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EDITORIAL

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Understanding adverse events related to perioperative immunotherapy: A primer for thoracic surgeons

The emergence of immune checkpoint inhibitors (ICIs) in operable non-small cell lung cancer (NSCLC) has resulted in very promising early outcomes in several neoadjuvant ICI phase I/II clinical trials[1–4] as well as a large, randomized multi-institutional trial of chemotherapy combined with nivolumab followed by surgery for stage IB–IIIA NSCLC (CheckMate 816).[5] There has been a rather uniform observation that combined chemotherapy plus ICI results in more pathologic tumor regression than either chemotherapy or ICI treatment alone. Moreover, the level of pathologic regression often correlates poorly with tumor response criteria using standard RECIST criteria. While thoracic surgeons are familiar with perioperative adverse events (AEs) related to systemic chemotherapy, toxicities associated with ICI therapy are not as well understood. As the use of ICI and related immune-oncology drugs becomes more standard in the treatment of stage IB–IIIA NSCLC, it is important that thoracic surgeons appreciate the potential immune-related AEs (irAEs) associated with these drugs.

The recent expert opinion publication in *Thoracic Cancer* offers a comprehensive review of existing clinical trials employing neoadjuvant and adjuvant ICI ± chemotherapy, as well as an assessment and recommended treatment of related irAES.[6] While the American Society of Clinical Oncology guidelines[7] focus on irAEs across all cancer types, primarily in late-stage disease, this publication focuses only on patients with lung cancer and specifically those for whom surgery is part of the treatment plan. Heretofore, the more common irAEs observed in neoadjuvant monotherapy ICI studies include endocrinopathies, pneumonitis, and rash. The specific endocrinopathies most reported are hyper- and hypothyroidism and diabetes mellitus. However, instead of focusing solely on irAEs, it is increasingly appreciated that, in a multimodality treatment approach (i.e. ICI, chemotherapy, surgery), overall treatment-related AEs (TRAEs) may be a better assessment of toxicities associated with all treatments. TRAEs offer a more patient-centered assessment while potentially permitting an analysis of the unique surgical AEs and their contribution to the overall TRAE assessment.

There will be some hesitancy on the part of thoracic surgeons and their patients to introduce a neoadjuvant treatment protocol that involves ICIs, instead of moving directly to surgery. However, if the other large, randomized phase III clinical trials examining neoadjuvant chemotherapy plus ICI support the initial observations of CM-816 *and* if there is an associated improvement in event-free survival and overall survival, then this approach will likely become the standard of care for patients with operable stage IB–IIIA NSCLC who lack targetable oncogenic driver genomic alterations. As such, thoracic surgeons need to be familiar with the important points raised in this expert opinion document on irAEs. A relevant, surgeon-specific concern is whether ICIs in the neoadjuvant setting will result in irAEs that would preclude the patient from undergoing surgery for their primary tumor. All studies reported to date of monotherapy ICI or combined chemotherapy plus ICI have not demonstrated an irAE profile that prevented the patient from undergoing surgery. While some irAEs are different from those commonly observed with chemotherapy alone, as discussed by the authors these irAEs can be medically managed prior to surgery, with most patients proceeding safely to surgical resection and 85–90% having an R0 resection. In my experience, compared to chemotherapy, ICI therapy is better tolerated by patients.

There remain many unanswered questions regarding patient selection for use of neoadjuvant and adjuvant ICI therapy; most notably, which tumors will respond to immunotherapy and which will not. Like with chemotherapy, there currently are no biomarkers that accurately predict response or resistance to ICI therapies. We also do not know how long ICI therapy should be continued in the adjuvant setting – the neoadjuvant ICI trials (AEGEAN, IMpower030, and KEYNOTE-617) as well as the adjuvant IMpower010 study and others all have an additional year of ICI therapy. As mentioned previously, we do not know if the dramatic pathologic tumor regression as measured by complete pathologic response or major pathologic response will translate into improved event-free or overall survival in patients. Finally, to avoid the toxicity profile of chemotherapy, other neoadjuvant immune-priming approaches, such as combined stereotactic radiation and ICI followed by surgery as reported by Altorki et al., deserve more attention.[8]

The role of the thoracic oncologic surgeon in the management of patients with operable NSCLC is rapidly evolving. Over the past two decades, surgeons have been focused on adopting minimally invasive approaches for the resection of NSCLC. While this has been an advance in the field, the rapid development of next-generation sequencing, the discovery of and drug development for known oncogenic driver alterations, and the explosion of immunotherapy as a new backbone of systemic therapy are now an essential part of the care plan for patients with earlier stage NSCLC.[9] Thoracic surgeons need to refocus attention to these developments and how to best integrate pre-resection molecular testing, participation in clinical trials, and performing safe, complete surgical resections after targeted and immunotherapies. An awareness and understanding of the specific perioperative irAEs as reported by Ni et al. is an important part of this process.

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