Review Article

Locally-advanced non-small cell lung cancer: shall immunotherapy be a new chance?

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Abstract: Locally advanced non-small cell lung cancer (NSCLC) represents approximately one third of presentations at diagnosis. Most patients are judged non-surgical due to disease extension, and chemo-radiotherapy still represents the standard therapeutic option, with unsatisfactory results in terms of overall survival (OS) despite advances in staging and radiation therapy planning and delivery. Immunotherapy, and in particular immune-checkpoint inhibitors targeting the PD-1/PD-L1 axis, gained wide popularity for NSCLC in light of the positive findings of several trials in metastatic disease. Stage III unresectable NSCLC is a remarkably interesting setting for the combined use of chemo-radiation and immunotherapy, also considering the multiple experimental evidences in favor of a synergistic effect between radiation and immune checkpoint inhibitors, with the potential of enhancing immuno-modulating effects and overcoming resistance. We here summarized the biological rationale and the initial clinical experiences testing for this combination, and we briefly discussed ongoing trials and future options in this field.

Keywords: Radiotherapy; immunotherapy; locally advanced non-small cell lung cancer (NSCLC)

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Introduction

According to the tumor node metastases (TNM) international staging system, approximately thirty percent of patients affected with non-small cell lung cancer (NSCLC) are diagnosed with "locally advanced" disease (1). This group includes a wide spectrum of clinical presentations with often a considerable tumor burden (T3-T4 and N2-N3). Beyond stages III A and B, the latest TNM (8^{th} edition) also introduces stage IIIC, which refers to a massive parenchymal localization combined with contralateral lymph nodes involvement (T3-T4 and N3) (2). Most of stage III NSCLC patients are judged as non-surgical given the disease extension. Despite the absence of metastases their prognosis is severe (with differences across sub-stages), with 5-year overall survival (OS) rate of approximately 20% after concomitant or sequential chemo-radiation (3). As in phase 2 trials a progressive increase in radiation dose resulted associated to better local-regional control and OS, Radiation Therapy Oncology Group (RTOG) conducted a prospective phase 3 study to establish the safety and efficacy of increasing total radiation dose with concurrent carboplatin-paclitaxel, comparing 60 *vs.* 74 Gy, with negative results (RTOG0617) (4). The control arm (60 Gy) of this study reached a median OS of 28.7 months, a result previously unseen in any historical study, now representing a new benchmark for comparison. On the front of radiation dose escalation, other groups tested the possibility of delivering a stereotactic boost after conventional radiation therapy (RT) in order to selectively

increase tumor dose, with promising results in terms of feasibility and local control without survival benefits, and still unconfirmed results by high-quality prospective studies (5,6). Although the outcomes after concomitant chemo-radiation in this setting appear better than before, still not all patients are eligible, making this therapeutic choice limited to a selected group of generally younger and fit patients. Beyond radiation dose escalation, a logical step for improving survival for non-surgical stage III patients was to investigate for the combination of chemo-radiotherapy with targeted agents (gefitinib, erlotinib) and/or anti-angiogenic therapies (bevacizumab), following the positive results obtained for these drugs in stage IV. However, these attempts did fail in increasing survival, while adding significant toxicity (7).

A new window of opportunity emerged when immunotherapy gained exceptional popularity for its high efficacy for a heterogeneous group of metastatic solid tumors, including NSCLC. The first clinical applications, in particular the use of immune checkpoint inhibitors targeting the PD-1/PD-L1 axis, produced remarkable results in metastatic NSCLC, especially in patients overexpressing PD-L1 on cancer cells (8-11). These innovative immune-modulators were then tested for locally advanced disease in pivotal trials, and we here summarize the results obtained so far, as well as the ongoing trials and our perspective on the future options in this setting.

Rationale for the combination of immunotherapy and radiotherapy in NSCLC

Radiotherapy has consistently been shown to activate key elements of the immune system that may be responsible for resistance to immunotherapy (12-16); at the same time, radio(chemo)therapy may synergize with immunotherapy and possibly overcome resistance and potentiate the pro-immunogenic effects (17,18). As shown by several experimental studies, RT may convert a poorly immunogenic tumor into an immunogenic one, by increasing antigen release, T-cells priming and cross-priming in lymph nodes, T-cells trafficking to tumor site, and increased expression of MHC-class 1 molecules (19-21). These effects are partially counterbalanced by immunosuppressive effects, one of the most important being the enhanced PD-L1 expression on cancer cells, that can be neutralized promoting a synergistic effect when anti-PD-L1 agents are used in combination with RT (22). Targeting the PD-1/PD-L1 axis together with RT is seen as one of the most promising strategy for several solid tumors, and many trials are ongoing with the aim to explore the different possible combinations. Meanwhile, recent experimental findings showed that the interaction between RT and the immune system is far more complex than previously thought, and dose/fractionation may play a central role for activation, by a mechanism involving the STING pathway and type I interferon release (23). For NSCLC, the combination of immunotherapy and RT might potentially improve local control at the treated site as well as distant control, when a powerful "abscopal" effect is triggered potentiating specific anti-cancer immunity and inducing memory effect (19). RT, especially when combined with immune-modulators, has been shown to broaden the T-cell receptor (TCR) repertoire, achieving maximal tumor rejection (24). The beneficial effects of the combination are expected to be maximal when RT and immune checkpoint inhibitors are used concomitantly or in a close sequence. Moreover, as shown by the clinical results obtained so far (25,26), that will be discussed in details in the next paragraph, RT seems to potentiate the effects of immunotherapy also when given several months before immunotherapy, and this effect was, until now, uniquely observed in NSCLC patients (26). For locally advanced disease, a maintenance approach with anti-PD-1 inhibitors given sequentially seems also to be very effective (25). In these clinical trials, RT was used not as "immune-modulator" but as a radical or palliative treatment at conventional doses. In future studies, as pointed out by De Ruysscher D in a recent commentary (27), it would be possible that RT would be used as a pure trigger of the immune system, opening the possibility to irradiate only partial tumor volumes, or limited metastatic deposits.

Radiotherapy and immunotherapy for locally advanced NSCLC

The setting of locally advanced NSCLC is remarkably interesting for the combination of immunotherapy and (chemo)-radiotherapy. The main study investigating the efficacy of an anti-PD-1 axis inhibitor in association with radio-chemotherapy for locally advanced NSCLC was the PACIFIC trial (25). This trial compared the PD-L1 inhibitor durvalumab *vs.* placebo in patients with locally advanced, unresectable stage III NSCLC who did not progress following concurrent platinum-based chemo-radiotherapy. It included 713 patients, who

were randomized 2:1 to receive durvalumab 10 mg/kg every 2 weeks or placebo for up to 12 months. The co-primary endpoints were progression-free survival (PFS) and OS. Patients were stratified according to age, sex, and smoking habit (current or former smoker *vs.* never smoked). Durvalumab was given until disease progression, other therapy initiation, severe collateral effects, or withdrawal of informed consent. The secondary endpoints were duration of response, objective response rate, percentage of patients alive without disease at 12 and 18 months, time to death or distant metastasis, quality of life, pharmacokinetics and immunogenicity. Median PFS resulted significantly higher for patients receiving Durvalumab than for patients receiving placebo (16.8 *vs.* 5.6 months respectively). The authors pointed out how the gain in PFS was achieved independently of PD-L1 expression (<25% *vs.* >25%). The median time to death or distant metastases was 23.2 months for durvalumab *vs.* 14.6 months for placebo, respectively, the objective response rate was 28.4% *vs.* 16%, respectively, and the median duration of response at 12 and 18 months was 72.8% *vs.* 56.1% and 46.8%, respectively. Patients who received durvalumab had a lower incidence of new metastases (20.4% *vs.* 32.1%) and in particular a lower incidence of brain metastases (5.5% *vs.* 11%). The toxicity of the two arms was comparable, with and incidence of adverse events of any grade of 96.8% and 94.9% in patients receiving durvalumab *vs.* placebo, respectively. Grade 3 or 4 adverse events occurred in 29.9% and 26.1%, with 4.4% and 5.6% toxic deaths, respectively.

Pembrolizumab, an anti-PD-1 agent, demonstrated a clear efficacy in advanced NSCLC on phase 1 KEYNOTE 001 trial (28). PD-L1 expression in at least 50% of tumor cells was selected as cutoff. In a secondary analysis of this trial (26), the authors evaluated all patients enrolled and selected those who received radiotherapy at any time-point before the administration of the first pembrolizumab cycle. The main endpoint of the study was the evaluation of the impact of previous radiotherapy on PFS and OS, in comparison with patients who did not receive radiotherapy. As secondary endpoint, the toxicity profile of the combination was also evaluated. The status and expression of PD-L1 were determined and patients with a membranous PD-L1 staining at least 1% were considered positive. Pembrolizumab administration schedule was 2 or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks until progression of disease, important toxicity or withdrawal of informed consent. Radiotherapy was delivered on thoracic and extra-thoracic sites, mostly as palliative treatment. Of the 97 patients analyzed, 42 previously received any RT, 38 extracranial and 24 thoracic RT (43%, 39% and 25% respectively) with a median time of administration of 9.5 months prior to pembrolizumab. With a median follow-up of 32.5 months for surviving patients, there were 31 progressions in the group of patients undergoing previous radiotherapy and 49 in the group of patients who did not receive it. The combination of radiotherapy and pembrolizumab obtained a significantly longer PFS (4.4 and 2.1 months respectively). Patients who received prior extracranial radiation had a better PFS (6.3 and 2.0 months, respectively). Patients treated with RT also had better OS: the median survival of the first group was 10.5 *vs.* 5.3 months, and 6-month OS was 73% *vs.* 45%, respectively. Again, patients who received a previous extracranial RT had a better OS (11.6 *vs.* 5.3 months, respectively). Forty-four of 97 patients had grade 3 or greater pulmonary toxicity, without difference among RT *vs.* non-RT patients. A separate analysis showed that, as far as the side effects were closely related to treatment, 3 patients (13%) of the group who received prior RT compared to 1% of patients who did not receive it developed pulmonary toxicity (17). The combined results of these two trials were favorable in terms of the potential implementation of a chemo-radiotherapy plus immunotherapy approach with anti PD-L1 and PD-1 inhibitors for both locally advanced and stage IV NSCLC. These results are in line with most of the preclinical evidence suggesting that there is window of opportunity for improving tumor control when using radiation and differential immunotherapy strategies. However, the exact mechanism underlying these findings in NSCLC is still unknown, and many clinical questions remain to be answered before a wide application in clinical practice, especially the right group of patients, exact sequence of RT-IT, PD-L1 expression levels.

Tecemotide (L-BLP25) was conceived as an anti-tumor vaccine inducing a specific immune response against MUC-1, a glycoprotein overexpressed and unnaturally glycosylated in many tumors, including NSCLC (29,30). The aberrant protein stimulates cell proliferation, modifies cell adhesion, and promotes metastases. Tecemotide, once internalized by antigen presenting cells (APCs), is able to promote a T cell-mediated response against MUC-1 expressing tumors (31). In the START study, a randomized, international double-blind phase III trial, the authors enrolled 1,513 NSCLC

patients with inoperable stage III NSCLC, in objective clinical response or stable disease after definitive chemo-radiation. Patients were randomized to receive adjuvant tecemotide for 8 weekly cycles or placebo at a ratio of 2:1. OS was not significantly different between the two groups (25.6 *vs.* 22.3 months, respectively) even if, in a secondary analysis, patients who underwent concomitant chemo-radiotherapy had a better OS (30.8 *vs.* 20.6 months, respectively) (32). The INSPIRE study aimed at investigating the efficacy of tecemotide associated with best supportive care (BSC) as an alternative to placebo plus BSC after chemo-radiotherapy in stage III NSCLC East-Asian patients. Patients were randomized to receive 8 weekly doses of tecemotide plus maintenance for further 6 weeks, or placebo. The main endpoint of the study was OS, but unfortunately the study was prematurely closed (33). To our knowledge, at the time of writing no other reports were available on the combination of immunotherapy and radio (chemo) therapy for stage III NSCLC.

Ongoing studies and future perspectives

Radiation therapy for locally advanced NSCLC has evolved over several decades with the aim of developing specific protocols optimized to maximize local tumor control through radiation dose escalation, or the combination with chemotherapy. Many attempts in prolonging OS did fail, and at the same time standard chemo-radiation (platinum doublets and 60 Gy/6 weeks thoracic RT) reached unprecedented results in terms of median OS time in recent randomized comparisons, probably as a consequence of the better initial staging through the wide use of PET-CT, lower toxicity of RT through the use of advanced planning techniques, better quality of life, better supportive care. Despite these positive findings, still most of the patients relapse and die due to disease progression. The growing enthusiasm for immune-oncology and its possible applications in radiation oncology led to a tremendous expansion of pre-clinical and clinical studies testing various combinations of immunotherapeutic agents and radiation. We summarized the results obtained so far by combining chemo-radiation and immune checkpoint inhibitors in pivotal trials that explored this strategy for stage III NSCLC, with truly encouraging results. However, given the complexity of the field and the paucity of data, we still need to wait for other experimental findings prior to confirm the efficacy of this approach. Particularly, we need to revisit our current understanding of the radiation/immune system interactions in order to develop more tailored strategies in terms of dose/fractionation, timing, target volumes and drugs choice, in light of the recent advances in knowledge coming from translational studies.

In *Table 1* we present the ongoing studies retrieved by Clinicaltrials.gov, November 2017. As we can see from the Table, many different options are under investigation by several researchers across USA and Europe. In almost all trials, the target is the PD-1/PD-L1 axis, with the exception of a combination of anti-CTLA-4 and anti-

Table 1 Ongoing trials integrating immunotherapy in the therapeutic management of locally advanced NSCLC

Study	Number	Phase	Immunotherapy	Institution	Estimated completion date
Cisplatin and etoposide plus radiation followed by nivolumab/placebo for locally advanced NSCLC (RTOG 3505)	NCT02768558	III	Anti-PD-1, adjuvant	RTOG Foundation	October 2024
Nivolumab combination with standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B non-small cell lung carcinoma (NICOLAS)	NCT02434081	II	Anti-PD-1, concurrent	European Thoracic Oncology Platform	August 2020
Pembrolizumab in combination with radiotherapy in locally advanced non-small cell lung cancer (NSCLC) (PARIS)	NCT03245177	I	Anti-PD-1, concurrent and adjuvant	The Christie NHS Foundation Trust	November 2020

Table 1 (*continued*)

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Study	Number	Phase	Immunotherapy	Institution	Estimated completion date
Pembrolizumab, paclitaxel, carboplatin, and radiation therapy in treating patients with stage II-IIIB non-small cell lung cancer	NCT02621398	I	Anti-PD-1, concurrent, adjuvant	Rutgers, The State University of New Jersey	September 2019
DETERRED: MPDL3280A with chemoradiation for lung cancer	NCT02525757	II	Anti-PD-L1, adjuvant	M.D. Anderson Cancer Center	January 2020
Atezolizumab immunotherapy in patients with advanced NSCLC	NCT03102242	II	Neo-adjuvant, adjuvant anti PD-L1	Alliance Foundation Trials	March 2020
Consolidation pembrolizumab following chemoradiation in patients with inoperable/ unrespectable stage III NSCLC	NCT02343952	II	Anti-PD-1, adjuvant	Hoosier Cancer Research Network	December 2018
BLP25 liposome vaccine and bevacizumab after chemotherapy and radiation therapy in treating patients with newly diagnosed stage IIIA or stage IIIB non-small cell lung cancer that cannot be removed by surgery	NCT00828009	II	Vaccine	Eastern Cooperative Oncology Group	May 2017
Neoadjuvant immunoradiation for resectable non-small cell lung cancer	NCT03237377	II	Anti-PD-L1 concurrent and anti-PD-L1 and anti-CTLA-4, concurrent	Sidney Kimmel Comprehensive Cancer Center	September 2020
Neoadjuvant chemoradiation plus pembrolizumab followed by consolidation pembrolizumab in NSCLC	NCT02987998	I	Anti-PD-1, neoadjuvant and adjuvant	Case Comprehensive Cancer Center	January 2020
Neoadjuvant pembrolizumab	NCT02818920	II	Anti-PD-1, neoadjuvant	Merck Sharp & Dohme	January 2027

NSCLC, non-small cell lung cancer; RTOG, Radiation Therapy Oncology Group; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; NHS, National Health System.

PD-L1 agents. Multiple sequences are being tested: a predominance for the consolidation/adjuvant/maintenance setting is evident, however with many studies also integrating immunotherapy at the beginning of chemo-radiation. The latter schedule should be one of the most efficient way to harness at maximum the synergistic effects of chemo-radiation and immunotherapy in terms of boosting the immune-stimulating effects, particularly when using anti-PD-L1 agents, given that PD-L1 enhanced expression during RT may be one of the main causes of radioresistance. A particular attention should also be paid to those trials introducing anti-PD-1 agents before chemo-radiation, as neo-adjuvant: this innovative approach could be promising, by integrating radio-chemotherapy in a tumor micro-environment already modified by immunomodulators, and with a subsequent consolidation phase. When using anti-PD-L1 agents in this setting, PD-L1 expression levels would be probably necessary to stratify patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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