Combination immunotherapy in management of advanced melanoma

Sir,

Approximately, 50% of patients with advanced melanoma harbor BRAF V600E mutations.[1]

Vemurafenib and dabrafenib are the agents targeting BRAF and when administered to patients with BRAF-mutant melanoma, approximately 90% of the patients experience some degree of tumor regression early in the course of therapy. The median duration of progression-free survival (PFS) in clinical trials with these agents ranges from 5.5-7.0 months. In the BRIM3 Phase III trial, comparing vemurafenib and dacarbazine in BRAF V600E-positive metastatic melanoma, median overall survival was 9.7 months in the dacarbazine group, versus 13.6 months in vemurafenib-treated patients. In longer follow-up available from a vemurafenib Phase II trial, the estimated median overall survival was 16 months. Mitogen-activated protein kinase (MAPK) (MEK) is the immediate downstream signaling molecule from BRAF [Figure 1]. Blockage of this step by trametinib has been associated with better PFS and overall survival in BRAF V600 melanoma.

The dual combination of the MEK inhibitor trametinib and the BRAF inhibitor dabrafenib as a treatment for patients with metastatic or unresectable melanoma harboring a BRAF V600E or V600K mutation has been granted an accelerated approval by the United States-Food and Drug Administration. This approval was based on the results from an open-label Phase I/II trial by Flaherty et al.[2] which showed that trametinib combined with dabrafenib nearly doubled the duration of response and significantly improved overall response rates when compared with dabrafenib alone. The combination targeted therapy in advanced melanoma is a novel way of overcoming the resistance, which has been a major concern in extracting the benefits from the immunotherapy. Combination therapy with 150 mg of dabrafenib and 2 mg of trametinib (combination 150/2) was also safe in terms of dose-limiting toxic effects being observed only infrequently. Another major benefit from the combination was reduced chances of cutaneous Squamous cell carcinoma being observed in 7% of patients receiving combination 150/2 while in 19% receiving monotherapy (P = 0.09); however, pyrexia was more frequent in the combination 150/2 group than in the monotherapy group (71% vs. 26%). Median PFS in the combination group was 9.4 months versus 5.8 months in the monotherapy group (hazard ratio for progression or death, 0.39; 95% confidence interval, 0.25-0.62; P < 0.001). The rate of complete or partial response with combination 150/2 therapy was 76%, when compared with 54% with monotherapy (P = 0.03).

Wagle et al.,[3] have recently shown that the MEK2Q60R mutation conferred profound resistance to the combination of dabrafenib plus trametinib, as well as to single-agent dabrafenib and trametinib. On the other hand, MEK2Q60R did not confer resistance to treatment with an extracellular signal-regulated kinase inhibitor, which targets the MAPK pathway downstream of MEK1/2. Thus, the door for a tailored therapy in resistance to dual drug combination for advanced melanoma is open yet again. In the meantime, the results of Phase III trials combining the two targeted drugs are eagerly awaited to determine the exact benefits of the combination.

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Figure 1: Pathway of cell signaling in melanoma and site of action of targeted therapy
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REFERENCES