2021-2022 Management of Cutaneous Melanoma

BACKGROUND

Skin melanoma (from here on simplified as “melanoma”) accounts for 1.7% of global cancer diagnoses and sees growing incidences in developed countries (0.01% to 0.025% in Europe and 0.02% to 0.03% in the USA). 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 the 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]

The current standard of care for Stage I to Resectable Stage III Melanoma is excision plus or 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 (STI), i.e., B-type Raf kinase (BRAFV600) with Mitogen-activated protein kinase (MEK) inhibitors, chemotherapy, palliative local therapy (regional lymphadenectomy and radiotherapy).[4]

Based on mutational profiles, melanoma encompasses four major distinct subtypes, BRAFV600 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 poses challenges to improving patients’ survival.[5] With mutation-based subtypes identified, the current challenges for the treatment include the resistance to STI and ICI causing inefficacy, and the toxicities induced by STI therapies, among others [6–8].

For advanced-stage disease, recent developments in novel drug classes and combined therapies pave the way to lowering the death rate; diagnostic path and treatment should be improved during earlier stages to prevent/delay the progression of the disease.[6–8] It is vital that clinicians are aware of such advanced knowledge if they were to overcome the obstacles and address the unmet needs of improving patient benefit and survival of advanced melanoma.

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unaware of the recent success and setbacks of novel drug combinations and emerging therapies for advanced/unresectable melanoma stratified by its mutation-based subtypes.

Learning objective #1: Summarize and compare recent clinical trial data regarding the novel drug combinations and novel therapies for advanced/unresectable melanoma stratified by its mutation-based subtypes.

Physicians may be unaware of the recently developed novel drug therapies and combination therapies showing advantages over the monotherapies for both BRAFV600-wild type advanced melanoma and BRAFV600. Physicians should also note that the development of treatment options in other subtypes of mutational melanoma is still rare and lack improvement, which needs their effort to facilitate the discussion and conducting further clinical trials.

Advanced Melanoma or Unresectable Melanoma

Treatment options proved to be effective in advanced trials mainly include combination of ICI therapies as the first-line treatment.

ICI Combotherapy as the first-line treatment
In terms of delaying the progression of untreated advanced melanoma, nivolumab plus relatlimab combotherapy is more effective than their monotherapies. Updated results of the global phase 3

RELATIVITY-047 trial show nivolumab plus relatlimab delays progression significantly than nivolumab as a first-line treatment (median progression-free survival (PFS) 10.1 months vs. 4.6 months; hazard ratio (HR) 0.75; p = 0.006 by the log-rank test).[9]

Nivolumab plus ipilimumab shows a trend of improving long-term OS with respect to the monotherapies in their phase 3 trial (p value not reported). At min. 6.5 years follow-up, nivolumab plus ipilimumab patient subgroup achieved a median OS of 72.1 months, much longer than the monotherapy subgroups (nivolumab 36.9 months and ipilimumab 19.9 months). The OS rates are 49%, 42%, and 23%, respectively. The HR is 0.84 for combination group vs nivolumab group, and 0.52 for combination group vs. ipilimumab group.[10]

T-VEC combined with ICI not providing patient benefit vs. ICI

The recent Phase 3 trial indicated no significant improvement in survival through adding T-VEC to pembrolizumab in patients with advanced melanoma (median PFS 14.3 months with combotherapy vs. 8.5 months pembrolizumab; HR 0.86; p = 0.13).[11]

Tumor-infiltrating lymphocytes (TILs)

Additionally, tumor-infiltrating lymphocytes (TILs), a type of cell therapy, have emerged as a novel therapeutic route for advanced melanoma. TIL therapy utilizes the patient's own immune cells that have already identified and invaded the tumor. The tumor would be resected and the immune cells would be extracted from the tumor. Chemotherapy will be applied to the tumor to make space for the TIL therapy. An immune-boost called interleukin-2 (IL-2) would be administered to help the TILs grow throughout the body.

At a median follow-up of 33.0 months, TIL showed higher median PFS than ipilimumab (7.2 months vs. 3.1 months; HR 0.50; p<0.001), possible higher response rate (49% vs. 21%), complete response rate (20% vs. 7%), and possible longer median OS (25.8 months vs. 18.9 months; HR 0.83; p=0.39).[12]

BRAFV600 mutation Advanced Melanoma or Unresectable Melanoma

For BRAFV600 mutation advanced/unresectable melanoma, recent phase 3 trials focused on ICI plus STI combotherapies. One trial appear to show possible success for better efficacy than only STI therapies and the other one failed to show statistically significant improvement, as detailed below.

For unresectable advanced BRAFV600 mutation melanoma, atezolizumab was granted approval for first-line treatment used in combination with cobimetinib and vemurafenib, based on findings from Phase 3 double-blind IMspire150 trial in 2020.[13] Analysis by investigators showed that the addition of atezolizumab into the BRAF/MEK inhibitors significantly improved the median PFS than only STI therapies (15.1 vs. 10.6 months; HR 0.78; p=0.025). However, independent review committee-assessed data showed prolonged but not statistically significant median PFS (16.1 vs. 12.3 months; HR 0.85; p = 0.16) and 2-year OS rate (60% vs. 53%; HR 0.85; p =0.23).[14,15]

For unresectable/metastatic BRAFV600 mutation melanoma, the addition of spartalizumab into dabrafenib and trametinib failed to show statistically significant progression-free survival (PFS) benefit (p=0.42; HR 0.82) and demonstrated high toxicity (Grade>= 3 treatment-related AE in 55% treatment vs. 33% placebo group). Biomarker-driven studies did not identify patient subpopulations that may receive patient benefits from this treatment option.[16,17]

Gap #2: Clinicians may be unaware of the recently approved adjuvant drugs to treat Stage II and III melanoma and for adult and pediatric populations.

Learning objective #2: Summarize the recent clinical trial data of the recently approved adjuvant drugs to improve treatment outcomes for Stage II and III melanoma for adult and pediatric patients.

ICI adjuvant therapy for resected Stage II and resected High-Risk Stage III melanoma for adult and pediatric patients

Adjuvant pembrolizumab appears to bring long-term survival benefit in adult and pediatric patients with resected stage II and stage III melanoma.

The adjuvant pembrolizumab group significantly improved 3.5-year recurrence-free survival (RFS) (59.8% vs. 41.4%; HR 0.59; p<0.0001) and 3.5-year distant metastasis-free survival (DMFS) (65.3% vs. 49.4%; HR 0.60; p<0.0001) compared to the placebo group, as shown previously in phase 3 trial.[18] A recent 5-year long-term report confirmed such recurrence- and distant metastasis-free survival benefits. Recently, the long-term benefit is confirmed, i.e., 5-year RFS rate is 55.4% vs. 38.3%, with HR 0.61, and the 5-year DMFS rate of 60.6% vs. 44.5% placebo, with HR 0.62 (p value not reported).[19] In patients with resected Stage IIB and IIC melanoma, median DMFS did not reach 27.4 months. Median RFS reached 37.2 months vs. less in placebo group (HR 0.64 for both RFS and DMFS). [20]

For resected high-risk Stage III melanoma patients, adjuvant pembrolizumab obtained 5-year RFS rate of 55.4% vs. 38.3% (placebo) (HR 0.61), and a 5-year DMFS rate of 60.6% vs. 44.5% (placebo) (HR 0.62).[19]

Adjuvant pembrolizumab was approved for pediatric (≥ 12 years of age) patients with high-risk resected stage II melanoma. Pembrolizumab significantly reduced the risk of recurrence by 35% (p=0.00658) (data not specified for pediatric patients). [21,22]

STI adjuvant therapy for resected stage IIIB-D BRAFV600 mutation melanoma

Adjuvant dabrafenib plus trametinib show the trend of improving patient survival for resected stage IIIB-D BRAFV600 mutation melanoma. Adjuvant dabrafenib plus trametinib improves 5-year DMFS rates (65% vs. 54% placebo with HR 0.55, p value not reported) and 5-year RFS rates (52% vs. 36% placebo with HR 0.51, p value not reported).[23] One hurdle for the patients to continue this treatment is the severe pyrexia adverse event (9% permanent discontinuation), which triggered a part of the phase 3 trial for a new pyrexia management algorithm that appears to reduce the incidence of severe pyrexia outcomes (2.4% discontinuation rate).[24]

Gap #3: Clinicians may be unaware of the recent guidelines regarding diagnostic paths along with new effective diagnostic tools and methods.

Learning Objective #3: Integrate current diagnostic paths with emerging effective diagnostic tools and methods per new guidelines into clinical practice settings.

According to the new guidelines, physicians can potentially improve patient outcomes through adopting optimized diagnostic paths and emerging effective diagnostic tools and methods that ameliorate diagnostic accuracy.[1,5]

Diagnostic paths

Updated guidelines recommend tests of dermoscopic diagnosis, histopathologic diagnosis, and mutational tests, followed by encouraging eligible patients to participate in clinical trials before deciding their treatment options.[1,5]

Promising tools to improve diagnostic accuracy

To improve the accuracy of patient diagnosis, new tools and methods are proposed and recommended to be integrated into clinical practice.[1]

Dermoscopic diagnosis

In addition to dermatoscopy, whole-body photography sequential examinations and sequential digital dermatoscopy are recommended to improve the early detection response of melanoma. To increase diagnostic accuracy for equivocal lesions, reflectance confocal microscopy, may be useful for distinguishing the limits of the tumor with higher sensitivity and specificity.[1]

Histopathologic diagnosis

Besides the already-known histological features, such as the clinic-pathological subtypes, the new guideline recommends reporting on additional information including growth phase, presence/absence of regression, TIL, lymphatic emboli, and vascular or perineural involvement. in cases where the histological diagnosis is unclear of the nature of the tumor, Immunohistochemistry is recommended for further diagnosis.[1]

Molecular analysis

Besides BRAFV600 mutational analysis, if wild-type, the patient should be tested for NRAS mutation followed by a KIT mutation test to determine the eligibility for specific targeted therapies. Next-generation sequencing, which can comprehensively screen multiple genes, is recommended for mutational analysis, since it can be a less expensive and more time-effective. Other promising molecular analysis tools include tumor mutational burden (TMB), gene expression profiling (GEP), and liquid biopsies.[1]

TMB is defined as the number of somatic mutations per megabase of genes studied. TMB has been successfully used to predict response to immune checkpoint inhibitors in patients with melanoma (Keynote-158 study).[1]

GEP testing provides prognostic information on melanoma recurrence and progression based on the expression patterns of a selected panel of genes in the primary tumor. GEP testing can improve staging and guide interventions such as sentinel lymph node biopsy, surveillance imaging intensity, and adjuvant therapy; however, the routine use of GEP testing for melanoma malignancy has been under debate. Additional research data is required to prove that its prognostic information is independent of the known pathological factors.[1]

Liquid biopsy detects tumor cells, small molecules of tumor, or extracellular vesicles in blood samples. Liquid biopsy can possibly serve as a predictive biomarker that confirms baseline mutational status and monitors the treatment response and resistance to the targeted therapies.[1]

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CONCLUSION

A high mortality rate is associated with skin melanoma, especially with advanced or unresectable stage melanoma. To improve the survival period and rate of melanoma patients, it is essential for physicians to stay current with the latest treatment options and diagnostic technologies. First, it is urgent to make the right treatment decisions for advanced/unresectable melanoma patients, which requires physicians to master the knowledge of recently approved effective treatment combinations and novel classes of drugs stratified by subtypes of melanoma. Furthermore, it is imperative to prevent/delay the progression of the disease at earlier stages, which entails two parts of current knowledge: adjuvant drugs and diagnostic methods. Apart from the new adjuvant treatment options that can improve clinical outcomes, new diagnostic tools can aid physicians to diagnose the subtypes of melanoma accurately and early, so that physicians can make the right treatment decisions.

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