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Immunotherapy in the neoadjuvant settings: a new challenge for the thoracic surgeon?

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INTRODUCTION

Despite the recent advances in the treatment of non-small-cell lung cancer (NSCLC), there has been a slight improvement in the overall survival of patients with a 5-year survival rate ranging from 92% (stage IA) to 41% (IIIA) [1, 2]. Even if surgery remains the first option for patients with operable NSCLC, in recent years, major therapeutic successes have been achieved by targeted therapy and immunotherapy in advanced stages of NSCLC leading to an increase in overall survival. Efforts are now being made to replicate the success achieved using these innovative treatments in the advanced stage and in the early-stage of NSCLC in the setting of neoadjuvant treatments [3]. The idea of cancer immunotherapy originated with a better understanding of the immune surveillance whereby the immune system can recognize malignant cells as non-self, and then induce immune responses to eliminate cancer cells [3].

With patients' awareness of prognosis, the aim of neoadjuvant treatment is to enable more radical surgical interventions with pathological downstaging and to increase survival with a significant pathological response [3]. Previous literature evaluate the safest and most effective strategy to incorporate immunotherapy in the multidisciplinary management of patients with resectable NSCLC. If adjuvant trials demonstrate an improvement in survival, significant efforts will be needed to identify appropriate patients for induction and optimal duration of therapy. Trials with additional immunotherapeutic agents will build on current understanding and, it is hoped, that new therapies will improve the outcomes of patients with early-stage NSCLC.

BASIC IMMUNOLOGY FOR SURGEONS

The surgeon William Coley was the pioneer in the field of non-specific immunotherapy for lung cancer since 1891. This type of immunotherapy initiated before the advent of radiotherapy or chemotherapy was occasionally followed by the regression of even metastasizing tumours. However, the addition of vaccine-based immunotherapy increased the risk of adverse events [4]. The typical cellular immune response starts with the uptake of tumour antigens by antigen-presenting cells such as dendritic cells or macrophages. Antigen-presenting cells, then, process the antigens to T-cells, by presenting them on their surfaces via major histocompatibility complexes I and II. With the assistance of co-stimulatory signals, different downstream immune effectors (e.g. plasma cells, natural killer cells and cytotoxic T-cells) may be activated, consequently causing apoptosis (death) of tumour cells. However, immune surveillance may be limited by other factors. If there is an immunosuppressive microenvironment, even malignant tumour cells that carry unusual antigens can escape an immune-mediated attack. One such resistance mechanism involves a series of immune checkpoint molecules presenting on the cell surface including programmed death-ligand 1 (PD-L1) and other ligands to inhibit T-cell receptors, which can substantially suppress T-cell proliferation and its killing capacity [3].

Neoadjuvant treatments aim to enable more radical surgical interventions with pathological downstaging and to increase survival. Adjuvant and neoadjuvant treatment in early-stage lung cancer is a critical field to study because it is relevant to potentially curable patients who, with chemotherapy alone, have not achieved optimal overall survival results. In the advanced stages of the disease, overall survival benefits could be seen from immunotherapy and from the combination of chemotherapy and immunotherapy. Nevertheless, we must wait for the mature data of studies in progress to evaluate whether immunotherapy and/or combined chemo-immunotherapy will give the same results in the neoadjuvant settings by increasing operability and overall survival.

SIDE EFFECTS OF IMMUNOTHERAPY

While standard anti-neoplastic therapy is associated with immunosuppression and infections, some of the recent approaches could induce overwhelming inflammation and autoimmunity. Cytokine release syndrome describes a complex of symptoms including fever, hypotension and skin reactions as well as laboratory abnormalities. Treatment with antibodies by inhibiting immune checkpoints can lead to immune-related adverse events

where colitis, diarrhoea and endocrine disorders are the more frequently presented. Nevertheless, the limited knowledge of the pathophysiology and management of complications related to new cancer drugs presents the need for evidence-based algorithms [5].

HOW TO ASSESS THE RESPONSE TO NEOADJUVANT IMMUNOTHERAPY?

Radiological assessment of treatment response with computed tomography (CT) might not be accurate after neoadjuvant immunotherapy. Post-treatment CT most commonly shows stable disease or 'pseudo-progression' related to T-cell infiltration and peritumoural inflammation during the preliminary stages of treatment [6]. Therefore, some patients gain clinical benefit from immunotherapy without initial radiographic tumour shrinkage. This process occurs because of immune-cell infiltration into the tumour rather than real tumour growth. As supported by preclinical studies, neoadjuvant PD-L1 blockade might enhance the systemic priming of antitumour T-cells, thereby potentially eliminating micrometastatic cancer that might otherwise cause post-surgical relapse [7]. A patient's fitness for surgery at the time of diagnosis should be considered when deciding the timing of chemotherapy [8]. Relevant differences in both innate and adaptive immune responses between male and female can explain the different prevalence and mortality from autoimmune and infectious diseases and several types of cancers. Therefore, the accrual and design of trials immunotherapy might best be performed separately for male and female patients with proper sample size planning for both [9].

Theoretically, there are numerous potential biomarkers for immunotherapy in liquid biopsy; however, none of them has been identified to be reliable enough, particularly concerning the evaluation of their efficiency or even their selection following drug resistance [10]. Higher baseline neutrophil to lymphocytes ratio and platelet to lymphocyte ratio have shown a significant association with worse survival outcomes. The role of carcinoembryonic antigen (CEA) and CYFRA21-1 in monitoring tumour response during first-line chemotherapy has been demonstrated in a recent meta-analysis [11], but their role as predictive or 'treatment-monitoring' markers of response to immunotherapy have not yet been elucidated [12]. Should anyone get first-line immunotherapy? Are there negative selection features that should identify patients who should not receive PD-L1 blockers as a part of first-line therapy? There are some absolute contraindications to the use of PD-L1 inhibitors in the first-line setting: patients with severe and/or symptomatic autoimmune diseases, patients in whom organ function can be supported (e.g. dialysis). The safety and benefit of PD-L1 blockade in patients with pulmonary fibrosis and interstitial lung disease are mostly understudied but should be clarified [13].

WHICH SURGICAL APPROACH AFTER IMMUNOTHERAPY IN THE NEOADJUVANT SETTING?

Administration of neoadjuvant immunotherapy in patients with early-stage lung cancer does not delay planned surgery. In order to address the feasibility and safety of pulmonary resection after neoadjuvant immunotherapy, an evaluation of the perioperative outcomes in multiple clinical trials is necessary. Chaft *et al.* [14] suggested that pulmonary resection was feasible but cautioned that mediastinal and hilar fibrosis might develop because of the response to treatment. Bott *et al.* [6] concluded that pulmonary resection, although challenging, was feasible without undue morbidity. Yang *et al.* [15] demonstrated that resection was safe and feasible with perioperative outcomes like those in a cohort of patients who received neoadjuvant platinum-based chemotherapy. Another study by Bott *et al.* [16] showed unexpected morbidity or mortality after neoadjuvant immunotherapy in resectable NSCLC. Bott *et al.* [6] showed that pulmonary resection after neoadjuvant therapy with nivolumab did not result in undue morbidity or mortality. Significant pathological responses were identified despite the disease being stable radiographically. Whereas some studies have suggested that minimally invasive lobectomy after neoadjuvant chemotherapy is feasible in patients with stage IIIA (N2) disease [17, 18]. A recent analysis of the National Cancer Database showed that lobectomy was accomplished through a minimally invasive approach in only 25.7% of such patients [19]. Nevertheless, thoracotomy does not seem to have affected morbidity and early mortality rates [6].

CONCLUSIONS

In the near future, surgeons will be asked to perform pulmonary resections on an increasing number of patients who have received immunotherapy in the neoadjuvant setting. Although pulmonary resection might be challenging in these patients, thoracic surgery procedures can be accomplished safely with outcomes similar to the historical ones after neoadjuvant chemotherapy. The relative effectiveness of this strategy, compared to neoadjuvant platinum-based chemotherapy, will hopefully be clarified by the currently accruing clinical trials [6].

Conflict of interest: none declared.

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