

V559A and N822I double KIT mutant melanoma with predictable response to imatinib?

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Dear Editor,

Since the initial report of KIT mutations in subtypes of melanoma, several reports of KIT-targeted therapies have been published (Carvajal et al., 2009; Hodi et al., 2008; Lutzky et al., 2008). Activating KIT mutations have been documented in a variety of neoplastic diseases including, in addition to melanoma, mastocytosis, acute myeloid leukemia, seminoma and gastrointestinal stromal tumors (Went et al., 2004). Herein, we report a case of a KIT double mutation in anorectal melanoma not previously described in melanoma, but with a response to imatinib mesylate that might have been expected given the knowledge from other cancers.

The patient is an 87-year-old woman who developed constipation and a palpable rectal mass in the summer of 2009. Biopsy of the mass demonstrated an ulcerated melanoma invading the submucosa and muscle to a depth of approximately 11 mm with angiolymphatic invasion. Computerized tomography (CT) scans of the chest, abdomen and pelvis revealed metastatic disease in the pelvis, inguinal region and lungs. Substantial growth of the disease was documented on serial CT scans 3 months apart with the largest lung nodule increasing 44% (14 to 25 mm). The patient declined treatment with systemic chemotherapy and was not a candidate for the available clinical trials but she did express an interest in some form of therapy. Her melanoma was assessed for KIT mutational status. A double mutation was identified, comprising the exon 11 mutation V559A and the exon 17 mutation N822I. The patient subsequently initiated treatment with imatinib 400 mg daily in November 2009. Surveillance CT scans in February 2010 revealed that most metastatic lesions were stable to minimally decreased, including a right

inguinal lymph node (16 to 14 mm), a right upper lobe lung nodule (20 to 18 mm), a right lower lobe lung nodule (25 to 23 mm) and a right ischioanal lesion (19 to 15 mm). There was complete disappearance of multiple subcentimetre lung nodules; however, there was also some growth of other lung nodules, the largest of which increased from 25 to 28 mm. The findings were consistent with a mixed response, although in accordance with RECIST criteria, the patient's response would best be classified as stable disease (~7% decrease in sum of diameters of target lesions). No repeat biopsy was attempted. The dose of imatinib was titrated from 400 to 800 mg with the aim of overcoming any possible resistance to therapy and improving the patient's response. Unfortunately, the patient developed significant fatigue, dyspnea on exertion and lower extremity edema. Treatment was held, and after recovery from these acute symptoms, attempts were made to reinstate imatinib at the lower dose of 400 mg. The patient was not able to tolerate resumption of therapy, and she experienced further clinical decline and progression of disease; ultimately, she succumbed to her metastatic melanoma in August, 2010.

Efforts to define the genetic landscape of melanomas have led to the recognition that alterations in the KIT gene constitute the predominant mutation in melanomas arising from chronic sun-damaged skin and acral and mucosal anatomical locations (Curtin et al., 2005, 2006). KIT mutations in melanoma are now only beginning to be catalogued. The experience with KIT mutations in GISTs, however, is much more extensive, and this experience provides a conceptual framework for understanding the pathobiology of and therapeutic approaches to treating neoplastic diseases driven by KIT mutations (Corless and Heinrich, 2008). KIT mutations underlie approximately 85% of GISTs; and the vast majority (~70%) occurs within exon 11 corresponding to the autoinhibitory juxtamembrane domain. KIT exon 9 lies within the extracellular ligand-binding region, and mutations within this exon account for ~10 to 15% of KIT mutations in GIST. KIT mutations within the kinase domain (either exon 13 or exon 17) occur with much less frequency (<5%). To date, molecular analyses have identified approximately two dozen unique KIT mutations in melanoma (Woodman and Davies, 2010). Similar to GIST, the majority of KIT mutations in melanoma occur within the juxtamembrane autoinhibitory region encoded by exon 11. Unique to melanoma, though, the

L576P mutation represents the most frequent site of genetic alteration, accounting for one-third of all KIT mutations in melanoma. Mutations within the kinase domains, exons 13, 17 or 18 represent approximately one-third of mutations. And, to date, in melanoma, one case of a KIT mutation in the extracellular domain, exon 9, has been reported (Carvajal et al., 2009).

The recognition of KIT-mutated cancers has afforded the opportunity for targeted therapeutic interventions, specifically the implementation of tyrosine kinase inhibitors. Overall, between 75 and 90% of patients with GISTs who are treated with the tyrosine kinase inhibitor, imatinib, experience a clinical benefit (Heinrich et al., 2006). An individual patient's sensitivity to imatinib, though, in large measure depends upon the specific KIT mutation that they harbor. Exon 11 KIT mutations demonstrate the highest response rate to imatinib. Exon 9 mutations exhibit some resistance to imatinib; however, this resistance can be overcome by increasing the dose of imatinib (Debiec-Rychter et al., 2006; Gramza et al., 2009). KIT mutations within the exon 17 kinase domain show variable resistance. In GIST, as well as with seminoma, acute myeloid leukemia and mastocytosis, primary resistance to imatinib has been observed with the KIT exon 17 D816V, D816G and D820E/Y KIT mutations (Debiec-Rychter et al., 2005; Heinrich et al., 2003). In contrast, partial imatinib responses have been reported in patients with KIT exon 17 N822K, N822H or Y823D mutations (Debiec-Rychter et al., 2006; Heinrich et al., 2003, 2006; Kemmer et al., 2004). The experience with treating KIT-mutated melanomas with imatinib and tyrosine kinase inhibitors remains in the early phases. Thus far, though, reports of responsiveness in melanoma generally accord with the imatinib responses observed in other KIT-mutated neoplasms (Satzger et al., 2010).

Adding to the complexity of effective therapeutics, double KIT mutations have been documented in both GIST and melanoma. With GIST, both primary and secondary (post-imatinib therapy) double KIT mutations have been reported. Primary double KIT mutations, though, are rare in GIST. Heinrich et al. (2006) in a series of greater than 1000 patients with GIST reported a single primary double KIT mutation, K642E (exon 13) with N822K (exon 17). Four primary double mutations in melanoma have thus far been identified: N566D (exon 11)/K642E (exon 13) (Curtin et al., 2006), N463S (exon 9)/N655S (exon 13) (Carvajal and Al, 2009), K642E (exon 13)/N822I (exon 17) (Torres-Cabala et al., 2009) and V559A (exon 11)/N822I (exon 17) (this report). Secondary KIT mutations, after imatinib use, are much more frequent, with secondary KIT mutations in exons 13, 14 or 17 accruing to precedent exon 9 or 11 mutations (Antonescu et al., 2005; Chen et al., 2004; Corless and Heinrich, 2008; Debiec-Rychter et al., 2005; Grimpen et al., 2005; Heinrich et al., 2006; Tamborini et al., 2004; Wardelmann et al., 2005, 2006). To our knowledge, no secondary KIT mutations have been

reported in patients with melanoma after treatment with imatinib. But this is most probably attributable to the only recent therapeutic utilization of imatinib to treat melanoma.

With GIST, KIT double mutations respond variably to imatinib therapy. Frequently, KIT mutations that individually respond to imatinib may demonstrate resistance when they occur in tandem (Heinrich et al., 2006). In accordance with the observed responsiveness of single KIT mutations either at exon 11 or at exon 17 N822 position in GIST, the current report suggests that in melanoma, the exon 11 V559A + exon17 N822I double mutation remains to some degree imatinib sensitive, but the benefit is likely marginal. Resistance to imatinib has led to the assessment of alternative tyrosine kinase inhibitors for KIT-mutated cancers. For example, the tyrosine kinase inhibitors PKC412, sunitinib and nilotinib have all been observed to demonstrate selective activity against a variety of specific non-exon 11 imatinib-resistant KIT mutations (Chan et al., 2009; Growney et al., 2005), and utilization of these alternative tyrosine kinase inhibitors might appropriately be considered as first-line choices for patients when non-exon 11 mutations are identified.

The treatment options for metastatic melanoma remain limited. For patients with metastatic disease of the mucosal, anorectal or acral lentiginous type, KIT mutational analysis may reveal additional therapeutic opportunities. Continued progress will depend on the careful discovery and documentation of single and multiple KIT mutations in melanoma and their unique patterns of responsiveness to tyrosine kinase inhibition. The utility of such a strategy has previously been demonstrated in the treatment of other malignancies driven by tyrosine kinase inhibitor-sensitive mutations (Redaelli et al., 2009). The currently existing data on KIT mutations in melanoma as well as in other cancers, such as GIST, provide a relative predictability of response to tyrosine kinase inhibition that we believe should be used to guide future clinical trial designs and to personalize treatment regimens off protocol. The current report, demonstrating at best stabilization of exon 11 V559A + exon17 N822I double-mutated melanoma with imatinib therapy, contributes to this end.

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