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Acral Melanoma: Clinical, Biologic and Molecular Genetic Characteristics

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1. Introduction

Acral melanomas (AM) is a distinct subtype of melanoma affecting the palms, soles and nail apparatuses. It is mostly identical to acral lentiginous melanoma according to Clark's classification (Clark et al., 1986), but it may also include nodular melanoma and superficial spreading melanoma that developed on glabrous skin and nail apparatus (Curtin et al., 2005). While AM is the least frequent subtype of cutaneous melanoma overall in Caucasians, it is the most prevalent type of melanoma in people of color. Prognosis of AM is generally poor, which may be in part due to delay in diagnosis (Bradford et al., 2009).

The distinct histological and phenotypic characteristics suggest that AM might differ biologically from other types of cutaneous melanomas. Recent molecular genetic studies characterized AM as a unique type of melanoma showing higher frequency of chromosomal aberrations, especially focused amplifications of particular chromosome regions (Bastian et al., 2000; Curtin et al., 2005). Furthermore, recent discovery of frequent mutation or amplification of *KIT* gene in AM and mucosal melanoma has led to the molecular targeted therapy by approved drugs targeting KIT, such as imatinib, for advanced cases (Curtin et al., 2006). This would represent a first decisive step toward the individualized treatment of melanoma (Garrido &Bastian, 2010)

2. Epidemiology

Although AM accounts for 5% of all melanomas in the United States (Markovic et al., 2007)(Table 1), it is a predominant form of melanoma in individuals with darker skin (ie, Blacks, Asians and Hispanics) (Cormier et al., 2006). The proportion of AM among all melanoma subtypes is greatest in blacks followed by Asians/Pacific islanders and Hispanic whites (Bradford et al., 2009). The nation-wide survey in Japan shows that AM accounts for 41% of all melanomas (Ishihara et al., 2008)(Table 1), the rate being almost the same in Chinese (Chi et al., 2011). However, the absolute incidence of AM in darker-skinned individuals is similar to that in whites (Stevens et al., 1990; Bradford et al., 2009), who have a much higher incidence of melanoma overall due to the strong susceptibility to sunlight (Cormier et al., 2006). Thus, carcinogens other than ultraviolet light (UVL) equally affecting all ethnic groups or endogenous mutagenesis may play a role in the development of AM. Trauma may have a role in AM development, since 13% to 25% of patients with AM reported prelesional trauma, such as puncture wounds, friction blisters and stone bruises (Coleman et al., 1980; Phan et al.,

2006). The mean age at diagnosis of AM is 62.8 years, compared with 58.5 years for cutaneous melanoma overall. Incidence of AM significantly increases with each year of advancing age, which is seen across the different racial groups (Bradford et al., 2009).

Type of Melanoma[1]	United States (Markovic et al., 2007)	Japan (Ishihara et al., 2008)
SSM	70%	17%
NM	5%	20%
LMM	4~15%	7%
ALM	5%	41%
Unknown	5~11%	13%

[1]SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma

Table 1. Comparison of melanoma types between the United States and Japan.

Although acral volar skin and nail beds constitutes only a few % of skin surface, the fact that nearly half of cutaneous melanomas arise on these anatomical sites in darker-skinned individuals indicates that these are predilection sites of melanomas not causally related to UVL exposure. The melanocyte density in palmoplantar skin is five times lower than that found in nonpalmoplantar sites. Furthermore, the growth and differentiation of palmoplantar melanocytes are suppressed by dickkopf 1 (DKK1) secreted from dermal fibroblasts through the down-regulation of microphthalmia-associated transcription factor (MITF) and beta-catenin (Yamaguchi et al., 2004). The reason why such growth-suppressed melanocytes in palmoplantar skin are more susceptible to melanoma development is currently unknown.

3. Clinical features

Clinically, AMs on palms and soles begin with irregularly pigmented macular lesions. The soles of the feet are most commonly involved. Morphological characteristics of early AM lesions include variable shades of brown from tan to black color, irregular and asymmetric shape often accompanied by notching at the periphery, and over 7mm in diameter (Saida, 1989) (Fig. 1a).

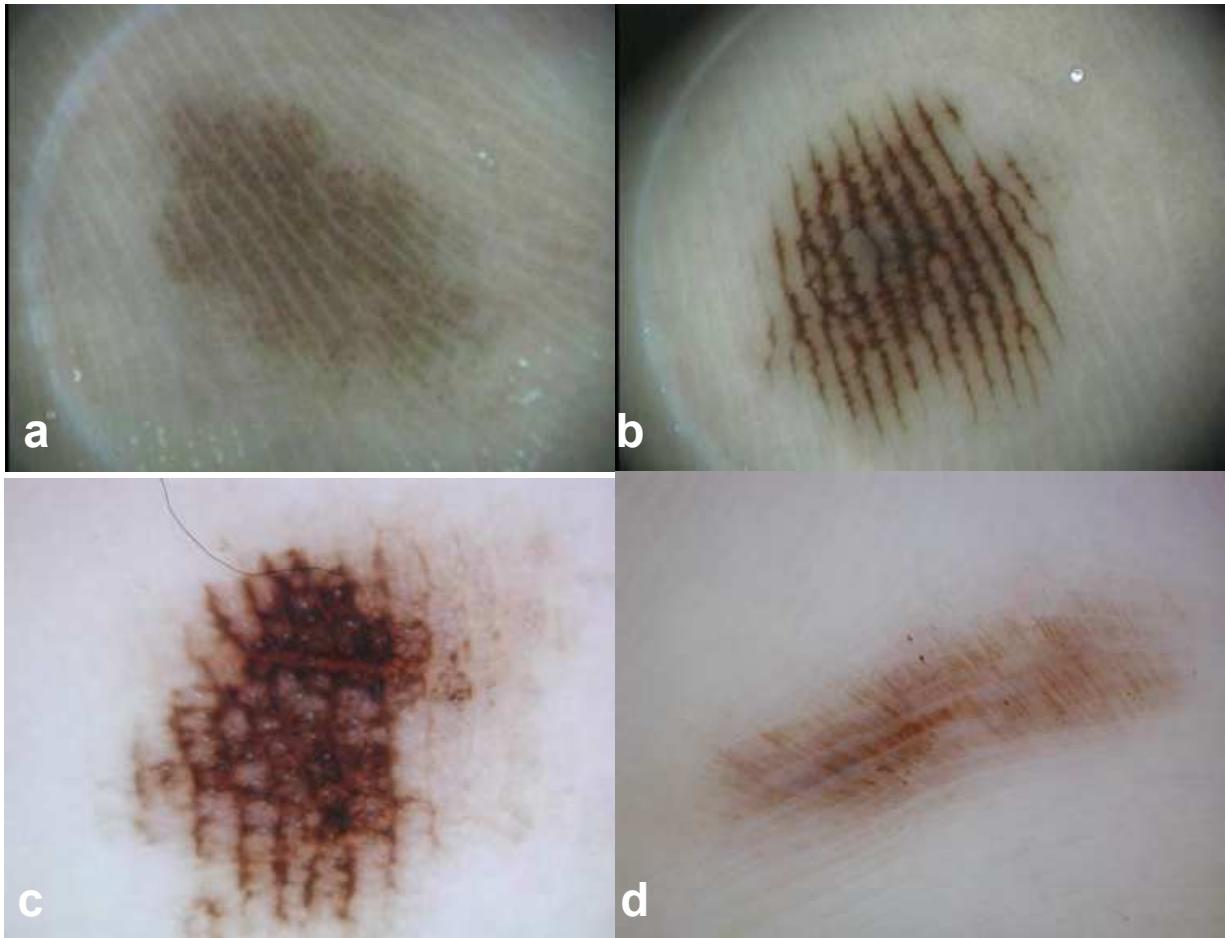Fig. 1. Clinical pictures of radial growth phase (a) and tumorgenic vertical growth phase (b) of AM.

Fig. 2. Dermoscopy of early AM (a) and melanocytic nevus on acral volar skin (b, c, and d).
a, palarelle ridge pattern; b, pararelle furrow pattern; c, lattice-like pattern; d, fibrillar pattern.

Dermoscopic observations of these early lesions show band-like pigmentation on ridges of the skin markings, designated as a "parallel ridge pattern"(Fig. 2a). This is in sharp contrast to the dermoscopic patterns in acral melanocytic nevi, which show parallel linear pigmentation along the sulci of the skin markings, designated as a "parallel furrow pattern"(Fig. 2b) and its variants "lattice-like pattern" (Fig. 2c) and "fibrillar pattern"(Fig. 2d) (Oguchi et al., 1998; Miyazaki et al., 2005). The sensitivity and specificity of the parallel ridge pattern in diagnosing early AM is 86% and 99%, respectively (Saida et al., 2004). A simple three-step algorism effectively discriminating early AM from acral melanocytic nevi has been proposed (Fig. 3) (Saida et al., 2011). This algorism classifies acquired pigmented lesions on acral volar skin by the dermoscopic findings and the maximal diameter, and recommends three management options including "no need to follow-up", "periodic follow-up", and "excision of the lesion for histopathological evaluation".

In contrast to the palmoplantar melanoma, nail apparatus melanoma more often affects fingers than the toes. The digits most commonly affected are the thumb followed by the great toe. If the AM is situated in the nail matrix, a longitudinal pigmented band of the nail plate is the earliest sign (Fig. 4a). As melanocytic nevi of the nail matrix also typically accompany longitudinal melanonychia, identifying early nail matrix melanoma is challenging. Dermoscopy again provides useful information for this differentiation. The suspicious dermoscopic features of early nail matrix melanoma are irregular lines on a

brown background, pigmentation of the cuticle (micro-Hutchingson's sign), a wide pigmented band, and triangular pigmentation on the nail plate (Fig. 4b) (Koga et al., 2011).
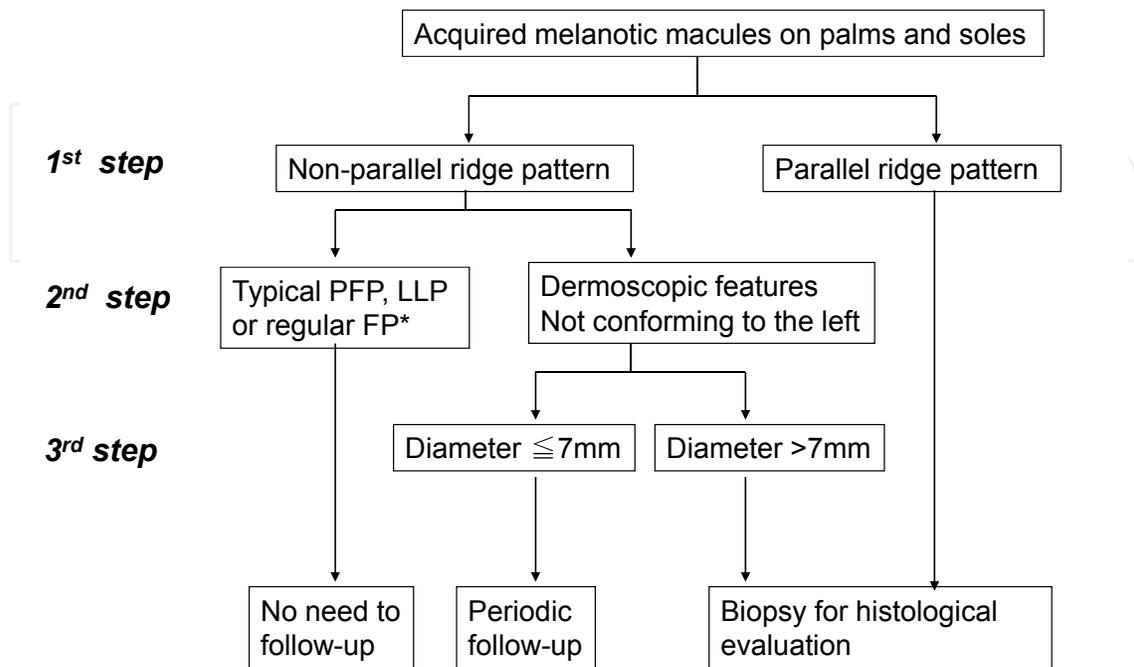
*PFP: parallel furrow pattern, LLP: lattice-like pattern, FP: fibrillar pattern

Fig. 3. Three-step algorism for the management of acquired pigmented lesions on plams and soles (Adapted from Saida et al., 2011, with permision).
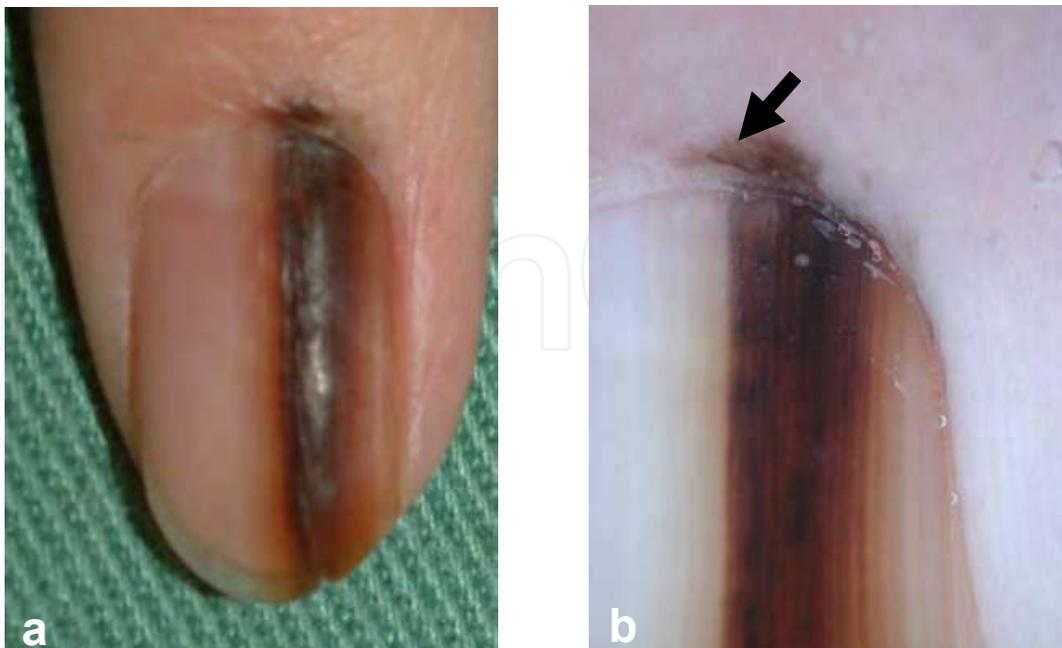

Fig. 4. Clinical (a) and dermoscopic (b) photographs of early nail matrix melanoma. The arrow indicates micro-Hutchingson's sign.

The tumorigenic vertical growth phase of palmoplantar melanoma is characterized by the development of a nodule often associated with ulceration (Fig. 1b). The development of a subungal tumor and the destruction of the nail plate are observed in the vertical growth phase of nail apparatus melanoma.

4. Histopathology

Histopathology of the earliest lesions of palmoplantar melanoma shows proliferation of solitary arranged slightly atypical melanocytes mainly detected in the crista profunda intermedia, the epidermal rete ridge underlying the ridges of the skin markings (Ishihara et al., 2006). In early nail apparatus melanoma, slightly atypical melanocytes proliferate in the epidermis of nail matrix. Eventually, large atypical melanocytes, frequently with prominent pigmented dendrites, proliferate as single cells in the basal layer of the hyperplastic epidermis while some tumor cells can be found in the upper layer of the epidermis. Nesting of melanocytes is not prominent, and tends to occur at the tips of the rete ridges. Brisk lichenoid lymphocytic infiltrate that may obscure the dermal-epidermal junction is common. In the vertical growth phase, atypical tumor cells are often spindle-shaped. Desmoplastic change is not uncommon (Clark et al., 1986).

5. Molecular genetics

There exists clinical heterogeneity in cutaneous melanoma with different susceptibility to UVL, which may be explained by differences in somatic genetic changes. Recent molecular genetic investigations have revealed that melanomas from intermittently sun-exposed skin, most of which are located on trunk and extremities, show frequent mutations in either *BRAF* or *NRAS* gene. In contrast, *BRAF* or *NRAS* mutations are rather infrequent in melanomas arising from sun-protected areas, such as acral skin, nail apparatus and mucosa (Table 2). Instead, these types of melanomas show a higher degree of chromosomal aberrations; specifically, genomic amplifications involving small portions of chromosome arms (Curtin et al., 2005). In AM, the most frequently amplified region is chromosome 11q13 which contains the *cyclin D1* gene. Narrow amplifications of other chromosome regions, including 4q12, 5p15, 11q14 and 22q11-13, are also found (Bastian et al., 2000). Target genes of 4q12 and 11q14 amplifications appear to be *KIT* and *GAB2*, respectively (Curtin et al., 2006; Chernoff et al., 2009).

	Acral melanomas	Melanomas from intermittently sun-exposed skin	Reference
BRAF	23% mutated	59% mutated	(Curtin et al., 2005)
NRAS	10% mutated	22% mutated	(Curtin et al., 2005)
KIT	14% mutated 24% amplified	0% mutated 0% amplified	(Curtin et al., 2006)
Cyclin D1	44% amplified	5% amplified	(Sauter et al., 2002)
GAB2	19% amplified	3% amplified[a]	(Chernoff et al., 2009)

[a] including one melanoma on face

Table 2. Comparison of somatic genetic changes between acral melanomas and melanomas from intermittently sun-exposed skin.

Cyclin D1 positively regulates the activity of cyclin dependent kinases, leading to phosphorylation of retinoblastoma protein promoting entry into mitosis, and acts as an oncogene (reviewed in (Tashiro et al., 2007)). Interestingly, while gene amplifications are usually found in association with disease progression in other cancers, *cyclin D1* gene amplifications in AM are detected early in the radial growth phase (Bastian et al., 2000). Furthermore, copy number increase of *cyclin D1* gene was observed even in normal-looking melanocytes in the epidermis beyond the histopathologically recognizable margin of melanoma (Bastian et al., 2000; North et al., 2008), as well as in very early acral melanoma *in situ* lesions, which shows slight increase of non-atypical melanocytes in the basal cell layer of the epidermis (Yamaura et al., 2005). These genetically aberrant cells with normal morphology are " field cells" (Bastian, 2003), which represent a latent progression phase that precedes the stage of atypical melanocyte proliferation in the epidermis. These observations suggest that amplification of the *cyclin D1* gene might be one of the earliest events in AM development. The presence of amplifications, however, indicates that other aberrations likely cause genomic instability (North et al., 2008). Investigations in a radial growth phase AM cell line SMYM-PRGP harboring *cyclin D1* amplification (Fig. 5) suggest that overly expressed cyclin D1 protein may act as a survival factor (Murata et al., 2007). While the progressive increase of the *cyclin D1* copy number from normal-looking melanocytes to the *in situ* portion to the invasive melanoma was observed, suggesting that the increased *cyclin D1* gene dosage confers a growth advantage during later stages of tumor progression (North et al., 2008), this may simply reflect the increase of genomic instability associated with melanoma progression (Takata et al., 2010).
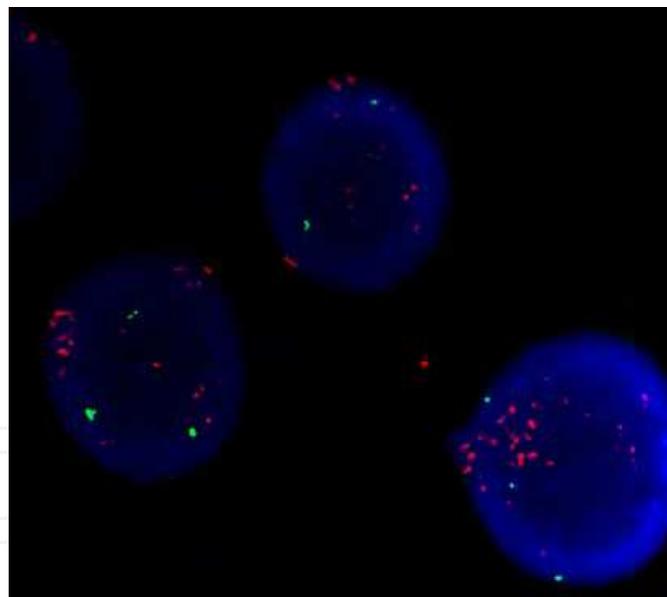

Fig. 5. Amplification of the *cyclin D1* gene in radial growth phase acral melanoma cell line SMYM-PRGP (Murata et al., 2007). Green signals, chromosome 11 centromere; red signals, *cyclin D1*.

While mutations of the *BRAF* and *NRAS* genes are infrequent in AM, a substantial number of AM harbor mutations or amplifications of the *KIT* gene encoding a receptor tyrosine kinase (Curtin et al., 2006). Recent studies have revealed *KIT* mutations and amplification in 14% and 24% of AMs, respectively (Table 2) (Woodman &Davies, 2010). About 30% of the tumors with *KIT* mutations also show increased copy number/amplification of *KIT*. The *KIT*

mutations identified in AM differ from those found in gastrointestinal stromal tumors (GIST). The majority of *KIT* mutations in GIST are deletions or insertions, whereas those found in melanoma are substitution mutations. In addition, *KIT* mutations are not present in exon 9, which is the location of 15% of *KIT* mutations in GIST. More than half of *KIT* mutations in melanoma are found in exon 11, which encodes juxtamembrane domain of KIT receptor, whereas mutations are also found in exons 13, 17 and 18 encoding kinase domains (Woodman &Davies, 2010).

GAB2 is a scaffolding protein that mediates interactions with various signaling pathways including RAS-RAF-ERK and PI3K-AKT signaling, and is a critical molecule for melanoma progression (Horst et al., 2009). A recent study found *GAB2* amplification in 5 of 23 (19%) AMs, while amplifications were rare in other types of cutaneous melanomas (Table 2). The majority of *GAB2* amplification occurred independent from genetic alterations in *BRAF, NRAS, KIT* and *cyclin D1*, suggesting a critical role of *GAB2* in a subset of AM (Chernoff et al., 2009).

6. Molecular targeted therapy

Since *KIT* mutations are detected in ~15% of AM, KIT is a promising molecular target of metastatic AM. Several *in vitro* experiments using melanoma cell lines harboring *KIT* mutations have actually shown significant growth suppressive effects of small molecular KIT inhibitors, such as imatinib, which are already approved for other cancers. Imatinib dramatically decreased proliferation, and was cytotoxic to a mucosal melanoma cell line demonstrating a highly amplified *KIT* exon 11 V559D mutation (Jiang et al., 2008). In contrast, cell viability of another melanoma cell line with *KIT* exon 11 L576P mutation, the most common *KIT* mutation in melanoma (34%) (Woodman &Davies, 2010), was not reduced by imatinib. However, dasatinib reduced cell viability of this cell line at concentrations as low as 10nM. Molecular modeling studies found that the L576P mutation induces structural changes in KIT that reduce the affinity for imatinib but not for dasatinib (Woodman et al., 2009). An acral melanoma cell line with non-amplified *KIT* exon 17 D820Y was also resistant to imatinib treatment. The *KIT* D820Y mutation usually arises as a secondary mutation in the setting of imatinib treatment in GIST, which was shown to be sensitive to sunitinib. As expected, treatment of the *KIT* D820Y cell line with 1 μM of sunitinib showed modest reduction in cell proliferation. (Ashida et al., 2009).

Clinically, dramatic response to imatinib therapy has been observed in several sporadic cases with metastatic acral and mucosal melanomas with *KIT* mutations, such as exon 13 K642E, 7-codon duplication in exon 11, and exon 11 V599A (Hodi et al., 2008; Lutzky et al., 2008; Terheyden et al., 2010). However, gene amplification and overexpression of wild-type *KIT*, which is frequently present in acral and mucosal melanomas (Woodman &Davies, 2010), did not translate into clinical efficacy of imatinib (Hofmann et al., 2009). Consistent with an *in vitro* study, metastatic melanoma patients with the *KIT* L576P mutation showed marked reduction (>50%) and elimination of tumor F18-fluorodeoxyglucose (FDG)-avidity by positron emission tomography(PET) imaging after dasatinib treatment (Woodman &Davies, 2010). Partial response by dasatinib was also observed in a patient with the *KIT* exon 13 K642E mutation (Kluger et al., 2010).

Three phase-II trials of imatinib in unselected metastatic melanomas were mostly disappointing, and highlighted the importance of proper patient selection (Ugurel et al., 2005; Wyman et al., 2006; Kim et al., 2008). There are currently three ongoing clinical trials

prospectively testing imatinib in selected patients with melanoma showing *KIT* mutations or amplifications (mostly acral and mucosal melanomas)(Table 3). The NCT00470470 trial selected stage III or IV patients with somatic mutations in *KIT*. Of the 12 evaluable patients, 2 demonstrated a complete response. Of note, these two patients had both amplification and mutation of *KIT*. A partial response was observed in two patients. All but two, who had mutations known to be resistant to imatinib in GIST, of the remaining patients had stable disease (Carvajal et al., 2009). In another phase-II trial of imatinib in patients with advanced melanoma from acral skin, mucosa or chronically sun-damaged skin (NCT00424515), five of ten patients with *KIT* mutations demonstrated a partial response. In contrast, none of the ten patients who had wild-type/amplified *KIT* showed a clinical response (Fisher et al., 2010). In the NCT00881049 trial which recruited Chinese patients with metastatic melanoma harboring *KIT* aberrations, a rate of 20% partial response and 40% stable disease was achieved, with 60% overall disease control rate (Guo et al., 2010). These results show clinical benefit of imatinib in a proportion of molecularly selected patients.

	Phase	NCT number	*KIT* aberrations required for eligibility
Imatinib	2	00470470	Mutation or amplification
Imatinib	2	00424515	Mutation or amplification
Imatinib	2	00881049	Mutation or amplification
Imatinib and temozolomide	1/2	00667953	Mutation
Nilotinib	2	00788775	Mutation or amplification
Nilotinib and dacarbazine	3	01028222	Mutation
Sunitinib	2	00631618	Mutation or amplification
Sunitinib	2	00577382	None
Dasatinib	2	00700882	None
Dasatinib and dacarbazine	1/2	00597038	None

Table 3. Clinical trials of KIT inhibitors for melanoma (Modified from Romano et al., 2011).

Nilotinib is a second-generation tyrosine kinase inhibitor of KIT, PDGFR and BCR-ABL. Nilotinib is potent as imatinib against mutant *KIT*, and is significantly more potent than imatinib against wild-type *KIT*. A phase-II trial of nilotinib in patients with melanoma characterized by a *KIT* mutation or amplification is ongoing, and a randomized phase-III, open-label study to compare the efficacy of nilotinib versus dacarbazine for treatment of patients with metastatic melanoma harboring a *KIT* mutation has been initiated. Phase-II trials testing other tyrosine kinase inhibitors targeting KIT, such as sunitinib and dasatinib, for melanoma are also ongoing (Table 3).

7. Conclusions

It is now clear that melanoma arises from multiple pathways, with initiating and promoting factors differing for each. Melanomas on intermittently sun-exposed skin preferentially affect Caucasians who have an inherently high propensity for melanocyte proliferation characterized by high nevus counts (Whiteman et al., 2003). Exposure to intense bursts of UVL radiation,

especially in childhood, is the major risk factor. This type of melanomas may arise from pre-existing melanocytic nevus, and the mutation of the *BRAF* gene may be a key initiating somatic genetic event (Michaloglou et al., 2008). By contrast, AM arises *de novo*, and equally affects all ethnic groups. The first genetic aberration affecting normal melanocytes in acral volar skin would be one that disrupts the maintenance of genomic integrity. This would lead to the amplification of *cyclin D1* and the selection for clonal expansion of affected melanocytes. Then, acquiring activating mutations in oncogenes, such as *KIT* (Curtin et al., 2006), may be a crucial step inducing proliferation of transformed melanocytes (Takata et al., 2010). Understanding molecular pathogenesis in different types of melanomas will lead to the development of effective prevention and treatment strategies for individual patients.

8. Acknowledgments

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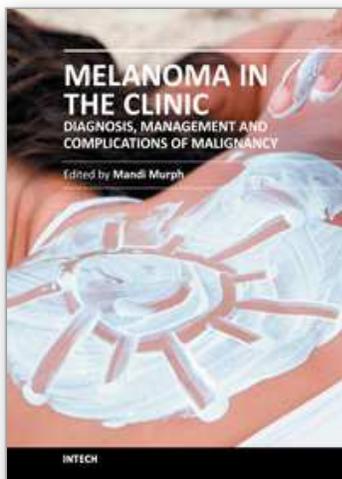
Melanoma in the Clinic - Diagnosis, Management and Complications of Malignancy
Edited by Prof. Mandi Murph

This book provides an excellent overview of how melanoma is treated in the clinic. Since oncologists and clinicians across the globe contributed to this book, each area also explores the unique burdens that geographical areas experience from melanoma subtypes and how these are treated in different settings. It also includes several chapters that illustrate novel methods for diagnosing melanoma in the clinic using new technologies, which are likely to significantly improve outcomes. Several chapters cover surgical techniques and other present very rare or challenging clinical cases of melanoma and how these were treated. The book is geared towards informing clinicians and even patients how melanoma arises, what tools are available and which decisions need to be made by patients and their families in order to treat this devastating disease.

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