COMMENTARY

Shifting paradigms in the management of metastatic and unresectable melanoma

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Cutaneous melanoma is regarded as the most aggressive form amongst all skin cancers. Although representing only 4% of all cancers, of the 132,000 people diagnosed globally each year, 37,000 will die. In 2017, approximately 87,110 new cases of melanoma will be diagnosed in the United States, of which approximately 9,730 patients will succumb to the disease[1,2]. More than 80% of cases occur in developed countries and melanoma forms the sixth most common cancer in the developed world. The incidence of melanoma has witnessed an upward trend in the last five decades and the number of new cases diagnosed annually is increasing faster than for any other cancer in most of the developed countries[3]. The mainstay of management of melanoma is essentially early detection and surgical excision, and five-year survival rates of >90% and 80% for stage I and II lesions, respectively, have been reported. The chances for cure for locoregionally advanced and metastatic disease decrease drastically, with a survival of 50% for Stage III patients while Stage IV patients historically had a median survival of about 8–9 months and a three-year overall survival rate of about less than 15%[4,5]. Systemic treatment with a definitive survival benefit appeared to be a remote possibility traditionally. There has been recently established data which indicates an encouraging therapeutic response for metastatic melanoma with the evolution of several heterogeneous novel agents, and there is a hope for better overall survival for such patients, most of whom were deemed unfit for any curative systemic therapy until recently[6].

Traditionally, the systemic treatment for metastatic melanoma was characterized by low response rates and significant toxicities. One such agent was dacarbazine, which used to yield a response rate of about 20% and median response of a duration of about six months without any benefit in overall survival. Another such agent was high-dose interleukin (IL)-2, which provided about 6%–16% response rate and a progression-free survival of about 13 months. Interferon (IFN)-α was approved as the first agent in the adjuvant setting for selected high-risk resected cases and resulted in significant improvement in disease-free survival (DFS) and in some prospective randomized trials, with a benefit on overall survival in some studies; however, its use was associated with significant toxicity. Temozolomide is an oral alkylator with a cytotoxic effect identical to dacarbazine. Unlike the later drug, temozolomide is administered easily through oral route and it crosses the blood-brain barrier, thus exhibiting cytotoxic effect on brain metastases. Combination chemotherapy has also been tested in several studies, without showing any improvement in response rates[7,8].

Immunotherapy for advanced and metastatic melanoma has been extensively evaluated in the recent years, and
the encouraging results have resulted in the approval of immune checkpoint inhibitors targeting cytotoxic 
T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1)\[^6\]. The CTLA-
4 and PD-1 immune checkpoints are negative regulators of T-cell immune function. Inhibition of these targets, 
resulting in increased activation of the immune system, has led to new immunotherapies for melanoma which has significantly lesser systemic toxicities as compared to cytokine-based immunotherapy. Ipilimumab, a monoclonal 
antibody that targets CTLA-4, has been granted approval for use in the advanced unresectable disease. Nivolumab and pembrolizumab, which target the PD-1 inhibitors and thereby prolonging overall survival in patients with advanced or metastatic melanoma and also in relapsed or refractory cases, have been provided accelerated approval by competent authorities\[^9–11\]. The combination of ipilimumab and nivolumab provides higher response rates, greater tumor control, and longer progression-free survival as compared to monotherapy with either of these agents. Ipilimumab alone is no longer considered as the first-line therapy option, as CheckMate 067 phase III trial proved that improved outcomes are feasible with anti–PD-1 monotherapy or nivolumab/ipilimumab combination therapy\[^12\].

Hyper-activation of the MAPK-pathway has been noted in more than 90% of melanoma cases, with about 50% of all patients exhibiting mutations in the kinase BRAF and about 28% of all patients having mutations in the MAPK-pathway up-stream regulator NRAS. This formed the basis for the development of BRAF and MEK inhibitors, the therapeutic use of which has resulted in dramatic survival responses. Raf-MAPK pathway inhibition with the BRAF inhibitors vemurafenib and dabrafenib, either as monotherapy or in combination with a MEK inhibitor, has evolved as the preferred treatment approach in patients with BRAF-mutated metastatic melanoma. However, majority of patients treated with BRAF inhibitor monotherapy display limited duration of response and ultimately suffer from the development of acquired resistance. For such patients, the ideal treatment regimen includes BRAF/MEK inhibitor combination therapy with dabrafenib/trametinib or vemurafenib/cobimetinib, or single-agent BRAF inhibitor therapy with vemurafenib or dabrafenib. Both vemurafenib and dabrafenib have gained approval as single-agents for the management of metastatic or unresectable BRAF V600E-mutated melanoma. Dabrafenib/trametinib and vemurafenib/cobimetinib combination therapy regimens have been accepted for the treatment of these patients and BRAF V600E or V600K mutations should be confirmed by an FDA-approved test\[^13–15\].

The treating oncologists continue to face the challenge of the development of acquired resistance to BRAF/MEK inhibitor combination therapy, and other strategies need to be formulated to overcome this barrier, one option being exercised is the use of sequential and intermittent schedules. So far, the studies involving the combination of BRAF or MEK inhibitors with immunotherapy have shown promising results. Similarly the initial results from studies involving triple combination therapy with BRAF/MEK inhibitors and anti-PD-L1 antibodies have shown encouraging response for this new strategy to treat patients with BRAF-mutated metastatic melanoma. Reliable predictive biomarkers are needed to guide management decisions and to help identify patients with BRAF V600 mutations who are most likely to benefit from first-line BRAF/MEK inhibitor therapy rather than immunotherapy, and vice versa. The appropriate selection of systemic therapy, choice of agents to be used alone or in combination, and sequencing of these novel agents continue to evolve as more and more results are being made available\[^12,16\].

The standard of care for upfront management of unresectable or metastatic disease includes checkpoint immunotherapy and BRAF-targeted therapy for patients with BRAF-mutated disease, as clinically indicated. All patients, especially those with advanced and metastatic disease, should undergo exhaustive mutation testing of tumor tissue prior to treatment decisions. PD-1 checkpoint blockade either alone or combined with CTLA-4 blockade should be offered as initial therapy to patients with unresectable metastatic melanoma, independently from BRAF status. BRAF-inhibitors for BRAF-mutated patients are best given in combination with MEK inhibitors. Systemic chemotherapy can be offered to patients with good performance status who have developed resistance to the immunotherapeutic agents\[^4,12\]. Ongoing research is likely to address certain challenging issues such as drug development against novel immune targets, genetically modified oncolytic viruses, optimization and sequencing of combination strategies, and consensus on predictive biomarkers to help select appropriate treatment regimen\[^7,17–20\].
To summarize, the availability of immunotherapeutics and novel agents have shown promising role in the management of advanced and unresectable melanoma patients. All such cases should be discussed multimodally and the likely survival benefit be titrated against the potential complications. The management of such cases needs to be individualized and all institutes should formulate their own protocols based on the consensus guidelines of scientific societies.

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