Editorial

Intrathoracic core needle biopsy and repeat biopsy for PD-L1 evaluation in non-small cell lung cancer

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Over the past years, the improved knowledge on the biological, genetic and molecular heterogeneity of tumors, together with the development of pharmaceutical technologies, has allowed the identification of several targets for novel therapeutic strategies. This fast process has led to the overall reconsideration of the biological peculiarities that can make each tumor a pathology on its own. Non-small cell lung cancer (NSCLC) has been object of extensive research, showing clearly different pathologic and biomolecular features, and an in-depth analysis of tumor genomes and signaling pathways may currently define a set of distinct diseases with specific genetic and cellular features (1). Until recently, genetic mutations or cytogenetic abnormalities (i.e., *EGFR* mutation, *ALK* translocation and many other targetable genetic lesions) have been the main drivers for a personalized therapeutic approach (2). As the therapeutic role of immune checkpoint inhibitors targeting programmed death-1 (PD-1 inhibitors, nivolumab, pembrolizumab) and programmed death ligand-1 (PD-L1 inhibitors, atezolizumab, durvalumab) rapidly raised popularity, by showing striking survival gains for NSCLC patients, both when used as single agents or in combination with chemotherapy or chemo-radiotherapy, in second line and first line, PD-L1 expression evaluation and re-evaluation on tissue samples became crucial both at diagnosis and after therapy (3). PD-L1 expression is currently assessed by immunohistochemistry (IHC), with a very wide range of positivity, ranging from 1% to 100% (4).

While tumor molecular profiling for genetic alterations such as *EGFR* mutation or *ALK* translocation became part of the routine diagnostic workflow, we and others started reporting the feasibility and accuracy of tumor mutational screening in aspirated lung cancer cells [fine needle aspiration (FNA)] through imaging guidance (5-7). At the same time many other groups showed the feasibility and reliability of core needle biopsy (CNB) for lung cancer molecular profiling. FNA cytology was recently shown to be as accurate as CNB for PD-L1 testing in retrospective studies (8,9), but a recent study by Tsai and collaborators (10) shed new light on this topic, describing for the first time the feasibility and diagnostic accuracy of CT-guided transthoracic CNB for PD-L1 expression in a prospective series of 110 biopsies derived from the KEYNOTE-001 study population; 91.8% of these procedures were performed as repeat biopsies subsequent to a previous diagnostic procedure, as pembrolizumab was tested in second line, and 84.5% were performed after therapy. Results showed that specimens were adequate in 96.4% of biopsies, and the median number of cores obtained was 8, consistently higher than previously reported. One of the most interesting findings was that the complication rate was not significantly increased in patients undergoing repeat biopsy after therapy (systemic including pembrolizumab, radiation, surgery), being pneumothorax the most common reported complication.

CNB gained popularity in many centers worldwide

given the progressive increasing need of tumor material for diagnostic purposes, in parallel to the increasing understanding of the disease biology and the identification of novel actionable targets, with tumor re-biopsies at disease progression being progressively incorporated into clinical practice with the aim to detect acquired resistance to targeted therapies (11). These practice changes have sometimes privileged CT-guided CNB *vs.* CT-guided FNA. In this scenario, the work by Tsai *et al.* (10) clearly demonstrates the role of CNB as an effective method aimed at obtaining tissue for IHC expression analysis of PD-L1, retrieving data from a high-quality prospective patients' series and reporting accuracy and complication rates for mostly second biopsies (91%), adding important information to the present knowledge. CT-guided FNA might also be ideal for repeated biopsies, but only retrospective data are currently available on its performance in evaluating PD-L1 expression. A theoretical advantage for FNA for repeat biopsies is the expected slightly lower rate of toxicity, however it was generally reported in early uncontrolled retrospective series and a significant difference is not clearly established (12). The two options (CNB and FNA) seems equivalent for molecular subtyping, and studies have shown satisfactory concordance of PD-L1 testing on cell block and cytology smears with histology blocks; however, there are only few reports on performance, utility, and satisfactory results of cytology specimens for PD-L1 testing (13). Two aspects might be underlined in regards to the possible role of FNA: (I) the development of the cell block method, a complementary approach to conventional FNA cytology, has allowed for a higher quality molecular diagnosis (14,15) and may also be used for PD-L1 expression assessment together with direct smear in FNA samples obtained from lung or lymph nodes with transbronchial or transthoracic image guidance, with 2–3 aspiration specimens (8); (II) the possibility to combine the cell block technique with IHC staining, that has been reported to significantly improve the adequacy of CT-guided FNA samples for standard diagnosis, molecular subtyping and immunosuppressive molecule expression profile, being a convenient strategy in terms of safety and costs (8).

In conclusion, we congratulate Dr. Tsai and collaborators for their precious work, highlighting the current role of CNB for PD-L1 expression evaluation for initial and especially repeat biopsies in advanced stage lung cancer patients who are candidate to immune checkpoint inhibitors, with an acceptable 25% complication rate. The high number of samples per patient obtained (mean =8) is safe and seems to be correlated to a high diagnostic accuracy, offsetting lung cancer spatial heterogeneity.

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Footnote

Conflicts of Interest: Dr. C Bortolotto: consulting or advisory role: Bracco Imaging; Dr. AR Filippi: consulting or advisory role: Astra Zeneca; Speakers' Bureau: MSD, Astra Zeneca; Dr. GM Stella has no conflicts of interest to declare.

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