Commentary

Pulmonary sarcomatoid carcinoma: Future prospects of adjuvant immunotherapy in advanced management

Sarcomatoid carcinoma is an infrequent form of cancer exhibiting mesenchymal–epithelial transition component affecting multiple organs, including skin, bone, thyroid, breast, liver, pancreas, urinary tract, and lung, and can metastasise to central nervous system, adrenal glands, small bowel, rectum, or kidney with terrible prognosis. It has also been cited that sarcomatoid carcinoma may develop due to collision of two independent cancers or the transformation from carcinomatous to sarcomatous components or vice versa.[1,2] Moreover, pulmonary sarcomatoid carcinoma (PSC) is a group of poorly differentiated nonsmall cell lung carcinoma with the incidence ranging from 0.1% to 0.4% of all lung malignancies and presents in only 0.52% of all diagnosed cases of nonsmall cell *lung cancer* (NSCLC).[3] Pleomorphic carcinoma is the most common subtype of PSC (>50%), followed by spindle cell carcinoma, giant-cell carcinoma, carcinosarcoma, and pulmonary blastoma. It usually affects geriatric strata with male predominance, except pulmonary blastoma subtype, for which the average age at diagnosis is 35 years without gender predilection. Besides this tobacco smoking in the form of cigarettes, cigars, or pipes, as well as exposure to asbestos used in building construction and electrical insulation highlighted as significant risk factor for PSC. According to clinicopathological studies, pleomorphic carcinomas in association with squamous cell component as well as carcinosarcoma may frequently present as endobronchial fungating growth, though peripherally it manifests as a rounded large mass with well-defined margins which often invade the chest wall. Moreover, it is very aggressive in nature, though paraneoplastic activity due to PSC have not been reported yet in English literature. In fact, the median survival of affected population with PSC, reported as 10 months, besides this estimated 5-year survival rate, is extremely low around 15%. However, TNM stage as well as used therapeutic modality were significant prognostic parameters according to various multivariate analyses. Perhaps it is quite difficult to diagnose these tumors using small biopsy samples, while immunohistochemistry can be useful in selected settings.[1] In 2015, the World Health Organization recommends molecular testing to the known genetic abnormalities with histologic findings in PSC.[4] Sarcomatoid carcinoma presents with mutations such as KRAS, epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or MET in up to 70% of cases; pan cytokeratin (CAM 5.2 and LP 34) has also been reported to be present in sarcomatoid carcinoma of the lung. Recently, MET amplification and exon 14 mutation have been reported in 22% of cases, including some cases with MET exon 14 mutation plus ALK translocation in the same tumor. Perhaps 75% of cases of lung sarcomatoid cancers (pleomorphic, spindle cell, and giant cell) are positive for programmed death ligand-1 (PD-L1). However, PD-L1 expression attributed to poor prognosis, though makes the patient a suitable candidate for targeted immunotherapy.[5]

Sarcomatoid carcinoma reveals highly aggressive biological behavior with highly resistance to chemotherapy. Platinum-based chemotherapy has very dispiriting results in PSC, with significant patients experiencing disease progression compared to the nonplatinum group. Immunotherapy has changed the prospects of patients with lung cancers, as their survival has improved exponentially.[6] In the Phase III PACIFIC study, durvalumab, a selective PD-L1 inhibitor, significantly improved survival in patients with Stage III without disease progression after concurrent chemoradiotherapy. Similarly, in KEYNOTE-024 trial results, pembrolizumab, a selective PD-1 inhibitor, a monoclonal IgG4 kappa isotype antibody against the PD 1 pathway, for NSCLC lacking targetable EGFR or ALK mutations, is administered as first-line treatment for patients with advanced NSCLC with PD-L1 expression on ≥50% of tumor cells. Studies showed improved treatment response when it was added to platinum-based chemotherapy.[7] Recent research at molecular level revealed that pembrolizumab and nivolumab bind PD-1 and block the PD-1–PD-L1/PD-L2 axis, while durvalumab selectively blocks PD-L1 binding to PD-1 and CD 80 without inhibiting PD-L2; furthermore, anti-PD-1 exhibited favorable survival outcomes and a safety profile comparable to that of anti-PD-L1.[8]

Therefore, targeted immunotherapy has immense potential to significantly change the outcome in biologically aggressive PSC, as an adjuvant therapy to wean off the effect of resistance in conventional chemotherapy. Although more comprehensive studies are needed at molecular as well as genetic level, globally to explore more specific target receptors for immune checkpoint inhibitors to get the optimal impact of immunotherapy in the management of PSC in near future to enhance the life expectancy of affected population.

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