

Tumor heterogeneity: multiple needle biopsies from different lesion sites – key to successful targeted therapy and immunotherapy

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Submitted Dec 27, 2017. Accepted for publication Jan 10, 2018.

doi: 10.21037/tlcr.2018.01.07

View this article at: <http://dx.doi.org/10.21037/tlcr.2018.01.07>

Non-specific cytotoxic agents were the tip of the arrow for several years. However, in the past 5 years novel therapies have emerged based on the pharmacogenomics of lung cancer and in specific non-small cell lung cancer (NSCLC) (1). Regarding small lung cancer (SCLC) we have data indicated that we could have in the future novel therapies such as immunotherapy, however, we are still awaiting results from several trials (2,3). Regarding NSCLC we have targeted therapies with tyrosine kinase inhibitors (TKIs) based on the epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) and proto-oncogene tyrosine-protein kinase ROS-1 (*ROS-1*) are used for treatment in NSCLC patients (4). In the last 18 months we have pembrolizumab can be used as first line treatment when programmed death-ligand 1 (PD-L1) expression is >50% and as second line treatment when PD-L1 expression is >2% (5). On the other hand, nivolumab can be used as second-line treatment indifferent of the PD-L1 expression (5). All these novel therapies have one thing in common, before drug administration treating physicians have to identify gene expression that has been previously described, without the status of the expression TKIs or immunotherapy cannot be administered except in the case of nivolumab as second-line treatment. Therefore, pulmonary physicians or interventional pulmonologists that

perform biopsies have to make sure that have acquired the “proper” sample. First, we have to take a step back in order to provide the most important parameter in the algorithm of pharmacogenomic therapy and this is the identification of tumor heterogeneity. It has been observed in surgical specimens that the tumor lesion or lymphadenopathy have different gene expression in different sites and also different matrix. Matrix is considered the architecture of the lesion (6-8). We have observed in tumor biopsies mostly with convex probe endobronchial ultrasound (EBUS) and in surgical specimens necrotic areas within the tumor or liquefaction of the tumor (8,9). In other words, once again “tissue is the issue”. The same words again are essential today. Several years ago, it was observed that in patient targeted therapy could not applied since all the aforementioned genes were not identified, however, upon re-biopsy from another lesion of the same patient or another site of the same primary lesion the aforementioned genes were identified. Today we have discovered novel targeted therapies when disease relapse is observed in previously treated patients with TKIs (10). In these patients we have discovered either with liquid biopsy or with re-biopsy novel gene mutation (such as, T790M) (10-12). Liquid biopsy is not as efficient as re-biopsy (=60% efficiency) (11,12), however, it is easier to perform than re-biopsy or in centers without the proper equipment could be considered a choice. Moreover, the treating

physician has to decide where to re-biopsy, while on the other hand with liquid biopsy we can have the information of tumor mutation from all lesions. Nowadays, since treating guidelines have changed we “tissue competition”, where we have to use our tissue sample for several genes simultaneously (13). Thanks to next generation sequencing, these investigations can be done from just one slice of block paraffin (14). Tissue sample should be acquired in all patients, it is unacceptable to acquire cytology specimen especially for NSCLC since BRAF, ALK, ROS-1 and PD-L1 cannot be performed in cytology specimens (14). Thanks to new technology such as convex-probe EBUS we can use biopsy needles of 19G, 21G and 22G. We can take biopsies from different lesions and different sites of a lesion. If acquiring a sample with convex probe EBUS is not possible then interventional radiologists can acquire a tissue sample with 19G or 18G needle (15,16). Radial EBUS can assist in acquiring tissue samples (17), however, biopsies are usually cytological specimens, since the biopsy is blindly performed (18). In any case cell blocks are essential when we are using biopsy techniques with needles (16). Elastography can also nowadays assist in the evaluation of a lesion/lymphadenopathy and with or without a previously positron emission tomography performed we can have the valuable information were to inject our needle and whether the investigated lesion/lymphadenopathy is benign or malignant or unspecified (19). Choosing needles were possible can definitely provide us tumor heterogeneity since ultrasound techniques provide us with visualisation of the needle while puncturing and therefore we can repeat the sample movement as many times as possible and from different parts of a lesion. Finally, currently there are data from the immunotherapy studies that PD-L1 expression is different in different lesions in patients with advance disease and moreover; PD-L1 expression might change during treatment of any agent (8,20). Therefore, we should consider for the future to evaluate definitely all NSCLC patients upon diagnosis for the PD-L1 expression and upon disease relapse re-biopsy NSCLC patients and check again all genes and their expression. Hopefully, in the future we could have a non-invasive technique that could identify/ investigate all the genes and their mutations as many times as necessary upon diagnosis and treatment follow-up.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Zarogoulidis P, Papadopoulos V, Maragouli E, Papatsibas G, Karapantzos I, Bai C, Huang H. Tumor heterogeneity: multiple needle biopsies from different lesion sites—key to successful targeted therapy and immunotherapy. *Transl Lung Cancer Res* 2018;7(Suppl 1):S46-S48. doi: 10.21037/tlcr.2018.01.07