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Editorial

Neoadjuvant chemo-immunotherapy for lung cancer: how much is too much?

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An estimated 2 million patients are newly diagnosed with lung cancer each year (1), which is the leading cause of cancer-related death in the world. Multimodal treatment approaches are the standard of care, encompassing a multidisciplinary team (MDT) and patient-centered regimens (2).

The neoadjuvant immuno-therapeutic landscape of non-small cell lung cancer (NSCLC) is evolving at an unmatched rate. In addition to the ongoing optimization of surgical resection and peri-operative care implementing enhanced recovery pathways (3,4), the diagnosis of lung cancer is occurring earlier in the oncogenic process, leading to advanced management protocols to target pre-metastatic disease. Because of increased access to molecular and immune profiling, thoracic surgeons and oncologists are now able to evaluate pathology in real time and assess possible oncogenic drivers, which in turn potentiates cancer interception (5). Additionally, radiomic and circulomic evaluation of pre-cancerous states via screening imaging and circulating tumor DNA affects the range of patients requiring treatment for NSCLC, and as such, the typical patient likely shift from having metastatic disease to local disease, and eventually, hopefully, to microscopic cancer states. This shift has already occurred in treatment protocols and standard of care. Initially, induction systemic therapy was only used for managing locally advanced and metastatic disease with limited disease burdens (6-8), however, in the present day, neoadjuvant treatment of NSCLC has become standard of care in early stage disease (IB–IIIA) (9). This approach to earlier stage disease with pre-operative systemic therapy serves to target micrometastatic disease (10), in addition to its historical aim which was to control the local tumor.

Blockade of the immune checkpoint (ICB) programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have received a lot of attention (11) for being efficacious for both metastatic and early stage lung cancers. As such, we have seen an incredible number of compelling field-changing clinical trials investigating the use of ICB with/without traditional chemotherapy targeting patients with lung cancer of early-stage NSCLC, with varying expression of tumor markers. In patients with advanced disease [resectable (12) and unresectable (13)], however, there remains experimental protocols (14) involving multimodal approaches such as chemo-radiotherapy (15,16) or immuno-chemotherapy (17) that continue to be refined.

Phase II trials have investigated the use of combination neoadjuvant ICB with nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) (18), or combined neoadjuvant immunochemotherapy with nivolumab and platinum-based chemotherapy, followed by adjuvant nivolumab in patients

with stage II and III resectable NSCLC (19), both of which have demonstrated convincing results for safety, and potential efficacy. Similarly, atezolizumab (PD-1 inhibitor) was associated with a 20% major pathological response rate in patients with NSCLC who received the agent in the neoadjuvant setting (20), an oncologic benefit that was maintained when patients were managed with combination atezolizumab/chemotherapy (21). Lastly, another phase II clinical trial investigated the use of durvalumab (PD-1 inhibitor) in the perioperative period, with the addition of neoadjuvant chemotherapy, with promising rate of major pathologic response (MPR), and a 1-year event-free-survival (EFS) of almost 75% (22).

As phase II trials established safety, the phase III clinical trial CheckMate-816 revealed the efficacy of combination nivolumab/chemotherapy (NC) versus chemotherapy (C) in the management of stage IB–IIIA resectable NSCLC, highlighting a median EFS of 31.6 months in the NC group compared to 20.8 months in the C group. Additionally, pathologic complete response was achieved at a rate of 24% and 2.2% in the NC and C groups, respectively (23). These encouraging results have led to the approval of neoadjuvant ICB plus chemotherapy as a standard of care option for patients with resectable early stage NSCLC. However, the majority of these trials have limited their enrolment to stage I–IIIA NSCLC, while patients with stage IIIB or IIIC NSCLC, who were traditionally treated by chemoradiation were rarely tested as surgical resection was not believed to be beneficial to these patients before the immuno-oncology era. Given the outstanding efficacy of ICB, particularly when combined with chemotherapy in NSCLC patients, it may be worth revisiting the question: whether surgery after induction chemo/ICB should be a reasonable option for at least a subset of patients with stage IIIB or IIIC NSCLC. Another important question to be yet determined is how many cycles of chemo-immunotherapy are optimal in the neoadjuvant setting.

In this issue of *Translational Lung Cancer Research*, a study lead by Deng and colleagues (24) attempted to address these important questions. The authors retrospectively reviewed 115 patients with stage III NSCLC who received neoadjuvant chemoimmunotherapy. While 61 patients presented with stage IIIA disease (N1: n=16, 26%; N2: n=37, 61%), the remaining 54 patients had stage IIIB–C NSCLC, of which 10 patients (9%) with N3 diseases. There were 3 patients with stage IIIA disease having single station mediastinal lymph node involvement, and 5 with multistation mediastinal lymph node involvement. With the relatively small sample size and retrospective nature of the study fully acknowledged, the encouraging data suggested that surgical resection may be a reasonable option for a subset of patients with stage IIIA NSCLC with multistation N2 disease and even stage IIIB–C diseases, who are candidates for chemoimmunotherapy.

The authors also attempted to address the other important question regarding the optimal cycles of neoadjuvant chemoimmunotherapy. In this cohort of patients, 44 patients (38%) received 3 cycles of neoadjuvant therapy, similarly to those in the CheckMate-816 clinical trial, while 29 patients (25%), 27 patients (23%) and 15 patients (13%) received 2, 4 and 5 cycles or greater respectively. This led to 66 patients (56%) achieving a major pathological response (<10% viable tumor cells) including 60% (49/81) of patients with N2 disease who achieved complete pathological nodal response. While adjusting for relevant clinical factors, the authors showed that 3 cycles [odds ratio (OR) =5.54] and 4 cycles (OR =10.52) were associated with better pathological response compared to 2 cycles while 5 cycles or greater did not make a significant difference on this outcome. The rationale for prolonged neoadjuvant treatment (>4 cycles) was either persistent N2 disease (unresectable based on MDT discussion), or significant response to therapy with negligible adverse events, prompting the addition of 1–2 cycles following MDT discussion.

Because the therapeutic strategy in managing locally advanced NSCLC should originate from MDT discussions, the decision to prolong neoadjuvant therapy and delay curative resection can be skewed by a multitude of incredibly complex factors. Some of which may surround the resectability of the disease, and whether downstaging has occurred after the standard of care (3 cycles). A point of debate must accompany the conclusion that an increased number of cycles (>5 cycles) is not associated with MPR, rather, it is possible that a lack of clinical response leads to extended neoadjuvant therapy, potentially in order to achieve resectable status. However, in this retrospective review, it appears that prolonging neoadjuvant immunochemotherapy did not impact pathologic response. Despite its small sample size (n=15 of which n=5 persistent N2, and n=10 significant response to neoadjuvant protocol), the group of patients who received >5 cycles should be closely considered, as neoadjuvant protocols can be associated with immune-related adverse effects, diminishing the potential oncologic benefits associated with this treatment regimen. Additionally, in future studies, comparison of outcomes between single station stage IIIA

versus multistation stage IIIA, and stage IIIB–C would be meaningful.

As immunotherapy containing stratagems increasingly become standard of care for patients with NSCLC, patient selection, and peri-management optimization will undoubtedly be important. With improved understanding the molecular determinates of benefit from chemoimmunotherapy, novel biomarkers may be able to guide selection of patients, including those stage IIIB–C disease, for neoadjuvant chemoimmunotherapy if high likelihood of good response and downstaging is expected. Regarding the optimal cycles of neoadjuvant chemoimmunotherapy, rabidly adapted newer technologies such as liquid biopsy via circulating tumor DNA (25) to assess micro-metastasis may provide more objective guidance. In due time, this will lead to highly patient-centered protocols, undoubtedly informing neoadjuvant protocol choice, and possibly treatment length. Modulation of these therapeutic paradigms can lead to optimization of oncologic benefits based on multidimensional factors. As such, the encouragement of studies such as that performed by Deng and colleagues must continue in order to generate conversation. Specifically, patients with locally advanced disease, requiring extended induction therapy, with or without resection should be investigated for optimal treatment length, including with consolidation/maintenance therapy.

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