2022–2023 Management of Cutaneous Melanoma

Background

Skin melanoma (hereon simplified as "melanoma") accounts for 1.7% of global cancer diagnoses and is growing in incidence in developed countries (0.01% to 0.025% in Europe and 0.02% to 0.03% in the USA per 100,000 cases every year). Melanoma is responsible for over 80% of skin cancer deaths.[1,2] The 5-year overall survival (OS) of melanoma has risen to 93.3% in the US, but the survival rate for advanced disease remains only 30%.[2] There is no cure for advanced-stage melanoma, and the management goals focus on prolongation of survival and delay of progression.[3]

Melanoma exacts a substantial financial burden. The average annual cost of melanoma treatment increased by 288% from 2002 to 2006 and from 2007 to 2011, much higher than 25% for all other cancers combined. Melanoma skin cancer treatment costs $3.3 billion in the United States each year.[4]

The causes of start and progression of skin melanoma include oxidative stress, UV exposure, and perhaps alcohol consumption.[5-7] Current treatment modalities include surgery, radiotherapy, conventional chemotherapy, targeted therapy, and immunotherapy.[8] The current standard of care for stage I to resectable stage III melanoma is excision with/ without lymph node management (lymphatic mapping and sentinel lymph node biopsy and others applicable for each stage). For unresectable stage III, stage IV, and recurrent melanoma, the standard treatment options include intralesional therapy (talimogene laherparepvec [T-VEC]), immunotherapy (immune checkpoint inhibitors [ICI]), signal transduction inhibitors (i.e., B-type Raf kinase [*BRAF*V600] with mitogen-activated protein kinase [MEK] inhibitors, briefly BRAF/MEK inhibitors), chemotherapy, and palliative local therapy (regional lymphadenectomy and radiotherapy).[9]

Based on mutational profiles, melanoma encompasses four major distinct subtypes, *BRAF*V600 mutation melanoma (in 45% of patients), neuroblastoma *RAS* (*NRAS*) mutation melanoma (15%), *KIT* mutation melanoma (5% to 10%), and wild-type melanoma. They differ in responses to treatment, which complicates management decision making.[10] With mutation-based subtypes identified, the current challenges for the treatment include resistance to BRAF/MEK inhibitors and ICI, and the toxicities induced by BRAF/MEK inhibitors therapies, among others.[11-13]

Despite the enormous effort of clinicians, diagnostic path and treatment should be improved during earlier stages to prevent/delay the progression of the disease.[11-13] Furthermore, awareness of recent clinical data in novel drug classes and combined therapies for late-stage disease should be improved in order to lower the death rate.

The Expanding Treatment Paradigm

Recently, cancer experts have found that combining two or more drugs may treat advanced melanoma more effectively than either drug for certain patients.[14] Indeed, a leading clinician in cutaneous oncology and clinical immunotherapy has commented:

Combination of immunotherapy is like a car at an intersection with three or four traffic lights in front that have to turn green for the car to progress through the intersection. In immunotherapy, an immune cell inside the cancer tumor needs one or perhaps more green lights (drugs) to be able to attack the cancer in front.

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However, despite the expert commentary, not all combination therapies have proven successful in phase 3 clinical trials. Clinicians need to be aware of updated data to make treatment decisions.[10]

Gaps in Care

The cutaneous melanoma clinician community is well-apprised of common diagnostic approaches and treatment pathways. However, currently the unstructured approach to skin melanoma early detection and treatment decision implies concerns in variable quality of care, sociodemographic inequalities, excision of many benign lesions (i.e. overdiagnosis), gaps in workforce training, and health system inefficiencies.[15] "To Improve Melanoma Outcomes, Focus on Risk Stratification, Not Overdiagnosis". - Robert A. Swerlick, MD.[16] This means that the optimal diagnostic pathway is not well-known. Furthermore, higher-volume hospitals are likely to result in higher survival rates of care compared with smaller volume counterparts.[17] Finally, clinicians may be unaware of new successes and failures of drug data obtained in phase 3 clinical trials or above to treat advanced melanoma.

Diagnosis pathways

Early diagnosis of skin melanoma is crucial to reduce potential deaths. Indeed, early detected melanoma patients have better prognosis than those diagnosed at late stages. Late-stage diagnosed patients require much higher health system costs. [11-13,15] Yet early diagnosis is hard to implement because the USA is in short supply of dermatologists. Diagnosis is thus the responsibility of primary healthcare physicians (PHP). Most PHPs do not provide skin examinations and are not familiar with recent technologies.

The knowledge/behavior gaps of PHPs include:

- Not providing skin examinations. Such behavior of PHPs is hard to change if the education intervention is not intensive enough.[18]
- Not knowing/implementing new technologies for diagnoses. The most recent diagnostic tools include gene expression profiling tests, dermoscopy, artificial intelligence-assisted tools and teledermatology, etc.[19,20] Dermoscopy can be used to distinguish benign from invasive lesions.[21] Teledermatology can even help diagnoses in remote areas, where people are at high risk of skin melanoma and have less access to clinicians. A European consensus-based interdisciplinary guideline published in 2022 recommended tests of dermoscopic diagnosis, histopathologic diagnosis, and mutational tests, followed by encouraging eligible patients to participate in clinical trials before deciding their treatment options.[1,10]
- Implicit bias toward patients with darker skin, whose presentation of the disease differs from those of patients with lighter skin. Such educational content is only depicted in less than 5% of textbooks for physicians.[22]

***Needs Summary/Education Gap 1*:** Some primary care physicians (PCPs) may not provide enough screening for skin melanoma patients, and the knowledge and technologies of PCPs may not be up-to-date.

New success and failures to treat advanced melanoma

Physicians may be unaware of the recent successful and failed therapies shown in phase 3 trials for both

*BRAF*V600-wild type and *BRAF*V600 advanced melanoma.

American Society of Clinical Oncology (ASCO) guidelines published in 2020 recommend combotherapies as follows: In the adjuvant setting for patients with resected stage IIIA/B/C/D wild-type melanoma, nivolumab or pembrolizumab should be offered to adult and pediatric patients.[23] In resectable BRAF-mutant counterpart disease, either of those two agents or the combination of dabrafenib and trametinib should be offered.[24] These therapies are further proven successful as of 2022.[25,26]
In unresectable/metastatic stage wild-type melanoma, ipilimumab plus nivolumab, nivolumab alone, or pembrolizumab alone should be offered to patients. In BRAF-mutant disease of the same stage, those three regimens or triple therapy, i.e., combination with BRAF/MEK inhibitor therapy (dabrafenib/trametinib, encorafenib/binimetinib, or vemurafenib/cobimetinib) are recommended.

Furthermore, recent successful combotherapies include nivolumab plus relatlimab and nivolumab plus ipilimumab.[27,28] Unsuccessful combotherapy there is T-VEC plus pembrolizumab.[29] A novel cell therapy tumor-infiltrating lymphocytes (TILs) emerged as a successful treatment.[30] For BRAF-mutant disease in the advanced stage, a triple therapy atezolizumab plus cobimetinib/vemurafenib] was approved but lacks mature evidence.[31-34] A failed triple therapy is spartalizumab plus dabrafenib/trametinib.[35,36]

***Needs Summary/Education Gap 2*:** Physicians may be unaware of the recent clinical data regarding new successful and failed therapies for advanced melanoma with different genetic types.

Summary

Standard of care or guidelines regarding skin melanoma should be updated more frequently due to the ever-changing landscape of skin melanoma care; e.g., European consensus-based interdisciplinary guidelines for melanoma published in 2022 did not include diagnoses of how to identify skin melanoma in patients with darker skin.[1,10] Furthermore, the PHP education needs to be improved in terms of content and format to reinforce sustainable practice changes.[37,38] The most common barriers reported by PHPs include lack of dermatologic training (89.4%), time constraints (70%), and competing comorbidities (51%).[39]

PHPs play a key role in early diagnoses and management of skin melanoma compared with specialists. Targeted educational content can equip PHPs with diagnostic pathways, technologies, and remove bias toward patients with darker skin, and maintain positive clinical practice changes. On the other hand, CME programs can target specialists with knowledge of novel therapies that can delay the progression of late-stage skin melanoma and ensure optimal patient outcomes.

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