Editorial

Locally advanced non-small cell lung cancer treatment: another step forward

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Despite several revisions of the TNM lung cancer staging system, the N2 descriptor still brings together in one single category, a very different group of patients with dissimilar overall prognosis, ranging from microscopical/small single station N2 to multiple/bulky disease (1,2). At one end of this spectrum, the disease appears to be resectable, whilst, at the other end, it is obviously unresectable. In patients with suspected N2 disease, a preoperative careful staging algorithm is therefore fundamental. Thoracic CT scan, ^{18}F-fludeoxyglucose positron emission tomography (PET-CT scan), and possibly, lymph node biopsy (by endobronchial ultrasound-EBUS or cervical mediastinoscopy) are the common tools currently used to prove mediastinal lymph nodal involvement. In general, the prognosis of locally advanced neoplasms depends on the importance of nodal invasion but generally remains poor, even if in recent studies, overall survival could also reach 24 months.

The standard of care for locally advanced non-small cell lung cancer (NSCLC) remains concurrent platinum-based chemotherapy (CT) and radiotherapy (RT) up to 60–66 Gy (3,4). Furthermore, cisplatin-etoposide CT + RT scheme demonstrated its superiority compared to pemetrexed-cisplatin + RT one (5).

With the discovery of driver genes and the application of targeting drugs, patients with advanced lung adenocarcinoma have recently acquired a significantly prolonged survival (6). However, advances in treating advanced stage squamous NSCLC are still inadequate, and the overall 5-year survival rate remains unfortunately, around 17% (7). Therefore, the development of new treatments is urgently needed.

The new advances in the understanding of immunology and antitumor immune responses have led to the clinical evaluation of new immunotherapies, including vaccination approaches and monoclonal antibodies that inhibit immune checkpoint pathways. Cancer cells may, in fact, survive even in immunocompetent patients, since they acquire tolerance mechanisms letting them to escape immune surveillance. Recent results demonstrated that so-called releasing the brakes (also including the inhibition of immune checkpoints) is effective against cancer cells.

One of the most relevant breakthroughs in recent cancer therapy is therefore the application of immune checkpoint inhibitors in clinical trials.

The cornerstone of immunotherapy development is the knowledge of different process of the T-cell immune system activation and, consequently, of the balance between inhibitory and activating signals dysregulated by tumor cells. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death 1 (PD-1) are two examples of immune checkpoint pathways involved in controlling T-cell immune responses. PD-1 binds to the programmed death ligand-1 (PD-L1) and PD-L2, with T-cell proliferation reduction, cytokine production alteration and, finally, T-cells exhaustion and/or apoptosis induction (8). Once they interact with their corresponding ligands, the activity

of T cell is inhibited and the immune response to the tumor antigen is attenuated, thereby preventing T cell from attacking tumor. Moreover, antibodies that block CTLA-4 and PD-1 receptors and one of their ligands (PD-L1) have shown impressive response rates in solid tumors, first in melanoma, and subsequently in renal cell carcinoma as well as in NSCLC. Currently, two PD-1 inhibitors are available in clinical practice for treatment of advanced NSCLC: nivolumab and pembrolizumab.

Results of recent clinical trials using nivolumab are encouraging: in the NSCLC subgroup of patients [129] treated with escalating doses of nivolumab, the objective response rate was 17%, with a median response duration of 74 weeks (range, 6.1–133.9 weeks) (9). In particular, many of these patients have been heavily pretreated, and more than 50% of them received 3 prior CT schedules. Furthermore, in a phase II single-arm trial (CheckMate 063), patients with advanced-stage NSCLC were treated with third-line therapy and beyond: the partial response rate was 14.5% and 26% of these patients had stable disease. The overall survival was 8.2 months, with a 1-year survival of approximately 41% (10). In a recent phase II Japanese trial, the objective response rate was 25.7% for patients with squamous cell NSCLC compared to 19.7% for those with non-squamous cell one (11). In addition, in another phase II study (CheckMate 153), 824 patients were treated for 1 year with nivolumab: the partial response and stable disease rates were 12% and 44%, respectively (12). CheckMate 017 study was the first who referred the beneficial effect of nivolumab assessed by patient-reported outcomes. Those who received Nivolumab had greater symptom improvement compared to those who were treated with docetaxel. Moreover, the time to first disease-related deterioration was longer in the nivolumab group (13). Finally, efficacy and safety of single-agent nivolumab in the first-line therapy was described in the CheckMate 012 study. Adverse effects occurred in 71% of patients, with the most common of which being fatigue (29%), rash (19%), nausea (14%), diarrhea (12%), pruritus (12%) and polyarthralgia (10%). The overall response rate was 23% and the progression-free survival and overall survival were 3.6 and 19.4 months, respectively (14).

Immune-related adverse events (ir-AEs) observed with anti PD-1/PD-L1 therapies are usually less severe compared to those associated with CTLA4 targeted agents (e.g., ipilimumab). Nivolumab demonstrated a better safety profile comparing to standard second-line therapy in squamous and non-squamous NSCLC (15). Although ir-AEs are generally of low grade, these can occur with rapid onset, and prompt medical attention and diagnosis are paramount to efficiently manage them.

The addition of RT to platinum-based CT improved the outcome of advanced-stage NSCLC patients, being the current standard of treatment (16); radiochemotherapy demonstrated to be superior to RT alone (17). The standard dose and volume were historically established by the Radiation Therapy Oncology Group (RTOG) dose escalation trial 7301 (18). Since then, a number of changes in the treatment occurred, including the addition of concurrent chemotherapy and the application of three-dimensional conformal radiation therapy (3DCRT). Intensity-modulated RT (IMRT) with definition volumes improved by the use of FDG PET-scan has been recently proposed, with the aim to increase the local disease control. Interestingly, several phase I–II trials showed that with concurrent chemoradiation, maximal tolerated dose of normo-fractionated radiotherapy was 74 Gy, even if a clear demonstration that this regimen may produce better results compared to the traditional 60 Gy schedule was not achieved (19). Indeed, there was no significant difference in terms of grade 3 or worse toxic effects between the 2 radiotherapy groups; however, more treatment related deaths in the high-dose chemoradiotherapy, especially resulting from heart toxicity, were observed. Finally, adaptive radiotherapy is a promising and feasible perspective in several cancers, including NSCLC to increase dose in biological target volume defined on ^{18}F-FDG PET/CT imaging performed during the course of radiotherapy.

In conclusion, the management of locally advanced NSCLC is challenging, especially now, when new CT drugs become available. Nivolumab and pembrolizumab raided in second-line therapy of squamous cell tumor, but there are still unsolved questions: (I) which kind of treatment is desirable and more effective (first, second or third-line treatment? Single or combined therapy? Combined chemotherapy or radiotherapy?); (II) the combination of two kinds of immune checkpoint inhibitors has been recently adopted in the treatment of advanced melanoma (20): does this treatment have the same effects also in NSCLC? Even with these problems still unresolved, the immune checkpoint inhibitors will revolutionize the future clinical practice of lung cancer, since these agents do not directly target and destroy the neoplastic cells but reactivate a patient's own immune system to target cancer cells, and, therefore, their toxicity is generally mild. Trials that include anti-PD-1 immune checkpoint inhibitor in the standard treatment of locally advanced NSCLC (21) with the aim

to improve patient's overall survival, progression-free survival as well as quality of life and other patient-reported outcomes are therefore welcome. Physicians also await the results of long-term follow-up of large cohort of patients treated with immune checkpoint inhibitors, to confirm that the initial survival advantage could translate in an acceptable survival at 3 years and beyond.

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None.

Footnote

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

References

1. Legras A, Mordant P, Arame A, et al. Long-term survival of patients with pN2 lung cancer ac-cording to the pattern of lymphatic spread. Ann Thorac Surg 2014;97:1156-62.
2. Guerrera F, Renaud S, Tabbó F, et al. Epidermal growth factor receptor mutations are linked to skip N2 lymph node metastasis in resected non-small-cell lung cancer adenocarcinomas. Eur J Cardiothorac Surg 2017;51:680-8.
3. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for pa-tients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187-99.
4. Bradley JD, Moughan J, Graham MV, et al. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell lung cancer: phase I results of RTOG 0117. Int J Radiat Oncol Biol Phys 2010;77:367-72.
5. Senan S, Brade A, Wang LH, et al. PROCLAIM: Randomized Phase III Trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus Thoracic Radiation Therapy Followed by Consolidation Chemotherapy in Locally Advanced Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:953-62.
6. Jänne PA, Engelman JA, Johnson BE. Epidermal growth factor receptor mutations in non-small-cell lung cancer: implications for treatment and tumor biology. J Clin Oncol 2005;23:3227-34.
7. Molina JR, Yang P, Cassivi SD, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc 2008;83:584-94.
8. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.
9. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.
10. Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immu-ne checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung can-cer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol 2015;16:257-65.
11. Takeda K. Phase II studies of nivolumab in patients with advanced squamous or non-squamous NSCLC. Presented at World Conference on Lung Cancer; September, 2015; Denver, CO, USA.
12. Hussein M, McCleod M, Chandler J, et al. Safety and efficacy of nivolumab in an ongoing trial of a PD-L1 +/- patient population with metastatic NSCLC. Presented at World Conference on Lung Cancer; September, 2015; Denver, CO, USA.
13. Gralla RJ, Coon C, Taylor F, et al. Evaluation of disease-related symptoms in patients with ad-vanced squamous NSCLC treated with nivolumab or docetaxel. Presented at World Conference on Lung Cancer; September, 2015; Denver, CO, USA.
14. Gettinger S, Rizvi NA, Chow LQ, et al. Nivolumab Monotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2016;34:2980-7.
15. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
16. Aupérin A, Le Péchoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. Ann Oncol 2006;17:473-83.
17. Rolland E, Le Chevalier T, Auperin A, et al. Sequential radio-chemotherapy (RT-CT) versus ra-diotherapy alone (RT) and concomitant RT-CT versus RT alone in locally advanced nonsmall cell lung cancer (NSCLC): two meta-analyses using individual patient data (IPD) from randomised clinical trials (RCTs). J Thorac Oncol 2007;2;S309-10.
18. Perez CA, Stanley K, Rubin P, et al. A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable

non-oat-cell carcinoma of the lung. Pre-liminary report by the Radiation Therapy Oncology Group. Cancer 1980;45:2744-53.
19. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for pa-tients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187-99.
20. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in un-treated melanoma. N Engl J Med 2015;372:2006-17.
21. Gerber DE, Urbanic JJ, Langer C, et al. Treatment design and rationale for a randomized clinical trial of cisplatin and etoposide plus thoracic radiotherapy followed by nivolumab or placebo for locally advanced Non-Small-Cell Lung Cancer (RTOG 3505). Clin Lung Cancer 2017;18:333-9.

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