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EDITORIAL

Is the chemotherapy era in advanced non-small cell lung cancer really over? Maybe not yet

Giuseppe Lo Russo, Martina Imbimbo, Marina Chiara Garassino

Thoracic Unit, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan - Italy

ABSTRACT

Lung cancer is one of the most frequently diagnosed tumors in both the male and female population. In Italy it is the leading cause of cancer deaths in men and the third in women. Although the 5-year survival rate has moderately increased in the last years, the diagnosis remains associated with a very poor prognosis. However, in the last decade significant progress has been made, also in the treatment of advanced-stage non-small cell lung cancer. The advent of targeted therapies and the recent explosion of immunotherapy seem to have limited the role of chemotherapy. But is this completely true? The aim of this editorial is to discuss some of the most controversial aspects of the therapeutic scenario in non-small cell lung cancer, with particular attention to the role that chemotherapy still plays.

Keywords: Chemotherapy, Immunotherapy, Non-small cell lung cancer, Target therapy

Lung cancer in Italy is the second most frequently diagnosed tumor in men and the third in women. It accounts for 11% of all newly diagnosed neoplasms. Lung cancer is the leading cause of tumor death in men and the third in women and, although the 5-year survival rate has moderately increased in the last years, its diagnosis remains associated with a very poor prognosis (1). In the early stages, surgery is the most useful strategy available. Instead, it has a very limited role in metastatic cases. Unfortunately lung cancer is often an insidious disease that becomes symptomatic only when it is already at an advanced stage. In these patients the only therapeutic option available is systemic therapy, with a consequent drastic reduction of 5-year survival. However, in the last 20 years, while almost nothing has changed in small cell lung cancer, significant progress has been made in the treatment of metastatic non-small cell lung cancer (NSCLC) (2).

The most important step forward has surely been the advent of targeted therapies in patients with specific molecular targets (EGFR mutations and ALK rearrangements); such patients represent about 15% of NSCLC cases. EGFR tyrosine kinase inhibitors (TKIs) and ALK inhibitors have radically changed the treatment paradigm of these specific subgroups (3). Several randomized trials have provided data comparing EGFR TKIs (gefitinib, erlotinib or afatinib) versus platinum-based chemotherapy as first-line treatment in patients with activating EGFR mutations, showing the evident superiority of targeted therapies in this setting (4). Moreover, after progression with these drugs, third-generation molecules (AZD9291, rociletinib) are being tested and they are showing high activity, mainly in patients harboring the acquired EGFR T790M mutation (5, 6). Similarly to EGFR TKIs, ALK inhibitors (crizotinib, alectinib, ceritinib) have proved to be superior to standard chemotherapy in all the treatment settings in which they have been tested, including in patients resistant to a previous line with another ALK inhibitor (7, 8). According to such results it is undoubtable that in these subgroups of patients targeted therapies will continue to have increasing importance in the first and subsequent treatment lines while chemotherapy is a useful option only when a targeted treatment is not available.

In the last few years immunotherapy has clearly been on the rise. The new immune checkpoint inhibitors targeting CTLA-4, PD-1 and PD-L1 are showing exciting results in patients with advanced NSCLC. Nivolumab is a human anti-PD-1 monoclonal antibody that blocks the PD-1 receptor on activated T cells, causing a boost of the immune-mediated antitumor response. In a phase III study (CheckMate-017) conducted in patients with squamous histology, nivolumab compared to docetaxel significantly improved median overall survival (OS) and reduced the risk of death by 41%. This study did not show any correlation between outcomes and PD-L1 expression assessed by immunohistochemistry (9). Recently Borghaei et al (10) presented the results of a similar study conducted in nonsquamous histologies (CheckMate-057). The trial was stopped prematurely because the primary end point was reached at the first interim analysis. Nivolumab

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Corresponding author:
Giuseppe Lo Russo, MD
Thoracic Unit
Department of Medical Oncology
Fondazione IRCCS Istituto Nazionale dei Tumori
Via Giacomo Venezian 1
20133 Milan, Italy
giuseppe.lorusso@istitutotumori.mi.it

compared to docetaxel in the second-line setting showed a significant improvement in median OS. Contrary to the previous study, in this trial the expression of PD-L1 seemed to play a decisive role in selecting patients who have a better response to the experimental drug (10). Similar results have been obtained with pembrolizumab (11) and other immunological agents (12). These data have prompted the US Food and Drug Administration (FDA) to approve nivolumab and pembrolizumab in NSCLC patients progressing after a platinum-based regimen (pembrolizumab only in PD-L1-positive patients). Although these results are really outstanding and can be considered a major advance in the treatment of lung cancer, it is important to point out that a large segment of patients do not respond to these therapies. Considering the health, social and economic costs, the selection of patients who will benefit from immunotherapy is a critical issue.

So the majority of patients with advanced NSCLC do not harbor activating mutations and we still do not have a clear tool to select those who are more likely to benefit from immunotherapy. For these patients different treatments are now available. In this context, the choice of the right therapy and the right sequences is crucial and it is surely an unmet need. Chemotherapy still plays a fundamental role.

Standard first-line chemotherapy for advanced NSCLC is based on platinum derivatives in combination with third-generation anticancer drugs. Several studies have shown significant improvements in survival when chemotherapy was added to best supportive care in the metastatic setting (13, 14). In recent years, many first-line trials have demonstrated that histology is critical in the choice of the right regimen. In the nonsquamous histologies, carboplatin-paclitaxel-bevacizumab and pemetrexed-platinum can be considered currently as standard treatments (15-17). In squamous histology, necitumumab, a new EGFR antibody, added to cisplatin-gemcitabine, has shown a statistically significant improvement in OS (11.5 vs. 9.9 months; hazard ratio [HR] 0.84, 95% confidence interval [CI] 0.75-0.96; p = 0.01) (18). In patients having benefit from first-line chemotherapy, maintenance therapy is an efficacious option. Such patients account for almost 70% of patients with nonsquamous histology. Data from the PARAMOUNT trial have established the certain role of pemetrexed in the maintenance setting (19, 20). Single-agent bevacizumab or bevacizumab-pemetrexed continuous maintenance are other feasible options. However, the results from the ECOG 4599 trial are eagerly awaited to understand the real efficacy of such strategies (21-23).

Chemotherapy is still an active treatment that must be considered also in second line (24-27). In recent years many attempts have been made to improve its efficacy in this subgroup of patients. In a randomized, double-blind phase III study, ramucirumab, a new antiangiogenic drug, added to docetaxel and compared to placebo significantly improved the median OS in all patients with NSCLC after 1 prior platinum-based chemotherapy regimen (10.5 vs. 9.1 months; HR 0.86, 95% CI 0.75-0.98; p = 0.023) (28). Data from the LUME-Lung 1 phase III randomized trial seem to point in the same direction. In this study, nintedanib, a triple angiokinase inhibitor, was tested in combination with docetaxel vs. placebo plus docetaxel in patients progressing after first-line platinum-based regimens. It showed in the overall population a significant improvement in progression-free survival (PFS) but not OS. However, it is interesting that patients with adenocarcinoma histology and rapidly progressing disease after first-line therapy (<9 months) experienced a significant improvement both in PFS and OS, although at the cost of increased toxicity (29). These data in November 2014 led the FDA and the European Medicines Agency (EMA) to approve nintedanib in combination with docetaxel as second-line treatment in patients with advanced lung adenocarcinoma, while ramucirumab has been approved by the FDA for all NSCLC histologies.

In conclusion, chemotherapy plays and will continue to play a crucial role in the management of a large proportion of patients with advanced NSCLC. In patients having a wild-type genotype a multitude of active drugs (chemotherapy, immunotherapy and antiangiogenics) are available and, in the strategy of the continuum of care, it is fundamental that each of these options can be fully exploited. At present, all wild-type patients should be treated with first-line chemotherapy according to their histology. In those achieving any benefit, continuous maintenance therapy is an efficacious and feasible option that is strongly recommended as it significantly delays the need for second-line therapy. Recent results obtained in immunotherapy trials have led many clinicians to treat patients earlier with immunotherapy, reducing the total duration of first-line and maintenance treatment, because of the recent availability of these new drugs. Undoubtedly such therapies are going to change the clinical history of NSCLC; however, to date there has been no scientific evidence supporting the superiority of an early start of immunotherapy compared with standard maintenance therapy or its use in treatment-naïve patients. Several studies are ongoing with the aim of moving immunotherapy to first line, either as an alternative to standard chemotherapy or associated with it, but the available data are still very preliminary. As regards second-line therapy, immunotherapy is certainly a new standard in patients with squamous NSCLC. Nevertheless, its role in patients with nonsquamous histologies has yet to be established on the basis of a selection tool which is still far from being defined. Many efforts have been made to elucidate the factors that in some individuals are related to long-term responses. PD-L1 and other potential prognostic and predictive factors are being studied, but the results are contentious. Similarly histology, smoking status and mutational load are under investigation for the selection of patients. Other grey areas are the treatment of elderly patients and patients with performance status 2. Thus the long-term survivors' fraction that actually benefits from these treatments could be about 25%-30%. This means that there is a conspicuous percentage of patients that would potentially benefit more from chemotherapy with or without new antiangiogenic drugs. The identification of prognostic and predictive markers for each of these classes of drugs is pivotal and may lead to proper treatment personalization.

The future is bright in the treatment of NSCLC: treatment options that were limited until yesterday are increasing day by day.

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