Cutaneous Melanoma—A Review in Detection, Staging, and Management

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KEYWORDS

• Melanoma • Malignant melanoma • Cutaneous melanoma • Immunotherapy
• Targeted therapy • Sentinel lymph node biopsy

KEY POINTS

- Melanoma is an increasingly common cancer in the United States that is highly curable with low morbidity local, surgery alone if diagnosed early, although there is insufficient evidence for routine screening.
- Advances in immunotherapy and targeted therapy over the past decade have dramatically changed treatment paradigms and improved the prognosis for advanced-staged disease.
- In the future, promising advances in diagnostic accuracy via technological improvements and in staging via molecular markers will likely further improve the ability to diagnose and treat melanoma and further enhance its prognosis.

INTRODUCTION

Melanoma, a tumor arising from a melanocyte (the cell responsible for producing pigment), continues to carry the potential to be a deadly disease. In the United States, 91,320 new cases are predicted to be diagnosed in the year 2018, continuing a long-standing trend of rising incidence since 1975.[1] Cutaneous melanoma (CM) is the leading cause of death from skin cancer, with 9320 deaths predicted in 2018.[1] Although 5-year melanoma-specific mortality rates are relatively low, at 8.2%, the spectra of melanoma looms large.[1] It is the eighth most common cause of cancer death in Australia,[2] and in young adults (15–29 years old) living in the United States, it is the second most commonly diagnosed cancer.[3]

Although the rise in incidence likely points to improved detection, the lack of a corresponding drop in mortality has led to concern that the detected CMs were not reliably destined to be lethal and that much work remained to improve earlier detection of

Disclosure Statement: No disclosures.
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Hematol Oncol Clin N Am 33 (2019) 25–38
https://doi.org/10.1016/j.hoc.2018.09.005 **hemonc.theclinics.com**

deadly melanomas. There recently has been, however, a stabilization of melanoma mortality in the United States.[4]

Melanoma has also been the tumor to watch in the past decade because of advances in the treatment of metastatic disease. Breakthroughs in immunotherapy that are relevant to melanoma biology have paved the way for treatment of other cancers. In addition, significant changes in pathologic staging and surgical management are all worth noting.

This review provides an evidence-based overview on the detection and staging of melanoma as well as a brief review of the current surgical and medical management. A deeper look into the nuances of the medical management of metastatic melanoma is beyond the scope of this review. The authors highlight the areas where questions remain and end with a discussion on prevention strategies.

DIAGNOSIS AND DETECTION

CM as highly curable if detected early. There are numerous established risk factors, with age and white race the 2 most obvious from US epidemiologic data (**Box 1**).[1] Indoor tanning,[5] classified as a carcinogen by the World Health Organization,[6] is also a risk factor, especially in young women. Most risk factors individually confer a small increased risk, except genetic syndromes, such as familial malignant melanoma (CDKN2a mutation), which is also associated with pancreatic cancer.[7] Although the vast majority (more than 90%) of melanoma is cutaneous, it can initially present as ocular, mucosal, and of unknown primary.[8]

Although physician-detected CMs are thinner than patient-detected,[9] the US Preventive Service Task Force has found insufficient evidence for routine skin cancer screening, by either patients or health care providers.[10] The largest screening study to date is an observational nationwide skin cancer screening program in Germany by general practitioners that found no change in melanoma-specific mortality.[11]

CM is initially diagnosed via visual skin inspection. Diagnostic clues include asymmetry, border, color, diameter, and evolution (ABCDEs) and the ugly duckling sign[12] (**Fig. 1**). Importantly, use of dermoscopy by experienced providers can improve diagnostic accuracy.[13] Additionally, several new technologies seek to improve prebiopsy

Box 1
Risk factors for melanoma development

- Male gender
- Increasing age
- Family history of melanoma
- Dysplastic (atypical) nevus
- Multiple (≥100) nevi
- Fair complexion
- History of sunburns
- Indoor tanning use
- History of skin cancer

Data from Final recommendation statement: skin cancer: screening. U.S. preventive services task force. 2016. Available at: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/skin-cancer-screening2. Accessed August 29, 2018.

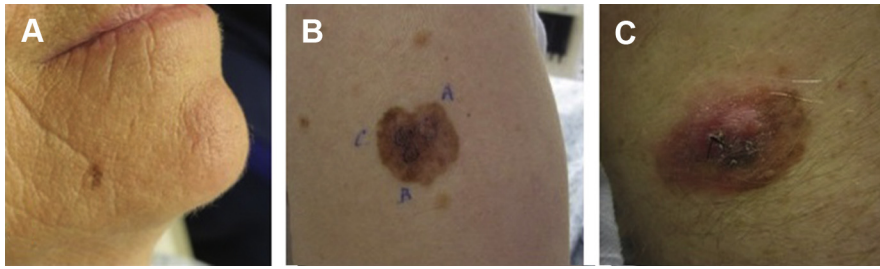

Fig. 1. Clinical photos of CM; most CM evolve over time. (*A*) Melanoma in situ on sun-damaged skin can exhibit few features except for irregularity of pigmentation and early dermoscopy signs. (*B*) T1 melanomas can develop a prominent radial growth phase, initially growing outward, but careful examination demonstrates gray stippling in the area marked "C" as evidence of early invasion. (*C*) Late-stage tumors, such as this T3 lesion, have developed a vertical growth phase and developed a nodule in this preexisting nevus. Vertical growth phase and nodular components of melanomas can grow rapidly and are more likely to be amelanotic.

diagnostic accuracy. These include artificial intelligence image analysis, whole-body 3-D imaging, reflectance confocal microscopy (RCM), optical coherence tomography (OCT), and epidermal genetic information retrieval from adhesive tape stripping. Although they offer potential advantages, none at present is used regularly clinically except for digital photographic monitoring. CMs detected by whole-body photography and sequential digital dermoscopy are thinner than those detected by conventional means.[14] Increasingly, RCM and OCT are used in conjunction with other data points, for instance, to determine the borders of lentigo maligna (LM) in vivo.[15] As the technology becomes more facile and accessible, RCM and OCT will likely be used increasingly in the future.

A diagnosis of CM is confirmed by skin biopsy, typically performed with local anesthesia using 1 of 3 techniques: saucerization shave biopsy, punch biopsy, or narrow excision with 2-mm margins. A narrow excision to the subdermal fat without undermining is preferred to avoid disruption of lymphatics because this can impair future sentinel lymph node biopsy (SLNB). On a limb, the scar should be oriented along the long axis. The biopsy should assess the invasion depth (Breslow thickness) because this is the most important prognostic indicator and guides treatment.[16] In general, biopsy of the entire lesion is ideal to avoid sampling error, although this may be impractical for certain locations or large lesions. Data suggest that although shave and punch biopsies more commonly transect tumors than excision, there is no adverse effect on survival.[17]

For patients with an unknown primary skin lesion presenting with a bulky lymph node or metastatic disease, fine-needle aspiration may be used with sensitivity and specificity above 90%.[18] There are rare reports of tumor seeding along the biopsy tract so it should be monitored clinically for recurrence.[18] If clinical suspicion is high and the fine-needle aspiration is nondiagnostic, an excisional biopsy should be performed to confirm the diagnosis.[18] Tissue confirmation is needed even in the setting of distant metastatic disease, and molecular sequencing for common mutations is now standard of care.

Histopathology of CM reveals increased atypical melanocytes/melanoma cells in the epidermis and/or dermis. Atypical melanocytes may be seen higher up in the epidermis, termed, *pagetoid spread*, and there also may be continuous atypical melanocytes along the dermal-epidermal junction, termed *lentiginous proliferation*.[19]

Markers for melanocytic differentiation may be used to highlight melanocytes, including HMB-45, Melan-A/Mart 1, MITF, and Sox-10. Diagnosis is not always clear-cut and the term, *melanocytic tumor of uncertain malignant potential*, is used for lesions difficult to distinguish from melanoma, such as Spitz tumors, cellular and/or epithelioid blue nevi, and deep penetrating nevi.[20] Such lesions should be excised completely given their uncertain malignant potential. The Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis reporting schema attempt to consolidate discordant terminology with coordinated treatment of melanocytic lesions based on biological potential.[21]

STAGING

The American Joint Committee on Cancer (AJCC) unveiled its eighth edition of melanoma staging to be implemented at the beginning of January 2018. The samples included in the eighth edition are stages I–III CM diagnosed since 1998.[22] Notably, stage IV patients were not updated in this edition in anticipation of changes in survival due to recent therapeutics. The strict requirement of a SLNB for all tumors T2 and above, and the inclusion of the nodal status if an SLNB was adhered to, resulted in an improved overall survival (OS) status for stage I and stage II patients because patients with occult nodal metastases were appropriately staged as stage III (**Table 1**). The staging system continues to include tumor depth, nodal status, and presence of metastases (TNM) (**Table 2**).

Changes in Tumor Staging

The major change in tumor staging is defining T1a as less than 0.8 mm and T1b as greater than 0.8 mm or less than 0.8 mm but ulcerated (previous transition point set at 1 mm in the seventh edition). Mitotic rate was removed because analyses revealed

Table 1
Survival percentages by TNM staging

American Joint Committee on Cancer, Eighth Edition	5-y Survival (%)	10-y Survival (%)
Stage IA	99	98
Stage IB	97	94
Stage IIA	94	88
Stage IIB	87	82
Stage IIC	82	75
Stage IIIA	93	88
Stage IIIB	83	77
Stage IIIC	69	60
Stage IIID	32	24
American Joint Committee on Cancer, Seventh Edition		**1-y Survival (%)**
Stage IV M1a		62
Stage M1b		53
Stage M1c		33

Data from Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27(36):6199–206; and Gershenwald JE, Scolyer RA. Melanoma staging: American Joint Committee on Cancer (AJCC) 8th edition and beyond. Ann Surg Oncol 2018;25(8):2105–10.

Table 2
TNM staging, American Joint Committee on Cancer, eighth edition

Tumor Classification	Thickness (mm)	Ulceration Status
T1	≤1.0	T1a, <0.8 mm without ulceration T1b, 0.8 mm to 1 mm without ulceration Or ≤1.0 mm with ulceration
T2	1.1–2.0	T2a, without ulceration T2b, with ulceration
T3	2.1–4.0	T3a, without ulceration T3b, with ulceration
T4	>4.0	T4a, without ulceration T4b, with ulceration

Nodal Classification	Number of Nodes	Clinical Detectability/ Microsatellite Metastases Status
N1	1	NX, reginonal nodes not accessed N0, no regional metastases detected N1a, clinically occult; no MSI N1b, clinically detected; no MSI N1c, 0 nodes; MSI present
N2	2–3	N2a, clinically occult; no MSI N2b, clinically detected; no MSI N2c, 1 node; MSI present
N3	>4	N3a, clinically occult; no MSI N3b, clinically detected or presence of any number of matted nodes; no MSI N3c, >2 nodes or any number of matted nodes; MSI present

Metastases Classification	Site	Serum Lactate Dehydrogenase
M1a–d	Skin/subcutaneous/nodule (M1a); lung (M1b); visceral (M1c); CNS (M1d)	Not assessed
M1a–d(0)	Skin/subcutaneous/nodule (M1a); lung (M1b); visceral (M1c); CNS (M1d)	Normal
M1a–d(1)	Skin/subcutaneous/nodule (M1a); lung (M1b); visceral (M1c); CNS (M1d)	Elevated

T0 = no known primary.
Tis = melanoma in situ.
(sn), add to nodal status if SLN positive but completion lymphadenectomy not performed.
Abbreviation: MSI, microsatellite, satellite, and in-transit metastases.
Data from Gershenwald JE, Scolyer RA. Melanoma staging: American Joint Committee on Cancer (AJCC) 8th edition and beyond. Ann Surg Oncol 2018;25(8):2105–10; and Gormally MV. New Haven (CT).

that 0.8-mm tumor thickness carried more prognostic significance than the presence or absence of a mitotic figure.[22] Nonetheless, mitotic rate should still be recorded, because over the entire range of mitoses, there is predictive value that will likely be further elucidated in future studies. The relevance of determining T1a/b status is the difference between less than 5% likelihood of SLN metastases versus 5% to 12%.[22] Therefore T1b is the cutoff at which SLNB is recommended (discussed later).

Changes in Nodal Staging

The major change in the staging of nodal status in melanoma is the inclusion of the tumor status in the overall staging. In the seventh edition, the presence of nodal status trumped whatever tumor stage was associated with it. The inclusion of tumor thickness and ulceration results in a more granular distribution of stage III staging, from 3 to 4 categories (stages IIIA, IIIB, IIIC, and IIID) (**Table 3**). Previous terms, *microscopic* and *macroscopic* metastases, are now termed, *clinically occult*, if the nodal metastases are detected by SLNB, versus *clinically evident*, if they are detected by clinical or radiographic examination. Finally, the presence of microsatellites, satellites, or in-transit metastases is automatically under N1c, N2c, and N3c depending on the number of tumor-involved lymph nodes (1, 2 or 3, and 4 or more respectively). Microsatellites are defined as microscopic cutaneous or subcutaneous tumors discontiguous from the primary but found on pathologic examination of the original primary site.

Changes in Metastases Staging

The major changes in the staging of metastases status in melanoma are (1) the addition of central nervous system (CNS) metastases as a new class, Md, and (2) the inclusion of LDH as an additional prognostic factor to each M stage.

Mutational Subtyping of Melanoma

Exomic sequencing of metastatic melanoma is regularly performed to determine key mutations that will influence treatment and prognosis. The Cancer Genome Atlas Network recently provided a schema for CM classification: *BRAF*, *RAS, NF-1*, and

Table 3
TNM staging, clinical stage American Joint Committee on Cancer, eighth edition, continued

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1a–T2a	N1a	M0
	T1a–T2a	N1b	M0
Stage IIIB	T0–T3a	N1b–N1c	M0
	T2b–T3a	N2a	M0
	T1a–T3a	N2b	M0
Stage IIIC	T3b–T4a	N1a–N2b	M0
	T0	N2b–N3c	M0
	Any T	N2c	M0
	T1a–T4a	N2c–N3c	M0
	T4b	N2c	M0
Stage IIID	T4b	N3a–N3c	M0
Stage IV	Any T	Any N	M1

Data from Gershenwald JE, Scolyer RA. Melanoma Staging: American Joint Committee on Cancer (AJCC) 8th Edition and Beyond. Ann Surg Oncol 2018;25(8):2105–10; and Gormally MV. New Haven (CT).

triple–wild type (WT)[23] (Table 4). Increasingly genomic classification will likely replace the current pathologic subtyping system of superficial spreading, nodular, acral-lentiginous, and LM melanomas. Mutational status of a patient's tumor represents a move toward personalized medicine both from prognostic and treatment points of view. The best example to date remains the highly selective targeting of the kinase domain of *BRAF* resulting in cessation of *BRAFV600* mutant metastatic melanoma.[24] In Table 4, treatment options specific to the listed mutations that have clinical relevance are provided, with many more that have demonstrated efficacy that are not included.

Molecular Predictors of Melanoma Outcome

The need for additional prognosticators beyond SLN is clear because further risk-stratifying early-stage tumors (stage I and II) currently is not possible. A recent study has highlighted the burden of mortality in stage I melanomas comprising 23% of all melanoma-related deaths in Queensland, Australia, even though the 10-year survival for stage I melanoma patients is 94% to 98%.[25] Circulating factors, cell-free DNA, tumor-infiltrating lymphocytes, and other immune biomarkers have all been investigated for prognostic ability in melanoma outcome. In addition, gene expression profiles, such as what has been released by Castle Biosciences, Inc., (Phoenix, AZ), has been shown to be an independent predictor of metastatic risk, including in patients with negative SLN biopsies.[26] This platform is available for clinical use, but association with improved patient survival or alteration in outcome as a result of the testing has not yet been demonstrated. Although there likely will be molecular predictors in the near future, none are currently recommended by major collective cancer groups, such as the NCCN or AJCC.

SURGICAL MANAGEMENT AND RADIATION

Initial definitive surgical management of CM with wide local excision (WLE) is critical to reduce local recurrence and melanoma-specific mortality. Recent data have

Table 4
Genomic classification of cutaneous melanoma

Gene	Hot Spot Mutations	Percentage	Characteristics	Treatment
BRAF	BRAFV600E, K	35–50	• Early driver mutation also seen in benign nevi (80%) • Younger patients	Combination BRAF and MEK inhibition
RAS	Q61K, Q61R	10–25	• Associated with thicker tumors, higher mitotic rate • Associated with nodular subtype	MEK inhibition
NF-1	—	14	• Older patients • High mutational burden	—
Triple WT	*c-KIT*; *GNAQ*	10	• Lack UV signature • Increased copy number alteration, structural rearrangements • Acral lentiginous, mucosal subtype	c-KIT inhibition

Data from Refs.[23,55,56]

suggested that mortality is improved when stage I patients undergo WLE within 30 days of initial biopsy, but no effect was seen for stage II and stage III patients.[27] The primary goal of WLE is tumor removal, with secondary goals of minimizing surgical site complications and cosmetic disfigurement.

Prior to the 1970s, WLE was empirically performed with margins up to 5 cm, but data from several RCTs suggest rates of local control and survival with narrower margins.[28] The recommended peripheral clinical margins for WLE depend on the Breslow thickness and range from 0.5 cm to 2.0 cm (**Table 5**).[29] The depth should be to the fascia; data suggest no additional benefit from deeper excision.[28] For LM, a type of melanoma in situ, the debate on the ideal surgical margin persists.

Breslow thickness predicts the likelihood of SLN metastases. The Multicenter Selective Lymphadenectomy Trial (MSLT) I examined SLNB in intermediate-thickness melanoma (1.2–3.5 mm) and found a positivity rate of 16.0%.[30] Additionally, SLN positivity was found the single most important prognostic factor.[30] For thin melanoma less than 1.0 mm, a depth greater than 0.75 mm is associated with a higher rate of SLNB positivity (6.2% vs 2.7%),[31] although the prognostic value is less clear.[29] Current guidelines recommend SLNB for melanoma staged T1b and greater (eg, < 0.8-mm thick with ulceration or $\geq$ 0.8-mm thick with or without ulceration).[29] The exception is pure desmoplastic melanoma, which tends to have lower rates of SLN positivity; thus, the role of SLNB in these cases is controversial.[29]

Historically, patients with a positive SLNB subsequently underwent complete lymph node dissection (CLND). This practice, however, has recently been challenged by the results of the MSLT II, which randomized patients with SLN positivity to CLND or observation with frequent nodal ultrasonography (every 4 months for 2 years then every 6 months for years 3–5) and CLND only if there was nodal recurrence.[32] The MSLT II found that immediate CLND increased the rate of regional control (92% vs 77%) and improved disease-free survival slightly (68% vs 63%), but melanoma-specific survival was unaffected (86% vs 86%).[32] Lymphedema was a significant complication in the group undergoing CLND (24.1% vs 6.3%).[32] Given CLND's morbidity and lack of survival benefit, the authors' institution forgoes immediate CLND and conducts active surveillance in patients with SLNB positivity using nodal ultrasonography as per the MSLT II timeframe.[32] Therapeutic lymphadenectomy is performed when there is nodal recurrence confirmed by FNA and no evidence of distant metastases, or if there is a bulky nodal disease.

For patients with resectable in-transit metastases without distant metastases, surgical excision is recommended to obtain pathologic clearance, but WLE margins are unnecessary.[29] For in-transit metastases not amenable to resection, treatment options include topical imiquimod, intralesional talimogene laherparepvec (T-VEC), and

Table 5
Surgical margins for wide local excision of primary melanoma

Breslow Thickness	Peripheral Clinical Surgical Margins
In situ	0.5–1.0 cm
<1.0 mm	1.0 cm
1.0–2.0 mm	1.0–2.0 cm
> 2.0 mm	2.0 cm

Adapted from Richard GBH, Langley. Skin cancer: an overview of non-melanoma cancers and melanoma. 3rd edition. Halifax (Canada); Cancer Care Nova Scotia: 2013; with permission.

radiation therapy (RT).[29] In patients with in-transit as well as distant metastatic disease, systemic treatment options should be considered.

RT is not typically used first line but is useful in select clinical scenarios. For unresectable LM, RT may be used with clearance rates reported of 83% when used in isolation and 90% when used in conjunction with partial surgical clearance.[33] Topical imiquimod also has high reported clearance rates clinically and histologically for unresectable LM (70% to 100%), although a phase 2 study demonstrated a complete clearance rate of 37% with imiquimod as a monotherapy in the treatment of LM.[29,34] RT may also be used in the adjuvant setting for primary melanomas where anatomic constraints prevent clear surgical margins (eg, head and neck). For desmoplastic melanoma, a locally aggressive subtype, RT may have an adjuvant role both for positive surgical margins and for negative surgical margins in the setting of high-risk features, such as neurotropism or Breslow thickness of 4 mm or greater.[35] Palliative RT also can be useful for metastases, in particular stereotactic radiosurgery or whole-brain radiation for brain metastases.

MEDICAL MANAGEMENT OF METASTATIC MELANOMA

Immunotherapy

In 2011, ipilimumab, a CTLA-4 inhibitor, was approved by the FDA for the treatment of metastatic melanoma, ushering in an era of therapeutics that reverse the immune system's natural ability to turn itself off. Prior to this, the last therapeutic approved for metastatic melanoma was interleukin 2 in 1998. CM is a known immunogenic tumor as evidence of regression is seen both clinically and pathologically. Previous attempts at immunotherapy and vaccination treatments focused on boosting immune response by increasing the number or efficacy of cytotoxic T cells. The recent wave of immunotherapy targets CTLA-4 and the programmed cell death protein 1(PD-1)/programmed death-ligand 1(PDL-1) pathways, immunomodulatory receptors expressed on T cells. These receptors and their ligands regulate T-cell exhaustion and the blockade of this pathway can revive exhausted $CD8^+$ cells. This normal compensatory pathway, important in chronic infections, is hijacked by tumor cells, such as those found in melanoma.

The initial phase III study demonstrated superiority of ipilimumab over glycoprotein (gp) 100 vaccine with an improved median OS (10 months vs 6.4 months).[36] Grade 3 or grade 4 immune-related events (IREs) were noted, however, in 10% to 15% of the ipilimumab arm (vs 3% in gp100 alone). Ipilimumab responders demonstrate a unique aspect of checkpoint blockade—responders frequently (20%) are long-term responders with the plateau starting at 3 years.[37] The PD-1 inhibitors, nivolumab and pembrolizumab, came shortly thereafter, and were demonstrated to have higher response rates as well as decreased incidence of grade 3 to grade 4 side effects. Nivolumab as a monotherapy in previously untreated *BRAF* WT patients compared with dacarbazine has a response rate of 40%, 1-year survival rate of 72.9% (vs 42.1), and a grade 3 or grade 4 adverse event rate of 11.7%.[38,39]

In a phase 3 study, the combination of nivolumab and ipilimumab proved superior to ipilimumab alone or nivolumab alone in terms of median progression-free survival (PFS) (11.5 months vs 2.9 months vs 6.9 months, respectively).[40,41] Combination therapy also had the highest response rate at 57.6% (compared with 43.7% nivolumab and 19% ipilimumab). At the 3-year update, the OS rate was 58% in the combination group and 52% in the nivolumab group compared with 34% in the ipilimumab group.[42] Treatment-related adverse events of grade 3 or grade 4 occurred in 59% of the patients in the combination group (vs 21% nivolumab and 28% ipilimumab). Taken together, the combination therapy offers a superior response rate but modestly better

OS compared with PD-1 inhibition alone with a higher IRE profile. As a result, not all patients receive combination therapy as first-line therapy.

The adverse event profile of immunotherapy is beyond the scope of this review, but the significance of having an IRE is important in that there are several lines of evidence suggesting a correlation between having an IRE and a disease response. For instance, in the 120 patients who discontinued combination therapy due to toxic effects, 67.5% had a response.[41] Predictors of response to immunotherapy is also an area of active investigation. Finally, several other checkpoint pathways are being studied in combination with CTLA-4 and PD-1 inhibition.

Targeted Therapy

The development of a highly selective oral inhibitor of BRAFV600E mutation was ground-breaking and heralded an influx of other highly specific kinase-targeting agents in all cancer treatment.[24] Although BRAF-inhibition (BRAFi) as a monotherapy for BRAFV600 mutant unresectable melanoma, was associated with a high response rate (approximately 50%) and a rapid onset (within 2 weeks), it was also almost universally associated with relapse with a median PFS of 6 months to 8 months.[43] This acquired resistance was due to paradoxical activation of the MAPK pathway. Combination therapy using both BRAFi and MEK-inhibition (MEKi) seems to negate the resistance pathways. In a phase 3 trial comparing dabrafenib/tramatenib to vemurafenib in previously untreated patients, combination therapy demonstrated improved OS of 72% versus 65% at 12 months.[44] The combination therapy also had improved response rate (64% vs 51%) and improved median PFS (11.4 months vs 7.3 months).[44] This study confirmed several other previous combination versus monotherapy studies that all concurred the superiority of combination therapy in the treatment of BRAFV600 mutant melanoma.[45,46] The current FDA-approved BRAFi/MEKi combinations include vemurafenib/cobimetinib; dabrafenib/tramatenib; and encorafenib/binimetinib.

The question of whether to start with targeted therapy versus immunotherapy is an important question that reflects clinical judgment and may be further teased out as more data on sequential treatments are analyzed. Of course, BRAF WT patients would not benefit from targeted therapy. Often, checkpoint blockade is used as first line given the high response rate and durable responses. In patients with BRAFV600E mutant melanoma and rapidly growing tumor, the kinetics of targeted therapy are much faster (in the order of weeks) compared with immunotherapy (months, and sometimes with a delayed effect), and often are used to provide symptomatic relief to a patient.

Additional targeted therapy treatments, such as the treatment of c-kit mutant melanomas with c-kit inhibitors like imatinib mesylate, are not discussed in this review.

Adjuvant Therapy

Demonstrated efficacy of these medications soon led to trials in the adjuvant setting.

In the adjuvant setting, pembrolizumab has demonstrated to be superior than ipilimumab and with a lower adverse event rate. A head-to-head phase III study of pembrolizumab (3 mg/kg weight every 2 weeks) versus ipilimumab (10 mg/kg every 3 weeks for 4 doses and then every 12 weeks) in the adjuvant setting was completed for patients undergoing complete resection of stage IIIB, stage IIIC, or stage IV disease.[47,48] At 12 months, recurrence-free survival was 70.5% in the nivolumab group and 60.8% in the ipilimumab group. Treatment-related grade 3 or grade 4 adverse events were lower in the nivolumab arm (14.4% vs 45.9%).

The combination BRAFi/MEKi, has also been approved for adjuvant treatment of BRAFV600E and V600K stage III patients after complete resection based on data

from the phase III COMBI-AD study.[49] At 3-year follow-up, patients on the treatment arm had an improved relapse-free survival compared with placebo (58% vs 39%).

SURVEILLANCE AND PREVENTION

All CM patients should undergo at least annual dermatologic examination indefinitely.[29] Approximately 2% to 10% of patients develop a second primary CM, approximately half of which occur within 1 year.[29] In addition to the risk of additional CM, patients are at risk for local and distant recurrence, although there is no proven survival benefit from earlier detection of recurrence.[29] Compared with later-stage melanoma, earlier-stage melanoma is less likely to recur but does so over a longer time horizon.[29] Current guidelines recommend that patients with stage IA to stage IIA melanoma undergo history, physical, and skin examination every 6 to 12 months for 5 years and annually thereafter.[29] Patients with stage IIB–IV melanoma should undergo such examination every 3 to 12 months for 3 years and annually thereafter.[29] In these patients, surveillance CT chest, abdomen, pelvis or PET/CT in addition to brain MRI may also be considered for the first 3 years postdiagnosis.[29]

Sun protection plays a key role in primary prevention of CM. A randomized controlled trial found reduced CM incidence (hazard ratio 0.50) in subjects randomized to daily rather than discretionary sunscreen use.[50] Numerous agents have been proposed for primary chemoprevention, including topical retinoids, polypodium leucotomos extract, nonsteroidal anti-inflammatory agents, and statins, but evidence is lacking to support regular use.[51] A meta-analysis found no association between vitamin D intake via diet and/or supplementation and CM incidence.[52] Vitamin D deficiency, however, is associated with worse prognosis in metastatic melanoma,[53] and a clinical trial is under way to examine vitamin D supplementation for tertiary prevention.[54] Given recommended sun-avoidant behavior, the authors regularly recommend vitamin D supplementation in CM patients.

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