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Editorial

Checkpoint Inhibitors in Checkmating Rare Cancers

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Rare cancers, defined as those with an incidence of fewer than six cases per 100,000 people per year, are extremely challenging to treat.[1] They have a poor prognosis when diagnosed at an advanced stage, the main reasons being two-fold: delay in diagnosis and limited therapeutic options. Rare cancers account for a significant number of new cancer diagnosis (> 20% of all cancer diagnoses) and cancer-related deaths. The rarity of some cancers varies with the geographic location; for example, cervical and gall bladder cancer are rare in Western countries but may not be so rare in countries like India.

There is a dearth of active research focusing on developing newer treatment strategies for rare cancers with the aim of improving treatment-related outcomes. It was for this very reason that the International Rare Cancer Initiative (IRCI) was established in 2011 to make practice-changing clinical trials for rare cancers possible. There are nine important cancers selected by IRCI for core activities on collaborative research. Similar to IRCI is the campaign Rare Cancers Europe developed by European Society for Medical Oncology to address the challenges and overcome hurdles in treating rare cancers.

Development of several immune checkpoint inhibitors (ICIs) in recent years has revolutionized the treatment of several solid tumors, notably melanoma and lung cancer. The knowledge and understanding of the interactions of tumor cells with immune cells in its microenvironment has been increasing exponentially, leading to increasingly newer approvals of immunotherapy in treatment of several cancers in various settings. Notable among these is the first tissue-agnostic/tumor-site agnostic drug approval for pembrolizumab in patients with unresectable or metastatic microsatellite instability high or mismatch repair-deficient solid tumors.[2] It is natural to explore the utility of ICIs in the treatment of rare cancers and address the unmet clinical need.

In this context, Naing et al[3] published an interesting phase II trial of pembrolizumab used as a single agent in patients with advanced rare cancers whose tumors had progressed on standard therapies. This was a basket study that enrolled patients into the following 10 tumor-specific cohorts: (1) squamous cell carcinoma (SCC) of the skin, (2) anaplastic thyroid carcinoma, later revised to small cell malignancies of nonpulmonary origin, (3) adrenocortical carcinoma, (4) medullary renal cell carcinoma, (5) carcinoma of unknown primary, (6) penile carcinoma, (7) thymic carcinoma, later revised to vascular sarcoma, (8) testicular cancer, later relabeled as germ cell tumor, (9) paraganglioma–pheochromocytoma, and (10) other rare tumor histology. A total of 127 patients were treated between August 15, 2016 and July 27, 2018. The objective response rate (ORR) was 14%, and an additional 25% of patients had disease stabilization for 4 or more months. All patients with a response to treatment had remained in the study for at least 8 months (range, 8.1–23.5 months), with almost three-quarters of them continuing in the study at last follow-up. Treatment-related adverse events were recorded for 52% of patients, with the most common being fatigue (20%), rash (13%), hypothyroidism (11%), and anorexia (9%). Grade 3 or 4 toxicities included anemia (3%), transaminitis (2%), and pneumonitis (2%).

Furthermore, Tawbi et al[4] conducted a single-arm, phase II study (SARC028) to assess pembrolizumab for safety and efficacy in patients with advanced soft-tissue or bone sarcoma. Of 84 total patients, 42 had advanced soft tissue sarcoma. Pembrolizumab was shown to have meaningful activity in patients with undifferentiated pleomorphic sarcoma or dedifferentiated liposarcoma with response rates of 40% and 20%, respectively.

Wilky et al[5] carried out a phase II trial of axitinib–pembrolizumab in patients with advanced alveolar soft-part sarcoma and other soft tissue sarcoma subtypes; the trial enrolled 33 patients. At a median follow-up of 14.7 months, the 6- and 12-month progression-free survival (PFS) rates were 47% and 28%, respectively. The best ORR was 25%, demonstrated in eight patients.

Notably, cemiplimab, a PD-1 inhibitor, has recently been approved by US Food and Drug Administration for the treatment of locally advanced or metastatic SCC of skin. An ORR of 47% was reported in metastatic patients. Adverse events occurring in at least 15% of patients were mainly diarrhea, fatigue, nausea, constipation, and rash; 7% of patients discontinued treatment because of an adverse event.[6]

A ray of hope was noticed in Merkel cell cancer (MCC), another rare and aggressive primary cutaneous neuroendocrine tumor in which ICIs have shown very promising results, with response rates of over 40%. Pembrolizumab and avelumab have received approval from the US Food and Drug Administration for first-line use in metastatic MCC. Avelumab, a PDL-1 inhibitor, has shown an ORR of 62%, with a median PFS and overall survival of 2.7 months and 12.6 months, respectively.[7] Only 5% patients had grade 3 toxicities, and there were no grade 4 or 5 toxicities. Pembrolizumab, a PD-1 inhibitor, showed an ORR of 56% in a phase II study of metastatic or locally recurrent MCC, with a median PFS of 9 months. Grade 3 or 4 adverse events were seen in 15% of patients.[8]

To conclude, although it has historically been difficult to treat the multitude of rare cancers with dismal outcomes in advances stages, the recent advances in immunotherapy have added new ammunition in the armamentarium of a medical oncologist dealing with these cancers.

References

1. American Cancer Society. Special section: rare cancers in adults. In: American Cancer Society, ed. *Cancer Facts & Figures 2017*. Atlanta, GA: American Cancer Society, 2017:30–39.
2. U.S. Food and Drug Administration. Hematology/oncology (cancer) approvals & safety notifications. Accessed Jan 27, 2021. www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications
3. Naing A, Meric-Bernstam F, Stephen B, et al. Phase 2 study of pembrolizumab in patients with advanced rare cancers. *J Immunother Cancer*. 2020;8:e000347.
4. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017;18:1493–1501.
5. Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20:837–848.
6. Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med*. 2018;379:341–351.
7. D'Angelo SP, Russell J, Lebbé C, et al. Efficacy and safety of first-line avelumab treatment in patients with Stage IV metastatic merkel cell carcinoma: a preplanned interim analysis of a clinical trial. *JAMA Oncol*. 2018;4:e180077.
8. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel cell carcinoma. *N Engl J Med*. 2016;374:2542–2552.