Acral Melanoma: Clinical Advances and Hope for the Future

Matthew C. Perez, MD,[1] Jane L. Messina, MD,[1,2] Lilit Karapetyan,[1] Rogerio I. Neves, MD,[1,3] and Vernon K. Sondak, MD[1]

[1]Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, Florida

[2]Department of Anatomic Pathology, Moffitt Cancer Center, Tampa, Florida

[3]Program in Plastic Surgery and Reconstructive Oncology, Moffitt Cancer Center, Tampa, Florida

Corresponding author:
Vernon K. Sondak, MD
Chair
Department of Cutaneous Oncology
10920 N McKinley Drive
Tampa, FL 33612
Email: Vernon.Sondak@moffitt.org

Abstract: Acral melanoma is a rare subtype of melanoma with unique histologic and biologic characteristics. Given its relative rarity compared with nonacral cutaneous melanoma, acral melanoma has been understudied and underrepresented in modern-day prospective clinical trials that have shaped the contemporary management of advanced cutaneous melanoma. Therefore, treatment principles for advanced acral melanoma are mostly derived from retrospective analyses or extrapolated from data largely based on nonacral cutaneous melanoma. Further studies are warranted to evaluate the efficacy of systemic immune and targeted molecular therapies, and to identify molecular targets for patients with advanced acral melanoma.

Keywords
Acral lentiginous melanoma, acral melanoma, cutaneous melanoma

Introduction

Acral melanoma is a rare subtype of melanoma that accounts for approximately 3% of all melanoma cases worldwide.[1] First described by Reed and Arrington in the 1970s, acral melanoma is a distinct subtype of cutaneous melanoma arising on acral (non–hair-bearing) skin, including the palms of the hands, the soles of the feet, and within nail units.[2,3] Given its relative rarity compared with more common subtypes of melanoma, such as superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma, acral melanoma has been understudied and underrepresented in large prospective randomized controlled trials that have shaped the contemporary management of advanced cutaneous melanoma. Consequently, the unique biological characteristics, mutational drivers, and role of modern therapeutics are not well understood in patients with acral melanoma.

To understand the unique histologic and biologic characteristics of acral melanoma, it is important to first define the disease accurately. Although the terms *acral melanoma* and *acral lentiginous melanoma* are commonly used interchangeably to describe melanoma on the hairless skin of the distal extremities and nail unit, they can represent distinct diagnoses.[4] The term *acral* pertains to peripheral

body parts and is typically used to describe melanoma on the hairless and volar skin of the distal extremities. Melanoma specifically arising within the nail matrix is a type of acral melanoma known as subungual melanoma.[5] The term *lentiginous* refers to the radial growth phase, or side-by-side arrangement of melanocytes, and therefore acral lentiginous melanoma represents a unique pathologic subtype of cutaneous melanoma with distinct histologic and molecular features, including a lack of ultraviolet-related mutational signatures.[6,7] It is important to note that not all melanomas in acral locations are lentiginous, as other subtypes of cutaneous melanoma may also arise in these areas, especially if they have been exposed to frequent sunlight.

Misuse and controversy with the terms *acral* and *acral lentiginous melanoma* continues to the present day. In a 2021 review, Bernardes and colleagues performed a PubMed search using the term "acral melanoma."[8] Among the original studies obtained from this search, 38% specified the histopathologic subtype, 78% reported the anatomic site, and 37% reported information on both; 21% of studies did not specify either histopathologic subtype or anatomic site. To further understand the histologic subtype of acral lentiginous melanoma, a more precise and consistent reporting of these terms in the literature is essential. In this review, we focus on the unique characteristics, management, and future directions of acral lentiginous melanoma, with the understanding that patients with nonacral cutaneous melanoma on acral sites may have been included in some of the cited literature.

Epidemiology

Although other subtypes of cutaneous melanoma predominately occur on sun-exposed skin in White populations, acral lentiginous melanoma typically develops on the hairless skin of distal extremities in areas that may lack frequent sun exposure. Unlike nonacral cutaneous melanoma, the incidence of acral lentiginous melanoma is similar across patients of different racial and ethnic backgrounds.[1,9,10] Additionally, it is the most common form of melanoma in patients of Asian, Latin American, and African descent, with studies reporting acral lentiginous melanoma to account for up to 80% of melanoma cases in African patients.[11-14]

The etiology of acral lentiginous melanoma is not well understood, as the common risk factors of ultraviolet exposure and fair skin type seen in other types of cutaneous melanoma are not applicable to acral lentiginous melanoma.[15] Given that many of these lesions occur in weight-bearing areas of the body, traumatic injury and/or mechanical stress have been suggested as possible etiologies for the development of acral lentiginous melanoma.

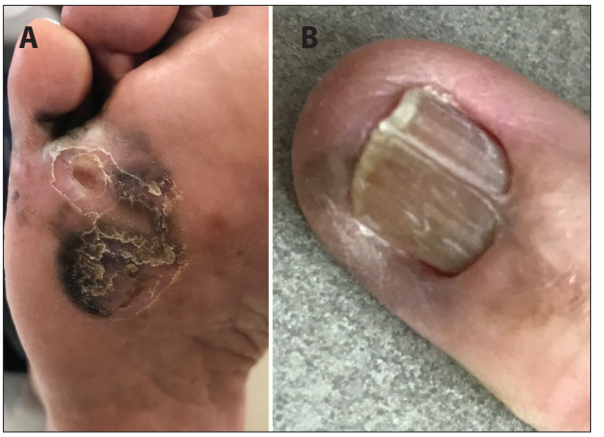

Figure 1. Acral lentiginous melanoma of the plantar foot (A) and nail unit (B).

In a retrospective review of 685 Chinese patients with acral lentiginous melanoma, 15.2% exhibited an association between prior trauma and development of melanoma at that site.[16] However, additional studies have reported conflicting evidence regarding the development of acral lentiginous melanoma in the areas of highest pressure on the plantar foot.[17-19] Therefore, further investigation is needed to determine if and to what degree trauma or mechanical stress may play a role in the development of acral lentiginous melanoma.

The relationship between benign acral nevi and acral melanoma has also been studied. Smalley and colleagues evaluated the mutational profile of 50 patients with acral nevi using targeted next-generation sequencing.[20] In this cohort, the incidence of *BRAF* V600E mutations was 50%, which is far higher than the known incidence of *BRAF* mutations found in acral melanoma (~18%). This discrepancy in *BRAF* mutation rates suggests that acral nevi are not precursor lesions for the majority of acral melanomas.

Clinical Presentation and Diagnosis

Acral lentiginous melanoma typically presents as an asymmetric pigmented macule in the non–hair-bearing skin of the distal extremities (Figure 1A). On dermoscopy, in situ and invasive acral lentiginous melanomas often demonstrate irregular diffuse pigmentation and a parallel ridge pattern (Figure 2). These characteristics may be useful in distinguishing them from an acral nevus.[21,22] Subungual melanoma presents with either partial or total melanonychia of the nail plate. When seen with periungual skin pigmentation, this is referred to as Hutchinson sign, which raises concerns for acral lentiginous melanoma (Figure 1B).[23]

The clinical diagnosis of acral lentiginous melanoma can be very challenging. It is often misdiagnosed as more common ailments of the hands and feet, such as traumatic

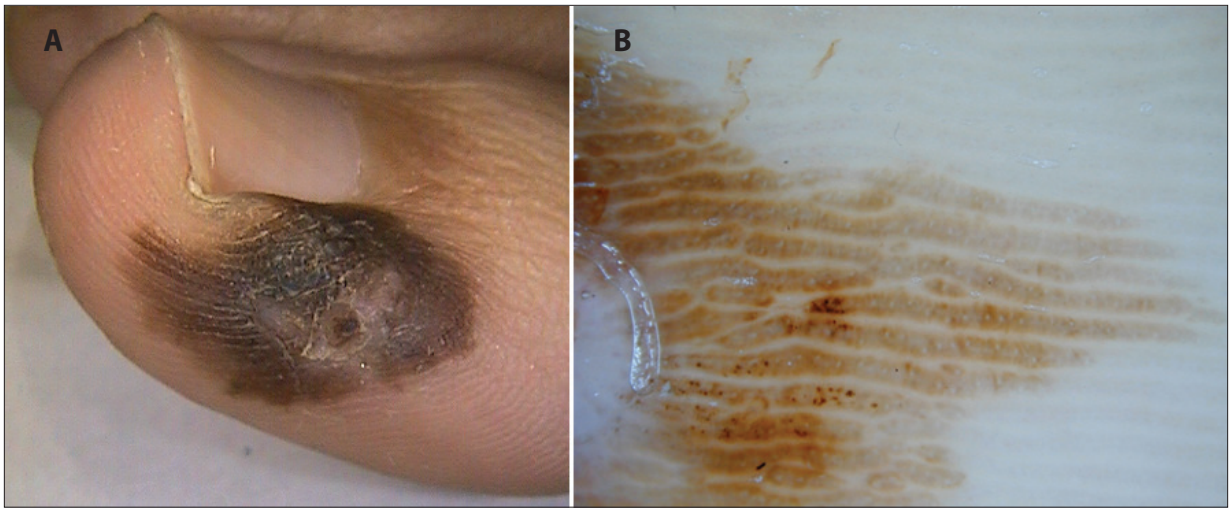

Figure 2. Acral melanoma in situ (A), with parallel ridge patterns on dermoscopy (B).

and diabetic foot ulcers, fungal infections, and warts, which often leads to increased tumor depth and more advanced disease at the time of ultimate diagnosis.[21,24-26] Biopsies should be performed for any suspicious pigmented lesions of the acral skin and nail apparatus, and considered for lesions that do not respond appropriately to a brief course of therapy for presumed benign conditions mentioned above. Although an excisional biopsy is the gold standard for the diagnosis of most melanocytic lesions, acral lentiginous melanomas frequently pose technical challenges that limit the ability to completely excise the lesion. For example, the limited laxity of acral skin can result in a complex wound, making it difficult or impossible to close when complete removal of the lesion is attempted. In addition, nail matrix biopsies may lead to permanent nail dystrophy. As a result, biopsy techniques such as 3-mm punch biopsy, lateral longitudinal excision, or shave biopsy are routinely performed, depending on the size and location of the lesion within the nail matrix.[27] Owing to these technical challenges, biopsies that partially sample the lesion are often performed and may result in understaging the lesion.[21,28] Weitman and colleagues conducted a review of 71 patients with partially sampled melanocytic lesions (atypical melanocytic proliferation, melanoma in situ, and melanoma) from both acral and nonacral skin.[29] In this retrospective review, additional sampling of the residual pigment led to an upstaging of the tumor, meeting the criteria for sentinel lymph node biopsy in 18.3% of patients and wider excision margins in 8.5% of patients.

The histologic characteristics of acral lentiginous melanoma are unique from other types of cutaneous melanoma. These features include a lentiginous or radial growth pattern of pagetoid melanocytes with increased nuclear-to-cytoplasmic ratio and dendritic morphology (Figure 3).[30] There is often deep extension within sweat gland epithelium, which is functionally melanoma in situ. Additionally, the unique dermatoglyphic pattern of furrows and ridges in acral skin has led to the recommendation of orienting biopsy and pathologic sections perpendicular to skin markings to optimize the evaluation of melanocyte distribution.[31] Subungual melanoma may be particularly difficult to diagnose owing to the aforementioned difficulties in obtaining a representative biopsy sample; biopsies should always be interpreted in the context of the clinical presentation and the location of the biopsy. For longitudinal melanonychia, the nail matrix, characterized by the presence of basaloid epithelium, should be sampled. Evaluation of melanocyte density, which is best aided by immunohistochemical staining for melanocytes (eg, SOX10 or Melan-A), is helpful in quantifying melanocytes and distinguishing nail unit melanoma from melanocytic activation or nevus. Benign processes show an average of 15 to 31 melanocytes per mm, whereas nail unit melanoma typically shows more than 40 cells per mm.[32] Recently, nail clippings have been espoused as an expeditious first step in evaluating pigmented nail lesions, resulting in minimal discomfort and disfiguration. The finding of melanocyte remnants in an adult, seen as hollow areas in the nail plate, is considered suspicious for an underlying melanocytic neoplasm. If found, such remnants should prompt a second biopsy of the underlying nail bed or matrix.[33]

Management of the Primary Lesion

Complete surgical excision is the standard of care for early-stage, localized melanoma, and multiple randomized controlled trials have been performed to support the National Comprehensive Cancer Network (NCCN)

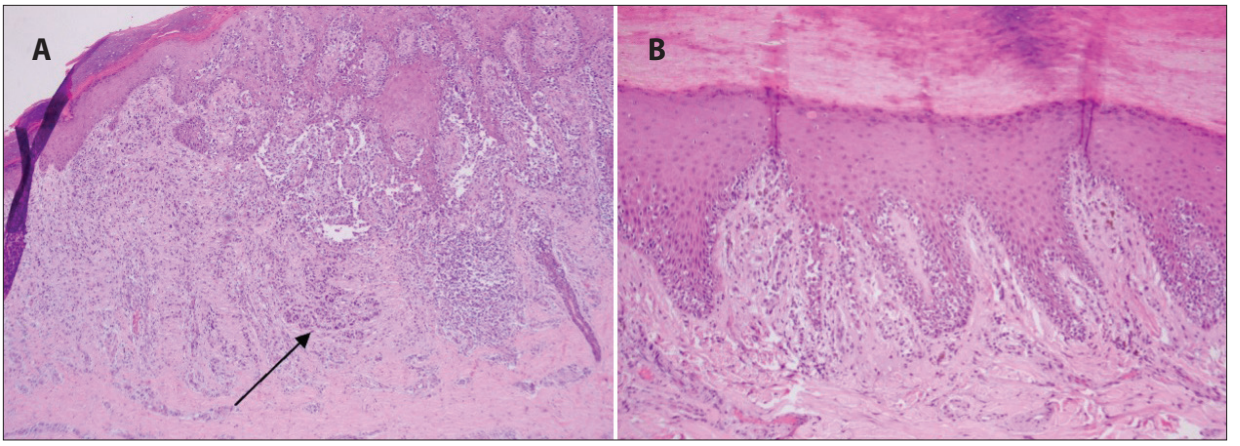

Figure 3. Histologic characteristics of acral lentiginous melanoma (A) and acral lentiginous melanoma in situ (B). Figure 3A shows large, hyperchromatic melanocytes that grow as nests and single cells with extension into adnexal epithelium and invasion of the dermis to a depth of 1.5 mm (see arrow; hematoxylin and eosin, 50×). Figure 3B shows characteristic large, dendritic-appearing single melanocytes growing with confluence in the epidermis (hematoxylin and eosin, 100×).

Guidelines of 1- to 2-cm margins, depending on the maximal depth of the primary tumor.[34-42] These trials, however, predominately included nonacral cutaneous melanomas. As a result, there is less evidence to guide the surgical management specifically for acral lentiginous melanoma. Given the inherent locations of acral lentiginous melanoma, excision often requires complex reconstruction with frequent use of skin grafts or tissue transfer. Additionally, acral lentiginous melanoma of the toes and fingers, including subungual melanoma, often requires amputation to achieve adequate surgical margins.

In recent years, the practice of wide margin excisions for acral lentiginous melanoma and universal amputation for cutaneous and subungual melanomas arising on the fingers and toes has been challenged. Nakamura and colleagues evaluated 62 patients with in situ or invasive subungual melanoma who underwent nonamputative wide excision with 0.5- to 1-cm peripheral margins and deep margins to the underlying bone.[43] Four of the 48 patients with subungual melanoma in situ experienced local recurrence requiring reresection, although only 1 patient ultimately required amputation. Among patients with invasive subungual melanoma who underwent a nonamputative wide excision, no patients developed local recurrence or died of disease at last follow-up. Although the majority (50/62) of patients in this study had either in situ disease or invasive melanoma with a maximal tumor depth of less than 0.5 mm, these results suggest that nonamputative wide excision may provide adequate local control for some subungual melanomas. A systematic review and meta-analysis of excision techniques in patients with in situ subungual melanoma was recently performed by Le and colleagues.[44] Pooled data from all 20 included studies revealed that the local recurrence rate was 8.69% (2 of 23 patients) with Mohs micrographic surgery, 4.72% (12 of 254 patients) with nail unit excision, and 2.94% (1 of 34 patients) with amputation. Although these differences were not statistically significant, the study cannot be used to show that Mohs micrographic surgery is equivalent to the current recommended surgical treatment because of the small sample size, publication bias, selective outcome bias, and the retrospective nature of the study. Further research in excision techniques for acral and subungual melanoma is warranted.

The guidelines for sentinel lymph node biopsy in patients with acral lentiginous melanoma are largely extrapolated from studies that include only a small proportion of patients with this subtype. Current NCCN Guidelines for sentinel lymph node biopsy are based on primary tumor depth and do not consider histologic subtype. In a large retrospective review of more than 60,000 patients with melanoma, including 959 patients with acral lentiginous melanoma, it was found that the acral lentiginous melanoma subtype was independently associated with the highest risk of sentinel lymph node positivity.[45] Additionally, a subgroup analysis demonstrated that acral lentiginous melanoma was independently associated with the highest risk for sentinel lymph node positivity in patients with stages IB and II disease. Given these findings, along with the risk of understaging disease owing to incomplete biopsies, it may be reasonable to routinely perform sentinel lymph node biopsy even in patients with T1a or in situ disease, especially if there is residual pigmentation after an initial partial biopsy.

Management of Advanced Disease

The past 15 years have seen dramatic changes in the man-

agement and prognosis of advanced cutaneous melanoma owing to the development of systemic immune checkpoint inhibitors and targeted molecular therapies. These agents have been shown to improve recurrence-free survival and overall survival (OS) rates in numerous randomized controlled trials for patients with advanced cutaneous melanoma.[46-50] Typically, acral lentiginous melanoma was not reported separately in these landmark trials, and therefore evidence for the efficacy of these agents in patients with advanced acral lentiginous melanoma is derived from retrospective analyses or extrapolated from prospective data based largely on nonacral cutaneous melanoma.

When compared with other subtypes of cutaneous melanoma, acral lentiginous melanoma has a lower mutational burden as well as lower frequencies in 2 of the most common driver mutations for cutaneous melanoma, *BRAF* and *NRAS*.[20,51,52] Recent reports have suggested that a tumor with a higher mutational burden is more likely to respond to immunotherapy.[53,54] Key trials for patients with advanced acral lentiginous melanoma are summarized in the Table.

Immune Checkpoint Inhibitors

Although not specifically designed to evaluate the efficacy of immune checkpoint inhibitors in patients with acral lentiginous melanoma, the KEYNOTE-151 trial included 39 of 102 patients (38%) with this subtype. This phase 1b study, which was conducted in China, evaluated the anti–programmed death 1 (PD-1) agent pembrolizumab (Keytruda, Merck) as second-line therapy in patients with advanced or metastatic melanoma. In this trial, the objective response rate (ORR) was 15.8% for patients with acral lentiginous melanoma.[55]

The CheckMate 172 trial evaluated patients with rare subtypes of melanoma who were treated with the anti–PD-1 agent nivolumab (Opdivo, Bristol Myers Squibb) following progression with the anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) agent ipilimumab (Yervoy, Bristol Myers Squibb) and included a cohort of 55 patients with advanced acral lentiginous melanoma. The primary endpoint of this single-arm phase 2 multicenter trial was the incidence of grade 3 treatment-related adverse events, and there were no observed difference among melanoma subtypes when compared with the total population. Similar survival outcomes were reported between patients with acral lentiginous melanoma (median OS [mOS], 25.8 months) and those with nonacral cutaneous melanoma (mOS, 25.3 months).[56]

A retrospective multicenter study was later performed by Shoushtari and colleagues in 2016, which identified 25 patients with advanced acral lentiginous melanoma who were treated with an anti–PD-1 agent either in previous clinical trials, in expanded access programs, or as standard of care following US Food and Drug Administration (FDA) approval.[57] In this analysis, most patients (85%) had received prior systemic therapy, mainly ipilimumab. The ORR was 32%, with a median progression-free survival (PFS) of 4.1 months. This response rate was close to that seen in prior prospective trials conducted in Western countries evaluating the use of second-line anti–PD-1 therapy in cutaneous melanoma.[58,59] Additionally, Nakamura and colleagues performed a retrospective analysis of 193 patients with unresectable stages III and IV acral lentiginous melanoma treated with anti–PD-1 therapy at any line of treatment across 21 Japanese institutions.[60] The ORR for all patients was found to be 16.6%, with an mOS of 18.1 months. Interestingly, the response rate was significantly higher in patients with acral lentiginous melanoma of the palms and soles vs those with subungual melanoma (21.1% vs 8.6%, respectively; P=.03), which was associated with a difference in OS (22.3 vs 12.8 months, respectively; P=.03).

Straker and colleagues performed a retrospective analysis using the National Cancer Database comparing the survival outcomes of more than 5000 patients diagnosed with acral lentiginous melanoma before the approval of modern immune and targeted molecular therapies (2004-2010) with those diagnosed afterwards (2011-2017).[61] When controlling for clinicopathologic and treatment factors on multivariable analysis, there was no OS advantage for patients diagnosed with acral lentiginous melanoma between 2011 and 2017. Additionally, no OS advantage was observed between the 2 different time periods when only patients with stages III and IV disease were analyzed.

Most recently, Wang and colleagues published the results of a phase 2 trial evaluating the use of apatinib, a tyrosine kinase inhibitor, along with the immune checkpoint inhibitor camrelizumab for treatment-naive patients with advanced acral lentiginous melanoma.[62] In 30 patients with locally unresectable or metastatic acral lentiginous melanoma, the ORR and disease control rate were 24.1% and 82.8%, respectively, with a median PFS of 7.39 months.

The effect of combination immunotherapy vs monotherapy in patients with advanced acral lentiginous melanoma has also been retrospectively reviewed. Bhave and colleagues performed a large multicenter retrospective analysis of 325 patients with unresectable stages III and IV acral lentiginous melanoma who were treated with a combination of anti–PD-1 therapy and ipilimumab vs ipilimumab or anti–PD-1 therapy alone.[63] The ORRs were 43% for combination therapy, 26% for anti–PD-1 therapy alone, and 15% for ipilimumab alone. PFS at 1 year was highest in the combination group (34%) vs the anti–PD-1 alone (26%) and ipilimumab (10%) groups. However, this

Table. Key Studies for Unresectable or Metastatic Acral Lentiginous Melanoma

Author	Study design	Number of patients	Therapeutic agent	Findings
Si et al[55]	Prospective phase 1b (KEYNOTE-151)	39	Pembrolizumab	ORR 15.8%
Nathan et al[56]	Prospective phase 2 (CheckMate 172)	55	Nivolumab	OS 25.8 months for acral lentiginous melanoma vs 25.3 months for nonacral cutaneous melanoma
Shoushtari et al[57]	Retrospective	25	Nivolumab or pembrolizumab	ORR 32%
Nakamura et al[60]	Retrospective	193	Nivolumab or pembrolizumab	ORR 16.6%
Straker et al[61]	Retrospective	5060	Immune checkpoint inhibitors and targeted therapy	No OS advantage in patients diagnosed with acral lentiginous melanoma after 2011
Bhave et al[63]	Retrospective	325	Combination immune checkpoint inhibitors vs monotherapy	ORR 43% with combination; 26% with anti–PD-1; 15% with anti–CTLA-4
Nakamura et al[64]	Retrospective	254	Combination immune checkpoint inhibitors vs anti–PD-1 monotherapy	ORR in subungual melanoma 61% with combination vs 10% with monotherapy; no difference in ORR in acral lentiginous melanoma of palms and soles
Tawbi et al[65]	Prospective phase 2/3	82	Combination immune checkpoint inhibitors (including LAG-3 inhibitor) vs anti–PD-1 monotherapy	PFS benefit seen with combination therapy in all subgroups, including 82 patients with acral melanoma (HR 0.84; 95% CI 0.50-1.39)
Kim et al[69]	Retrospective	19 *BRAF* V600E–mutant acral lentiginous melanoma or mucosal	Vemurafenib or dabrafenib and trametinib	ORR 78.9% for entire cohort of 27 patients, 19 of whom had acral lentiginous or mucosal melanoma
Bai et al[70]	Retrospective	21 *BRAF* V600E–mutant	Vemurafenib, sorafenib, or BGB-283	ORR 38.1%

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; HR, hazard ratio; LAG-3, lymphocyte activation gene 3; ORR, objective response rate; OS, overall survival; PD-1, programmed death 1.

trend in improved PFS was not statistically significant and did not correlate with improved OS.

Nakamura and colleagues evaluated the use of combination immune checkpoint inhibitors therapy vs monotherapy as first-line treatment in patients with advanced acral lentiginous melanoma.[64] In this study, 254 patients with unresectable stages III and IV acral lentiginous melanoma across 24 Japanese institutions were treated with either a combination of anti–PD-1 therapy and ipilimumab or anti–PD-1 therapy alone. Although there was no significant difference in ORR between the 2 treatment regimens for patients with palm and sole acral lentiginous melanoma, there was a significant improvement in ORR for patients with subungual melanoma receiving the combination (61% vs 10%; $P<.0001$).

Tawbi and colleagues recently evaluated the use of the anti–PD-1 agent nivolumab in combination with the lymphocyte activation gene 3 (LAG-3) inhibitor relatlimab (Opdualag, Bristol Myers Squibb) vs anti–PD-1 monotherapy for previously untreated metastatic or unresectable melanoma.[65] In this randomized trial, the combination vs monotherapy improved PFS in all subgroups, including the acral melanoma group, where the hazard ratio was 0.84 (95% CI, 0.50-1.39).

Targeted Molecular Therapy

Mutations in *BRAF* V600E are considerably less common in acral melanoma than in nonacral cutaneous melanoma. Additionally, targeted sequencing of *BRAF* V600E–mutant acral melanoma has revealed that these tumors

lack the characteristic gene amplifications that are seen in acral lentiginous melanoma, and that they actually resemble more-common subtypes of cutaneous melanoma.[66-68] The response rate to targeted treatment for acral lentiginous melanoma with *BRAF* mutations is also unclear. Kim and colleagues conducted a retrospective analysis of 27 patients with *BRAF* V600E–mutated metastatic melanoma who underwent BRAF-targeted therapy, of whom 19 had acral or mucosal melanoma.[69] In this combined subset of patients, the ORR was 78.9%. This ORR is consistent with those seen in randomized controlled trials for patients with nonacral *BRAF* V600E–mutated cutaneous melanoma. However, Bai and colleagues retrospectively evaluated 21 patients with *BRAF* V600E–mutated acral lentiginous melanoma treated with BRAF-targeted therapy and reported an ORR of only 38.1%.[70]

Adjuvant and Neoadjuvant Therapy

The role of these systemic therapies in the adjuvant and neoadjuvant setting is an area of current interest. Immune checkpoint inhibitors and targeted molecular therapies have been shown to improve recurrence-free survival and survival rates in patients with high-risk resected cutaneous melanoma.[71-73] Similar to the landmark trials for metastatic melanoma, patients with acral lentiginous melanoma constituted a minority of the cases in these adjuvant trials. Furthermore, concerns that acral lentiginous melanoma may be less responsive to immune checkpoint inhibitors than nonacral cutaneous melanoma are heightened in the adjuvant setting, where there is no measurable disease to assess for treatment response. Maeda and colleagues recently conducted a retrospective review of 27 patients with acral lentiginous melanoma at their institution who received adjuvant therapy; however, only 5 of these patients received immune checkpoint inhibitor therapy.[74] Although there was no observed difference in disease-free survival among the immune checkpoint inhibitor group vs the non–immune checkpoint inhibitor group, the small sample size limits any conclusions.

Although some studies have suggested higher response rates for unresectable acral lentiginous melanoma when treated with combination immunotherapy, the recent CheckMate 915 trial reaffirmed nivolumab as the standard of care for adjuvant therapy for patients with all cutaneous melanomas. In this trial, combination ipilimumab and nivolumab did not improve recurrence-free survival when compared with nivolumab monotherapy in patients with resected stages IIIB through IIID or IV melanoma.[73] Acral lentiginous melanoma accounted for less than 5% of patients in this trial, highlighting the importance of discussing with patients the limited data for adjuvant therapy in acral lentiginous melanoma.

The recently published results of the SWOG S1801 trial have drawn significant interest in neoadjuvant treatment for cutaneous melanoma.[75] In this prospective randomized trial for patients with resectable stages IIIB through IIID or IV cutaneous melanoma, 3 doses of single-agent neoadjuvant pembrolizumab followed by resection and adjuvant pembrolizumab for a total duration of 1 year had significantly improved event-free survival vs up-front resection and 1 year of single-agent pembrolizumab in the adjuvant setting. In contrast to adjuvant therapy, neoadjuvant treatment of melanoma allows for monitoring of in vivo tumor response to treatment. This is particularly appealing for acral lentiginous melanoma, where treatment response is less certain. Currently, the use of apatinib and camrelizumab in the neoadjuvant setting for acral lentiginous melanoma is under investigation (NCT04331093).

Regional and Intralesional Therapies

The role of regional therapies, specifically intralesional and intraarterial, for advanced acral lentiginous melanoma is not well studied. The nature of the recurrence patterns for these tumors of the distal extremities makes them particularly suited for regional approaches in cases of recurrent disease. Li and colleagues conducted a review of 150 patients who underwent a single isolated limb infusion in China between 2007 and 2016.[76] The ORR and complete response rate were 41% and 6%, respectively. These response rates were lower than those previously published in centers in the United States and Australia. Therefore, it is possible that this discrepancy is secondary to histologic subtype, as 79% of patients in the study had acral lentiginous melanoma. The OPTiM trial, which led to the FDA approval of talimogene laherparepvec, commonly known as T-VEC (Imlygic, Amgen) for patients with advanced melanoma, did not account for histologic subtype. However, Franke and colleagues recently published a case report on a patient with primary acral lentiginous melanoma who underwent intralesional therapy with T-VEC and achieved a complete response.[77,78]

Given the theoretical benefit of priming the immunologic tumor microenvironment with intralesional therapy while treating patients with concurrent systemic therapy, recent trials have evaluated the possible synergistic effect between these therapies in patients with all subtypes of cutaneous melanoma. In a phase 2 study, Chesney and colleagues found the addition of T-VEC with ipilimumab demonstrated a higher ORR (39%) vs ipilimumab alone (18%).[79] In the recent placebo-controlled randomized phase 3 MASTERKEY-265 trial, however, the addition of T-VEC to pembrolizumab failed to improve either PFS or OS when compared with pembrolizumab alone.[80] Further studies evaluating the efficacy of combining intralesional and systemic therapies will be required before this combination can be routinely considered.

Future Directions

Contemporary systemic immune and targeted therapies have vastly changed the treatment landscape and overall prognosis for patients with advanced cutaneous melanoma. Our understanding of the efficacy of these agents in patients with acral lentiginous melanoma is largely limited to retrospective reviews, which often involve small cohorts of patients and/or inconsistent response rates, as detailed in this review. The data, however, are still promising when compared with treatment regimens used just 15 years ago, when patients treated with cytotoxic chemotherapy had response rates of less than 20% and an estimated mOS of 6 to 9 months.[81]

There is growing evidence that acral lentiginous melanomas harbor unique biological characteristics with specific genomic and molecular drivers, such as amplifications in the long arm of chromosome 11, often involving cyclin D1.[7,82] In a whole-genome analysis, Farshidfar and colleagues identified focal amplifications in cytoband 22q11.21 to be strongly associated with acral lentiginous melanoma metastasis and inferior survival.[83] In this cytoband, they found the known tumor suppressor LZTR1 to be a key candidate oncogene and possible therapeutic target. Additionally, differences have been reported in the immune cell infiltrate within the tumor microenvironment of acral lentiginous melanoma when compared with nonacral cutaneous melanoma, including lower levels of tumor-infiltrating lymphocytes.[84,85] Li and colleagues recently conducted an analysis of the immune environment, including specific immune checkpoints, in 9 acral lentiginous melanoma tumors using single-cell RNA sequencing.[86] In this study, acral lentiginous melanoma was found to have a lower overall immune cell infiltrate when compared with nonacral cutaneous melanoma. However, the immune cells present within the microenvironment were found to express multiple checkpoints, including PD-1, LAG-3, CTLA-4, VISTA, TIGIT, and ADORA2, which may represent future therapeutic targets.

Conclusions

Given the rarity of acral lentiginous melanoma, its contemporary management is mostly extrapolated from trials comprised predominately of nonacral cutaneous melanoma. Nevertheless, multiple retrospective series have demonstrated favorable response rates and durations of response to modern-day systemic immune and targeted therapies for patients with advanced acral lentiginous melanoma. Additionally, ongoing research is continuing to identify unique genomic and molecular drivers inherent to acral lentiginous melanoma that may serve as therapeutic targets in the future.

Disclosures

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