Editorial

Changing paradigms of non-small cell lung cancer treatment

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Nowadays, the use of immune checkpoint inhibitors (ICI) in locally advanced and metastatic non-small cell lung cancer (NSCLC) is quickly gaining a general consensus due to interesting results in terms of tumor response and overall survival (1,2). Nevertheless, the role of ICI in an adjuvant or neo-adjuvant setting is still under investigation and restricted to clinical trials (3). Undoubtedly, the use of the immunotherapy in combination with radical local treatments might open new perspective for all medical experts (i.e., medical oncologists, surgeons, pathologists, radiation oncologists), who will have to face a radical change in the standard treatment of NSCLC.

Bott and colleagues (4) reported outcomes of 19 patients who underwent surgical resection for residual intrathoracic disease after ICI treatment for unresectable or metastatic lung cancer (mainly NSCLC and metastatic melanoma), between 2012 and 2016. Patients were treated, without an induction intent, with different immune checkpoint blockade agents: anti-PD-1 agents (nivolumab and pembrolizumab), anti-CTLA-4 agents (ipilimumab) or anti-PD-L1 agents (durvalumab and atezolizumab). Of note, all the patients present a resolution of the extra-thoracic disease after the ICI regimens. Authors reported a 32% rate of complete pathological response and 95% (all cases apart one) of radical resection. Concerning surgical technical aspects and post-operative complications, they observed one case of conversion from mini-invasive approach to thoracotomy, and one case of grade-4 pneumonitis with no post-operative mortality. Overall survival and disease-free survival were 77% and 42% respectively. Authors conclude that surgery after immunotherapy is feasible and safe, with good post-operative results and acceptable long-term outcomes.

To date, only few studies reported results of the use of ICI as pre-operative treatment for resectable NSCLC (5,6) but several trials are currently ongoing, and results will be available in the next years clarifying the possible benefits of this approach (7,8). Even though, preliminary reports seem to be favourable to this approach, as in the advanced disease, nevertheless the best setting for immunotherapy in combination with surgery is yet to be found. Indeed, ICI could be used either alone or in combination with radiotherapy or chemotherapy agents, and in adjuvant or neoadjuvant setting. These different approaches reflect diverse rationales and should be tailored on each specific patient. For instance, pre-operative immunotherapy could be used in order to achieve a tumour volume reduction, and consequently a higher rate of lung-sparring and/or of radical resection, while post-operative administration could be used in unexpected locally advanced disease (9). Therefore, the recognition of the correct time frame of medical treatment, the correct dose, the diverse chemotherapy combinations, and the possible combination with radiotherapy administration represents future challenges in this field. On the other hands, post-operative complications rate and intra-operative tissue changes (e.g., inflammation, fibrosis)

determined by ICI need to be elucidated, in order to define the best choice amongst different surgical resections achievable (e.g., lobar, sub-lobar, extended) and diverse surgical approaches available (classic *vs.* mini-invasive).

In this context, the results presented by Bott and colleagues are reassuring, with an impact on surgical procedures (e.g., conversion to thoracotomy, operative time) and on post-operative complications largely comparable with classical induction agents and a low rate of positive margins.

Surely, one of the greatest potential innovations of immunotherapy is to enormously enlarge the cohort of resectable cases. On one hand, it may assure a better control of unforeseen micro metastatic sites in early stage NSCLC, which would undergo to upfront surgical resection (10); on the other hand, it might open new perspectives and indications for surgery also in patients with a systemic disease at the moment of diagnosis (4). Pre-clinical studies have triggered these captivating questions: analyzing the role of immunotherapy for breast cancer in mice, Liu and coworkers (11) found a significant survival advantage when immunotherapy was administered in a neoadjuvant setting compared to adjuvant setting, also when compared with chemotherapy; this advantage was still present at metastatic sites regardless dimensions of metastasis. Authors propose that the additional survival advantage of immunotherapy as neoadjuvant treatment could lie in the activation of T cell antitumor immunity, which is not possible, or at least much less effective, with chemotherapeutic agents. The exact mechanism explaining why immunotherapy in a neoadjuvant setting showed an advantage in terms of survival and tumor control is still not clear (12); we can speculate that it might be due to a vaccines-like mechanism spurring the circulation of tumor antigens from dead tumor cells, that allow a prime and expansion of tumor specific T-cells and might also enhance their affinity for tumor cells (11). The perspective of a potential larger cohort of patients that could benefit from a surgical resection after an induction treatment using immune checkpoint blockade could reveal some important and challenging questions. Regardless of the use of minimally invasive techniques, surgery causes a temporary postoperative immunological unbalance [the so-called postoperative systemic inflammatory response syndrome (SIRS)] (13), which may vary considerably between different patients based on genetic susceptibility. Indeed, the development of SIRS is strictly related to postoperative complications, morbidity and mortality (14). Several risk factors for development of this syndrome have been analyzed and consequent therapeutically solutions have been proposed with disappointing results. The importance of an immunological disequilibrium seems to be even more dramatic in patients treated with immune checkpoint blockade, in whom this might results in a loss of immunological control of the cancer, causing even its growth and spread.

Remarkably, the authors reported that 32% of patients had not residual tumor found at the pathological evaluation of surgical specimens. Similarly, in a study analyzing early stage NSCLC patients treated with neoadjuvant nivolumab, some cases showed size increment of tumor lesion despite a major pathological response was identified in the specimen (5). As matter of fact, radiological re-evaluation after neoadjuvant treatment is usually based on dimensional criteria well-known as the RECIST guidelines (15), which are mainly based on unidimensional parameters; beside RECIST, WHO bi-dimensional criteria might also be use. Nonetheless, radiological and pathological re-evaluation are not always consistent, since a good radiological response might hide persistency of viable tumor cell (16). This inconsistency between radiological and pathological re-evaluation might be explained by the immune-cell infiltration of the tumor that is triggered by the therapy itself and cause some microenvironment change in the surrounding stromal tissue potentially misinterpreted by the imaging. Recently, developments in radiomics disclose new parameters that might be used and interpreted to define more precisely neoadjuvant response (17). In the light of these evidences, it might be important to rethink evaluation criteria of tumor response to therapies. Circulating tumor cells (18) or circulating biomarker will play a role of paramount importance, giving the real-time feedback of tumor status and possible treatment efficacy; these parameters could be therefore interpreted with radiological and clinical data in order to give a final report and a consistent base for surgical indication.

In conclusion, the immunotherapy has been changing our habitual every-day clinical decision process in the treatment of NSCLC. Surgery and medical oncology will have to redefine their roles and possibly a larger amount of patient will benefit from immunotherapy, chemotherapy and surgery in different settings according to clinic-pathological features of cancer patients. Medical oncologists and surgeons will be called to collaborate and find the best way to integrate new therapies for new patients in new settings.

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Footnote

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

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