiving the 400 mg daily dose. Ten patients (23%) had a partial response, 9 of whom had a KIT mutation in exon 11 or 13; 13 had stable disease; and 20 patients had early disease progression. Among 26 patients with only an exon 11 or 13 mutation, 9 (35%) had a partial response. Median duration of progression-free survival was 3.5 months. At the 24-month follow-up, the difference in median duration of progression-free survival between responders and non-responders was significant (9 versus 1.5 months, P<0.001), as was the difference in median duration of overall survival (15 versus 9 months, P=0.036).

Studies of other KIT inhibitors

Dasatinib is a potent inhibitor of KIT kinase, in addition to being an inhibitor of platelet-derived growth factor receptor beta; ephrin type A receptor 2; and Src kinases c-Src, c-Yes, Lck and Fyn. In a preclinical study conducted by Woodman and colleagues, dasatinib reduced the viability of WM3211 melanoma cells carrying an L576P *KIT* mutation more than other clinically available KIT inhibitors, including imatinib, nilotinib and sorafenib (44). The researchers also reported a case of significant tumor reduction in a dasatinib-treated patient with imatinib-resistant melanoma containing an L576P mutation in *KIT* (44). These findings suggest a possible superior clinical benefit of dasatinib treatment over imatinib treatment in patients with certain KIT mutations.

Kluger and colleagues conducted a phase II study of dasatinib in chemo-naïve patients with metastatic melanoma (45). That study's target population was not limited to patients with *KIT* aberrations. Among 36 evaluable patients, 2 had confirmed durable clinical responses lasting more than 24 weeks, and 3 others had minor responses. The median duration of progression-free survival was only 8 weeks. Of the two patients with mutations in *KIT*, a patient with an exon 13 mutation had a partial response, and a patient with an exon 11 mutation had early progression. A number of phase II studies are currently investigating the clinical efficacy of dasatinib in patients with metastatic melanoma with *KIT* mutations.

Several phase II studies have investigated the efficacies of other KIT inhibitors in treatment of melanoma. In a study of sunitinib in patients with advanced melanoma with *KIT* mutations, amplification and/or overexpression, three of four patients with a *KIT* mutation had clinical responses (two confirmed, including one complete response lasting for 15 months) (46). In contrast, only one of six patients with *KIT* amplification and/or overexpression and no *KIT* mutation had an unconfirmed response. In another small study, clinical responses were observed with nilotinib treatment only in melanoma patients with mutations in KIT. Two of three patients with *KIT* mutations (all in exon 11) had partial responses, whereas none of six patients with *KIT* amplification only had a response (47). These data suggest that newer-generation KIT inhibitors can be useful in treating patients with *KIT*-mutant advanced melanoma. Because the numbers of patients in the two studies were very small, the clinical activities of these agents need to be confirmed in larger studies. Currently, a phase III study is investigating progression-free survival of patients receiving masitinib (a newer-generation KIT inhibitor) or dacarbazine (NCT01280565) and a number of phase II studies is evaluating the clinical efficacy of nilotinib and sunitinib.

Conclusions

Despite the disappointing results of phase II studies of

imatinib in unselected patients, there is renewed interest in using KIT inhibitors to treat advanced mucosal melanoma in patients with KIT aberrations, especially KIT mutations. The response rate to imatinib in such patients can exceed 35%, with durable responses in some of the patients. However, the median duration of progression-free survival is still relatively short even in these patients, and imatinib alone is not likely to offer a significant clinical benefit to patients with *KIT*-mutant advanced melanoma. Despite the encouraging results of the small phase II studies, newer-generation KIT inhibitors, such as dasatinib, nilotinib and masitinib, are not likely to be optimal therapy options as single agents. To enhance the effectiveness of KIT inhibitors, it is crucial to understand the biological significance of each *KIT* mutation and identify specific *KIT* mutations characterizing disease that is likely to respond to a KIT inhibitor. In addition, it is essential to understand the mechanisms of resistance to KIT inhibitors and develop strategies for rationally combining those agents with drugs targeting other escape signal pathways. The effects of KIT inhibitors at the molecular level and correlation of those effects with clinical benefit will need to be assessed in well-designed mechanistic studies. Furthermore, evaluation of the checkpoint inhibitors anti-cytotoxic T lymphocyte antigen 4 antibodies and anti-programmed cell death protein 1 antibodies will be essential to understanding the immunologic aspects of therapy for advanced mucosal melanoma, with the goal of combining those agents with KIT inhibitors in an optimal way.

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