Editorial

PDL1 expression testing in head and neck squamous cell carcinoma: Bridging the gap

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The emergence of immunotherapy with checkpoint inhibitors against programmed cell death protein 1 (PD-1) and programmed cell death-ligand 1 (PD-L1) has led to a significant improvement in treatment outcomes in advanced head and neck squamous cell carcinoma (HNSCC).[1] PD-1 inhibitors pembrolizumab and nivolumab are approved by the US Food and Drug Administration (FDA) for recurrent and metastatic disease.[2] However, overall response rates of single-agent immunotherapy range from 13% to 18%.[2,3] PD-L1 expression testing by immunohistochemistry (IHC) is being widely used for selecting patients likely to benefit most from immunotherapy drugs, that is, checkpoint inhibitors. The IHC assays for PD-L1 have been a source of great uncertainty due to a wide range of FDA-approved assays with differential sensitivity and scoring system.[4] Access to these tests may be challenging at times in developing nations, where this disease has a very high incidence and resources are limited.

In the current issue of this Journal, Mishra *et al. have* published a retrospective analysis of IHC for PD-L1 expression using laboratory-developed technique (LDT) in cases of HNSCC and did correlation with the clinical parameters.[5] Ratcliff *et al.* reported fair concordance between the two commonly used FDA-approved assays comparing PD-L1 expression in 108 HNSCC biopsy samples and inferred that they can be used interchangeably.[6] Similarly, a meta-analysis of various PD-L1 IHC assays by Torlakovic *et al.* showed that a validated LDT may be used for the same purpose as the tests approved by the FDA, with very high specificity and sensitivity for 22C3 LDT.[7] However, a study by de Ruiter *et al*. showed moderate concordance among three different PD-L1 IHC assays and considerable differences in PD-L1 positivity while using clinically relevant cutoffs.[8] Though this is a retrospective, single-center study, it included data from 93 consecutive patients of HNSCC, which is quite a decent number. Also, this study is the first of its kind from India and bears significant relevance in the domain of PD-L1 testing in HNSCC patients. The method of IHC used is locally developed and can be of value in resource-constraint settings. The method used PD-L1 antibody clone 22C3 by DAKO and followed the standard procedure for IHC. The evaluation was done by calculating the combined proportion score (CPS) at ×20 magnification, and positive cases were further scored by a two-tiered system into low (≥1–49) and high expression (≥50).[5] Nevertheless, further standardization and validation are required before adopting this LDT for IHC. It is imperative to be precisely sure of PD-L1 positivity before subjecting patients to immunotherapy in advanced HNSCC. Low response rates and the high cost of immunotherapy further call for more accountability for PD-L1 testing. Another factor complicating PD-L1 expression testing is the presence of intratumor heterogeneity. The majority of samples in this study were small biopsies, which may lead to discordant results. Little can be done to eliminate this; however, ensuring at least three or four cores of the biopsy would have helped to reduce this. Comparing PD-L1 expression in tumor biopsies with surgical resections of the same tumor could enhance our understanding, but this is restricted to only operable tumors. A study by Scott *et al*., for example, showed high inter- and intratumor block concordance in a small number of HNSCC tumors using the SP263 assay.[9] For ensuring the standardization of different methods of PD-L1 IHC, Sompuram *et al.* described a new tool that allows the evaluation of IHC assays using analytic parameters including the limit of detection (LOD) and the dynamic range of PD-L1. It uses calibrators consisting of microbeads coated with a range of peptides representing the antigenic epitope portion of PD-L1 for each antibody/assay.[10] Tools like these and validation studies will help faster adoption of the LDT IHC method used in this study. In this study, PD-L1 expression in tumor specimens was scored by only two observers. Interobserver variability

plays an important role in diagnostics. However, the scores of the two observers in this study were highly concordant. Even though the technical part is taken care of by standardization, the interobserver variability still has the potential to confound the final results.

The authors also correlated the PD-L1 status with baseline clinical parameters, which showed no significant correlation. This is in line with a previously reported study by Muller *et al*.[11] Patients have not been followed up for clinical outcome, correlation of which would have been interesting from a clinical point of view. Although similar attempts in past have not revealed any significant association with overall survival, the real prognostic implication of PD-L1 status remains to be seen due to the relative dearth of such data.

In conclusion, although testing for PD-L1 IHC by LDT as reported in this study still requires further validation and may not be ready for widespread adoption now, this study does help in filling some gap in this area. This study is paving way for exploring LDT for detecting PD-LI expression by IHC, especially in a resource-constraint setting. Similar well-designed prospective studies with follow-up for clinical outcomes are the need of the hour for bridging the gap in PD-LI expression testing.

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