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Neoadjuvant treatment in non-small cell lung cancer: New perspectives with the incorporation of immunotherapy

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Abstract

The aim of neoadjuvant treatment in non-small cell lung cancer (NSCLC) is to eliminate micrometastatic disease to facilitate surgical resection. Neoadjuvant

chemotherapy (ChT) in localised NSCLC has numerous advantages over other therapeutic modalities and is considered standard treatment in resectable disease. Treatment with immune checkpoint inhibitors (ICI) improves long-term survival in advanced disease and has a better toxicity profile than conventional therapies. These immunotherapy agents (anti-PD1/PD-L1), administered with or without ChT, are currently being evaluated in the preoperative setting, with initial results showing better pathological response rates and more long-term benefits. Importantly, these drugs do not appear to increase the rate of severe adverse effects and/or postoperative complications. However, several questions still need to be resolved, including the identification of predictive biomarkers; comparative studies of immunotherapy alone *vs* combined treatment with ChT and/or radiotherapy; the optimal duration of treatment; the timing of surgery; the need for adjuvant treatment; appropriate radiologic evaluation and mediastinal staging; and the correlation between pathological response and survival outcomes. Here we review the current evidence for immunotherapy from a multidisciplinary perspective and discuss current and future controversies.

Key Words: Non-small cell lung cancer; Neoadjuvant; Immune checkpoint inhibitors; Immunotherapy; Anti-PD1; Anti-PD-L1; Complete pathological response

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Core Tip: Studies evaluating neoadjuvant immunotherapy in non-small cell lung cancer have reported extraordinary pathological response rates without any increase in postoperative complications. However, before immunotherapy is implemented in routine clinical practice, several issues still need to be resolved. This review analyses the current evidence for immunotherapy from a multidisciplinary perspective and discusses current and future controversies.

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INTRODUCTION

Approximately 30% of patients with non-small cell lung cancer (NSCLC) are diagnosed with early-stage disease and most will undergo curative intent surgery. However, a substantial proportion of these patients will develop distant metastases, leading to a poor 5-year overall survival (OS) rate (< 35%) in patients with stage IIIA disease. Platinum-based adjuvant chemotherapy (ChT) has shown a marginal benefit in these patients, increasing 5-year survival rates by an additional 5% [1].

Multiple studies have directly compared adjuvant to neoadjuvant (preoperative) treatment, but have failed to demonstrate differences in efficacy between these two strategies. Nonetheless, neoadjuvant treatment has several advantages over adjuvant therapy, including: (1) A reduction in tumour volume and disease stage (thus increasing the potential for complete surgical resection); (2) early treatment of micrometastatic disease; (3) assessment of *in vivo* response to systemic therapy; and (4) improvement in the patient's preoperative performance status, which may increase adherence to the therapeutic plan.

The introduction of immune checkpoint inhibitors (ICI), which have been shown to substantially prolong survival in many patients, has radically altered the therapeutic landscape in advanced NSCLC. By contrast, the role of ICIs in localised disease is poorly understood. In this context, the aim of this article is to provide a detailed review, from a multidisciplinary perspective, of the current status of neoadjuvant therapy and the future of immunotherapy in locally-advanced NSCLC.

CONTRIBUTION OF NEOADJUVANT TREATMENT TO SURGERY IN STAGE III NSCLC

Numerous studies have evaluated the role of neoadjuvant therapy—mainly ChT—in surgically-treated patients with stage IIIA NSCLC. However, this approach remains controversial, in part due to the contradictory findings. Randomised studies have failed to demonstrate a clear advantage for neoadjuvant ChT followed by surgery *vs* definitive chemoradiotherapy (CRT). It seems likely that these

conflicting results are due to the wide heterogeneity in study designs (patient selection, treatment regimens, and treatment duration periods). Moreover, the type of surgery can also have a large influence on the outcomes. For example, in the Intergroup 0139 trial[2], neoadjuvant therapy significantly improved 5-year survival compared to CRT, but only in the lobectomy arm, mainly due to the high postoperative mortality rate (26%) in the pneumonectomy arm. Similarly, a subgroup analysis of the EORTC 08941 trial[3] also found that lobectomy was a predictor of better survival. That trial also included patients with unresectable disease, many of whom were treated with sequential CRT. By contrast, the ESPATUE trial failed to confirm these differences in survival outcomes according to type of treatment or surgical procedure, finding no significant differences in 5-year OS between the neoadjuvant and CRT arms (44% vs 40%)[4].

CRT has also been compared to induction ChT alone in the neoadjuvant setting[5], with no clear differences between these approaches in stage IIIA disease. Several studies have found that CRT does not significantly increase mortality or postoperative complications, even in patients undergoing pneumonectomy[6,7]. A major limitation of neoadjuvant treatment is the increased surgical complexity caused by the presence of thoracic adhesions and fibrosis, although complications associated with these treatments have decreased in recent years[8].

NEW HORIZONS FOR PREOPERATIVE RADIOTHERAPY

Radiotherapy (RT) continues to play a fundamental role in the management of localised NSCLC, either as radical-intent monotherapy [*e.g.*, stereotactic body radiation therapy (SBRT)] or combined (pre- or postoperatively) with ChT. In advanced disease, palliative RT can help manage symptoms such as hemoptysis, pain, and dyspnea. For this reason, it is crucial to determine the optimal timing and treatment modality.

Although the immune system will trigger an effective innate response when it detects the presence of cancer cells, in some cases tumours may become resistant to this immune response[9,10]. Exposure to ionising radiation induces changes in the tumour microenvironment, triggering the release of antigens that stimulate the immune system through a “vaccine” effect. In this clinical scenario, immunotherapy can trigger both a local response as well as a systemic response against tumour cells located outside the irradiation field, known as the “abscopal effect”[11,12]. However, several studies have shown that the real incidence of these responses in clinical practice is low.

Based on the results reported to date, the combination of radiotherapy and immunotherapy in NSCLC appears to be a promising strategy, but more robust data are needed to definitively establish the most appropriate treatment regimen for this combined approach, especially in localised disease. More specifically, studies are needed to evaluate this combination in the neoadjuvant setting in NSCLC.

REINVENTING SYSTEMIC TREATMENT: ROLE OF IMMUNOTHERAPY

General aspects

The main advantage of neoadjuvant immunotherapy is its capacity to stimulate the production and activation of T cells. In this therapeutic approach, the primary tumour cells are used as a source of antigen production, thus activating different types or clones of effector T cells, which may then act against tumour cells throughout the body (primary tumour, metastatic sites, circulation, *etc.*), thus allowing systemic elimination of micrometastases[13]. Compared to adjuvant therapy, the structure of the pulmonary lymphatic system before surgery remains intact, which enhances the potential for tumour cell-immune interaction. This ability to maximize antigen exposure to T cells not only permits a stronger initial response, but a longer lasting one. However, neoadjuvant immunotherapy also has several possible disadvantages, including the lack of long-term survival and safety data, and the potential impact on the timing of surgery and surgical complications.

Clinical evidence for neoadjuvant immunotherapy in NSCLC

Neoadjuvant therapy with ICI monotherapy: The first study to prospectively assess the role of neoadjuvant immunotherapy in NSCLC was a pilot study by Forde *et al*[8], who evaluated 21 patients with stage I-IIIa NSCLC treated preoperatively with two cycles of the anti-PD-1 agent nivolumab. Of these, nine patients (45%) achieved a major pathological response (MPR) and two patients (10%) a pathological complete response (pCR). By RECIST criteria, most patients (85%) had stable disease and 10% showed a partial response. A stage reduction was observed in eight patients (40%). At a median follow-up of 18 mo, the disease-free survival (DFS) rate was 73%.

The phase II LCMC3 trial[14] was performed to evaluate the effects of two cycles of atezolizumab followed by surgery in stage IB-IIIb disease. Of the 181 patients included, 159 underwent surgery. In the surgically-treated patients without a known EGFR/ALK mutation, MPR was observed in 20% (30/147) and pCR in 7% (10/147). In 43% of patients (66/155), the tumour was downstaged. At 18 mo of follow-

up, the DFS and OS rates in patients with stage I-II disease were 79% and 91%, respectively, *vs* 77% and 87% in stage III patients.

Other anti-PD-1 or anti-PD-L1 agents have also been investigated in recent years. One study evaluated sintilimab in 40 patients with stage IA-IIIB NSCLC, with 40% of patients achieving MPR and 16% pCR[15]. Most patients (70%) in that study had stable disease on radiologic assessment. In contrast to many studies, the tumour histology in most patients (80%) was squamous cell carcinoma. Another study evaluated the effects of two cycles of pembrolizumab, another anti-PD-1 agent, in stage II-III A NSCLC, with similar results (MPR, 27% and pCR, 13%)[16].

In the phase II IONESCO trial[17], patients with stage IB-III A NSCLC received three cycles of durvalumab. The preliminary results ($n = 46$) showed an MPR and pCR of 18% and 7%, respectively, with an objective response rate (ORR) of 8%. Despite promising 12-mo DFS and OS (78% and 89%, respectively), the trial was closed early due to high postoperative mortality (9%).

The combination of nivolumab and ipilimumab was evaluated in the phase II NEOSTAR trial[18]. In the 37 surgically-treated patients, combined therapy achieved higher MPR (50% *vs* 24%) and pCR (38% *vs* 10%) rates than nivolumab alone. There were no significant between-group differences in severe (\geq grade 3) toxicity (13% *vs* 10%).

Neoadjuvant therapy: immune checkpoint inhibitors combined with chemotherapy: Several studies have been performed (or are currently underway) to evaluate immunotherapy combined with ChT in an attempt to further improve the survival and pathologic response rates observed with ICI monotherapy. In a single-arm open label trial, Shu *et al*[19] preoperatively administered four cycles of atezolizumab plus carboplatin + nab-paclitaxel in patients with stage IB-III A NSCLC (77% stage IIIA). The MPR, pCR, and ORR rates were 57%, 33%, and 63%, respectively, all of which are higher than typically achieved with monotherapy. Median OS has not yet been reached due to the short follow-up.

The phase II NADIM trial[20] evaluated the combination of carboplatin + paclitaxel + nivolumab for three cycles in 46 patients with stage IIIA disease followed by adjuvant nivolumab for six months. In the 41 patients who underwent surgery, the MPR, pCR, and ORR were 83%, 63%, and 76%, respectively. No cases of disease progression were observed during neoadjuvant treatment. At 2-years of follow-up, DFS and OS were 77% and 90%, respectively. Adverse events \geq grade 3 were observed in 30% of patients, but not associated with delays in surgery or death.

The findings of the phase II SAKK 16/14 trial in patients ($n = 62$) with stage IIIa NSCLC[21] were recently reported. In that study, patients received three cycles of cisplatin + docetaxel followed by two cycles of durvalumab and one-year of postoperative durvalumab maintenance therapy. The MPR, pCR, and overall response rates were 60%, 18%, and 58%, respectively. At 12 mo, the DFS was 73.4% (Table 1).

Unresolved questions

Assessment of response to immunotherapy: The ORR is a key indicator for evaluating the antitumour activity of neoadjuvant therapy; however, postoperative pathological findings are not always consistent with the radiologic response[22]. For this reason, fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT)[23] remains the gold standard for assessing response to neoadjuvant therapy. FDG-PET-CT imaging measures tumour metabolic activity to assess response and rule out distant disease. However, in some cases, neoadjuvant immunotherapy modifies the peritumoral inflammatory environment, and it can be difficult to determine whether there is a tumour response (increase or decrease) due to the presence of lymphocytic infiltrates. This phenomenon was described in the NEOSTAR trial[24] as “nodal immune flare”, which was observed in 11% of cases with proven histological pCR after surgical resection. Several of the aforementioned studies have reported this phenomenon.

Correlation with long-term survival: One of the most striking results of immunotherapy is the marked increase in the MPR and/or pCR rates; in fact, some authors[25] have proposed using these parameters as surrogates for OS. For this reason, the systematic, standardised evaluation of surgical specimens should be prioritised. Various algorithms have been proposed[26] and several groups have also published consensus statements aimed at standardising assessment of pathological response after systemic therapy (including immunotherapy)[27,28]. Given the higher pathological response rates observed in phase II trials[20], it seems highly likely that, when long-term data become available, OS rates should increase; however, this expected benefit needs to be confirmed in prospective randomised trials, many of which are still ongoing.

Biomarkers: The neoadjuvant scenario is an excellent context in which to explore biomarkers that may predict the benefit of immunotherapy. As in metastatic disease, PD-L1 expression and tumour mutational burden are the two most well-documented biomarkers in clinical trials of ICI[29]. Higher pretreatment PD-L1 expression levels have been associated with a greater probability of achieving MPR [18] or pCR[20]. However, no association has been observed between elevated PD-L1 expression and longer survival, and a substantial proportion of patients without PD-L1 expression also achieve MPR.

Table 1 Clinical evidence for neoadjuvant immunotherapy in non-small cell lung cancer

| Study | Phase | Stages | Treatment | Cycles | Patients included | Main endpoint | ORR | MPR | pCR |
|------------------------|-------|----------|---|--------|-------------------|------------------------|-------------------|-------------------|-------------------|
| Forde <i>et al</i> [8] | I | I-III A | Nivolumab | 2 | 21 | Safety and feasibility | 10% | 45% | 10% |
| LCMC3[14] | II | IB-III B | Atezolizumab | 2 | 181 | MPR | 7% | 20% | 7% |
| NEOSTAR[18] | II | I-III A | Nivolumab <i>vs</i> nivolumab + ipilimumab ¹ | 3 | 44 | MPR | 22% <i>vs</i> 19% | 24% <i>vs</i> 50% | 10% <i>vs</i> 38% |
| Gao <i>et al</i> [15] | IB | IA-III B | Sintilimab | 2 | 40 | Safety | 20% | 40% | 16% |
| NEOMUN[16] | II | II-III A | Pembrolizumab | 2 | 15 | Safety and feasibility | 28% | 27% | 13% |
| IONESCO[17] | II | IB-III A | Durvalumab | 3 | 46 | % R0 | 8% | 18% | 7% |
| Shu <i>et al</i> [19] | II | IB-III A | Atezolizumab + carboplatin + nab-paclitaxel | 4 | 30 | MPR | 63% | 57% | 33% |
| NADIM[20] | II | III A | Nivolumab + carboplatin + paclitaxel | 3 | 46 | PFS 24 mo | 76% | 83% | 63% |
| SAK 16/14[21] | II | III A | Cisplatin + docetaxel followed by durvalumab ² | 2 | 62 | DFS 12 mo | 58% | 60% | 18% |

¹Nivolumab x3 cycles with or without a single dose of ipilimumab.

²Cisplatin + docetaxel x3 cycles followed by 2 cycles of durvalumab. ORR: Objective response rate; MPR: Major pathological response; pCR: Pathological complete response; % R0: % complete resection; PFS 24 mo: Progression-free survival at 24 mo; DFS 12 mo: Disease-free survival at 12 mo.

A higher density of tumour infiltrating lymphocytes—especially CD3+, CD8+, and CD103+—has been described as a prognostic factor associated with longer survival. The NEOSTAR and LCMC3 trials both assessed the influence of these lymphocytes[30], finding that resected tumours in patients with MPR presented a higher level of infiltration by effector-memory T-cells (CD3+, CD8+, CD45RO+) compared to those without MPR, suggesting a possible predictive capacity.

Other predictive biomarkers in peripheral blood are being evaluated: T-cell receptor, circulating tumour DNA, and somatic mutations (KEAP, STK11, RB1)[20], although these all need to be validated in prospective trials.

Beyond immunotherapy: the role of targeted therapy

In patients with metastatic NSCLC with certain molecular alterations (EGFR mutations, ALK rearrangements), treatment with tyrosine kinase inhibitors has shown a large benefit. Preoperative administration of drugs such as erlotinib[31] and crizotinib[32] improves ORR, but not OS, and postoperative recurrence rate after treatment discontinuation is high[33]. In this regard, prolonged treatment after surgery will probably be needed to reduce the likelihood of recurrence. Several studies are currently exploring this strategy, including the phase III NeoADAURA trial (NCT04351555), which is evaluating neoadjuvant osimertinib as monotherapy or combined with ChT.

NEW CHALLENGES: CHANGES FROM THE SURGICAL PERSPECTIVE

The high MPR and pCR rates obtained in clinical trials with neoadjuvant immunotherapy, with or without ChT, suggest that more patients with stage II-III disease will be candidates for surgery, even with the same operability and resectability criteria.

However, immunotherapy can induce atypical radiologic response patterns (*i.e.*, pseudoprogression, hyperprogression), which can make it more challenging to identify patients with negativization of the mediastinal nodes and therefore ideal candidates for surgical resection. Traditional response assessment criteria may not be optimal to adequately classify patients after immunotherapy, especially with regard to mediastinal evaluation. For this reason, new protocols with specific restaging criteria need to be developed and validated.

In current treatment algorithms, the indication for surgery depends on the presence or absence of contrast uptake on the PET-CT scan after neoadjuvant therapy, considered together with the findings of invasive diagnostic tests. However, high mediastinal uptake on PET-CT images should not immediately rule out surgery in these patients, since this finding is more common after immunotherapy than induction ChT or radiotherapy. For this reason, the introduction of new PET-CT response criteria[34] is expected to lead to an increase in invasive testing. However, the diagnostic efficacy of these invasive

Table 2 Ongoing clinical trials of neoadjuvant therapy

| Treatment strategy | Study number (name) | Phase | Treatment |
|---------------------------|-----------------------------|--------------------|---|
| Anti-PD-1 + chemotherapy | NCT03838159 (NADIM II) | Phase 2 randomised | 3 cycles of carboplatin + paclitaxel +/- nivolumab → surgery → 6 mo of adjuvant nivolumab (experimental arm) |
| | NCT04728724 | Phase 2 | Grupo A: sintilimab 2-4 cycles → surgery; Group B: sintilimab + chemotherapy (carboplatin + pemetrexed/gemcitabine/paclitaxel) 2-4 cycles → surgery |
| | NCT04326153 | Phase 2 | 2 cycles of sintilimab + carboplatin + nab-paclitaxel → surgery → 8 cycles of sintilimab |
| | NCT04379739 | Phase 2 | 2-4 cycles of camrelizumab + apatinib or camrelizumab + chemotherapy (carboplatin + pemetrexed/ gemcitabine) → surgery |
| | NCT04061590 | Phase 2 | 2 cycles of pembrolizumab + chemotherapy (cisplatin + pemetrexed) → surgery |
| | NCT04638582 | Phase 2 | 3 cycles of pembrolizumab +/- chemotherapy (carboplatin + pemetrexed/paclitaxel) → surgery |
| | NCT04025879 | Phase 3 | chemotherapy +/- nivolumab → surgery → adjuvant nivolumab (experimental arm) |
| | NCT02998528 (CheckMate 816) | Phase 3 | 3 cycles of chemotherapy (platinum doublet) + nivolumab → surgery +/- adjuvant chemotherapy (one experimental arm) |
| Anti-PD-L1 + chemotherapy | NCT04646837 | Phase 2 | 2 cycles of chemotherapy (platinum-based + nab-paclitaxel) + durvalumab → surgery → durvalumab 1 yr |
| Anti-PD-L1 + anti-CTLA-4 | NCT02998528 (CheckMate 816) | Phase 3 | 3 cycles of nivolumab + 1 cycle of ipilimumab → surgery +/- adjuvant chemotherapy (one experimental arm) |
| Anti-PD-1 | NCT03197467 (NEOMUN) | Phase 2 | 2 cycles of pembrolizumab → surgery |
| Anti-PD-1 + anti-LAG3 | NCT04205552 (NEOpredict) | Phase 2 | 2 cycles of nivolumab +/- relatlimab → surgery |
| Anti-PD-L1 + radiotherapy | NCT04245514 | Phase 2 | 3 cycles of chemotherapy → 1 cycle durvalumab + radiotherapy → surgery → durvalumab 1 yr |
| | NCT03237377 | Phase 2 | 2 cycles of durvalumab +/- tremelimumab (antiCTLA-4) + radiotherapy → surgery → adjuvant chemotherapy |
| | NCT03871153 | Phase 2 | Carboplatin + paclitaxel + radiotherapy + durvalumab → surgery → durvalumab 1 yr |

tests in this clinical context are not known, and there is little data on the utility of EBUS-TBNA after immunotherapy[35].

Another question surrounding immunotherapy is the potential interference with the timing of surgery. In patients treated with monotherapy, surgery can be performed earlier (1-2 wk after treatment); by contrast, after combined treatment (immunotherapy and ChT), surgery will need to be delayed by 4-6 wk. Nevertheless, major changes in the timing of surgery are not expected.

Another issue is that the surgical procedure may be more technically challenging due to the possible presence of multiple inflamed lymph nodes induced by neoadjuvant immunotherapy. While thoracotomy is the most common route of access, minimally invasive surgery is generally indicated when an optimal resection is considered feasible. Nonetheless, several studies have reported a high conversion rate to open surgery (23%-54%)[36,37]. Minimally-invasive techniques are expected to become more standardised and reproducible as surgical teams gain more experience.

CONCLUSION

The emergence of immunotherapy with ICIs has radically altered the course of disease in advanced NSCLC. The results reported to date for neoadjuvant immunotherapy—demonstrating significant increases in major and complete pathological response rates—suggest that patients with localised disease could also benefit from ICIs, potentially increasing cure rates and prolonging survival in these patients.

The currently available pre- and postoperative safety data support the use of this therapeutic strategy. However, many open questions remain: (1) Does combined chemo-immunotherapy provide greater long-term benefits than immunotherapy alone? (2) Are there any predictive biomarkers of response? (3) What is optimal treatment duration and timing of surgery? (4) Is adjuvant treatment necessary in all patients? and (5) Are new protocols needed for re-evaluation and restaging?

Several ongoing studies are evaluating different therapeutic strategies (Table 2), and will allow us to answer these and other questions that may emerge in the future.

FOOTNOTES

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