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EDITORIAL

Controversies in NSCLC: which second-line strategy after chemo-immunotherapy?

Over the last 5 years we have witnessed revolutionary improvements in the first-line setting for advanced non-small-cell lung cancer (NSCLC): the introduction of combinations with platinum-doublets and immunotherapy as standard treatment of treatment-naive NSCLC has led to better response rates and overall survival (OS).[1-5]

Almost all patients, however, will eventually experience disease progression and require further therapeutic options and, notably, a significant proportion of patients will not receive any further treatment due to clinical deterioration. Pivotal clinical trials report that only between 30% and 46% of patients are able to receive subsequent therapies after chemo-immunotherapy. For patients with advanced NSCLC without actionable molecular aberrations, whose tumour progresses after first-line chemo-immunotherapy, standard options include treatment with docetaxel, pemetrexed or gemcitabine, or docetaxel in combination with anti-angiogenic agents such as nintedanib or ramucirumab.

Docetaxel is commonly used as it has historically been shown to prolong OS and improve disease-related symptoms over best supportive care in patients pretreated with platinum-based chemotherapy.[6] In clinical trials carried out more than two decades ago, second-line docetaxel achieved a modest overall response rate (ORR) of 7.1%-24% and a median OS of 7 months.[7] More recent data from the LUME-Lung1 study evaluating docetaxel plus nintedanib in the adenocarcinoma histology subgroup demonstrated an ORR of 4.7% and a disease control rate (DCR) of 60.2%, a median progression-free survival (PFS) of 4.4 months, and a median OS of 12.6 months.[8] In the REVEL trial, the addition of ramucirumab to docetaxel also demonstrated similar figures for PFS and OS (4.5 months and 10.5 months, respectively).[9]

These studies were carried out before approval of chemotherapy and immunotherapy in clinical practice. Recent data suggest that prior treatment with immunotherapy could confer a synergistic benefit to subsequent chemotherapy and therefore increase efficacy.[10,11] Much of the evidence guiding current management relates to small non-randomised studies and real-world evidence.

The VARGADO study evaluated the efficacy of nintedanib plus docetaxel after receiving chemotherapy and immunotherapy sequentially (cohort B) or concomitantly (cohort C). In cohort B, several patients included had poor prognosis characteristics (73% of patients with performance status [PS] 0-1; 20% with brain metastases at baseline), ORR was 50% and DCR 86%; with PFS of 6.4 months and OS of 12.1 months. In cohort C, after failure of first line, ORR was 35.4%, DCR 67.3%, and median PFS 4.7 months. These results were poorer among patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) $\geq$2: ORR 28.6%, DCR 50%, and median PFS of 2.1 months.[12] A *post hoc*, exploratory analysis of the subgroup of patients previously treated with immunotherapy in a non-interventional study of nintedanib plus docetaxel found inferior outcomes compared with VARGADO: ORR 18.2%, DCR 78.2%, median PFS of 4.6 months, and median OS of 8.8 months.[13]

A recent analysis evaluated 400 patients who had been treated with platinum-doublet and anti-programmed cell death protein 1/programmed death-ligand 1 (anti-PD-1/PD-L1) inhibitors (either sequentially or concomitantly).[14] Median OS of 9 months was reported for second- or third-line taxane monotherapy, whilst median OS for taxane combination therapy (with ramucirumab, carboplatin, carboplatin plus bevacizumab or gemcitabine) was 8.4 months. These data support the efficacy of these regimes observed previously in patients treated only with chemotherapy.

Real-world data also presented this year demonstrated a DCR of 38%, median PFS of 2.9 months, and median OS of 8.1 months for different second-line chemotherapy options given after initial progression to chemo-immunotherapy.[15] These outcomes, with slightly lower DCR and PFS than those observed in clinical trials, could have been due to the presence of poor prognostic factors in patients included in the analysis (22.9% had brain metastases, 51.1% had more than two metastatic sites and 46.3% were ECOG PS 2-3). Interestingly, those re-treated with platinum-based combinations showed a slightly superior outcome particularly in patients with PFS $\geq$6 months during first-line treatment. In these patients, DCR was 83%, 6-month PFS was 20%, and 6-month OS rate was 100%.

Maintained PD-1/PD-L1 inhibition after progression has shown minimal activity after immune checkpoint inhibitors in monotherapy. Responses following this approach have been low: ORR of 11% with rechallenge of anti-PD-L1/PD-1, and 2% with the addition of anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4) to anti-PD-L1 in the Lung MAP substudy S1400F.[16,17] These results have discouraged its use as second-line treatment after chemo-immunotherapy.

New combinations or therapeutic agents are currently being tested to improve outcomes for these patients. Several of these strategies share the aim of enhancing the immune response through different mechanisms. One of

them consists of combining checkpoint inhibitors with low doses of immunogenic chemotherapies. Interesting combinations underway include anti-PD-1, anti-CTLA-4 and oxaliplatin (NCT04043195) or anti-PD-1, cyclophosphamide and pixatimod (an immunomodulatory agent that inhibits the infiltration by tumour-associated macrophages and stimulates dendritic cells)[18] (NCT05061017). Targeting other novel immune checkpoints can be another option: examples include the combination of anti-PD-1 and anti-T-cell immunoglobulin and ITIM domain (NCT03739710), and docetaxel plus anti-PD-1 alone or in combination with anti-T cell immunoglobulin and mucin-domain containing-3 (NCT04655976). Targeting different cytokines such as transforming growth factor-β (TGF-β), interleukin 1b (IL-1b), IL-15, or CXC chemokine receptor 2 (CXCR2) in combination with either docetaxel or checkpoint inhibitors is another of the strategies pursued (NCT04396535, NCT03473925, NCT03473925).[19] In initial development phases, the use of vaccines and adoptive cell therapy is being explored—this has been reviewed deeply elsewhere.[20]

The interplay between angiogenesis and immune surveillance has been deeply established, and tumour cells are known to secrete different factors—vascular endothelial growth factor (VEGF) among them—that lead to the accumulation of myeloid-derived suppressor cells (MDSCs) in the tumour microenvironment.[21] These cells have a key role in the suppression of the immune response, and potentially the combination of immunotherapy and angiogenesis inhibitors may improve patients' outcomes. Recently, results were reported from the Lung-MAP master protocol substudy S1800A. In this phase II clinical trial, patients with previously treated NSCLC not eligible for a biomarker-matched treatment were randomized to receive pembrolizumab and ramucirumab versus the investigators' choice of standard of care (SoC). Of note, 47.8% patients in the pembrolizumab/ramucirumab arm and 60.9% in the SoC arm had previously received chemotherapy and immunotherapy combined, and most of the patients in the SoC arm received docetaxel combined with ramucirumab (65%). Outcomes in the combination and SoC arm were: ORR of 28% versus 22%, median PFS of 4.5 versus 5.2 months and median OS of 14.5 versus 11.6 months. Several other trials are currently testing combinations of immunotherapy and antiangiogenesis inhibitors (NCT03976375, NCT03906071, NCT04958811, NCT04921358, NCT04471428).[22] Other studies are evaluating concomitant treatment with antiangiogenic agents and chemotherapy (NCT04332367).

Novel targets are also being considered as potential therapeutic options in this setting. Trophoblast cell surface antigen 2 (TROP-2), a glycoprotein overexpressed in different types of cancers including NSCLC, is being used as a target for antibody—drug conjugates (ADCs) loaded with a topoisomerase inhibitor. A phase I clinical trial evaluating sacituzumab govitecan reported interesting results in a heavily pretreated cohort with an ORR of 17%, and median PFS and OS of 5.2 and 9.5 months, respectively.[23] A randomised phase III clinical trial, comparing sacituzumab govitecan with docetaxel is currently ongoing (NCT05089734). Another anti-TROP-2 ADC, datopotamab deruxtecan, demonstrated an ORR of 21%, a DCR of 67%, and a preliminary median PFS of 8.2 months.[24] A phase III clinical trial evaluating datopotamab deruxtecan versus docetaxel in previously treated advanced or metastatic NSCLC with or without actionable genomic alterations (TROPION-LUNG01) is also ongoing (NCT04656652). Carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5)-directed ADCs, such as tusamitamab ravtansine, are also being tested. A phase I trial demonstrated, for patients with NSCLC expressing moderate or high intensity of CEACAM5, an ORR of 7.1% and 17.8% in the moderate and high expressor cohort, respectively.[25] A phase III trial evaluating tusamitamab ravtansine versus docetaxel in previously treated, CEACAM5-positive metastatic non-squamous NSCLC patients (CARMEN-LC03; NCT04154956) is currently recruiting.

At progression after first-line chemo-immunotherapy, standard strategies such as single-agent chemotherapy or combination of docetaxel plus antiangiogenic agents offer modest activity, making this setting an area of unmet need. Data to guide treatment selection for these patients are limited and based on historical cohorts or retrospective analyses. Results of trials evaluating novel agents and combinations are eagerly awaited and greatly needed in order find alternative strategies that can improve survival outcomes and quality of life for these patients.

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