Commentary

Improving survival of patients with locally advanced non-small-cell cancer remains a challenge: comment to PROCLAIM

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Locally advanced non-small-cell lung cancer (NSCLC) is a heterogeneous disease with regard to biology and histopathology, location and extension of tumors, patient risk profiles and inter-institution diversities affecting both diagnostic procedures and treatments (1). Patient subsets include patients with incidental mediastinal lymph node involvement at the time of surgery, patients with potentially resectable disease, and patients with unresectable disease. Treatment is based on both local and systemic therapies. The type of treatment in individual patients, however, depends on tumor stage (IIIA versus IIIB), extent of lymph node involvement, performance status and co-morbidity of patients, and other factors (1). Local and distant metastases will develop in up to 40% and more than 50% of patients, respectively. Five-year survival rates of patients vary widely and are usually in the range of 15–30%.

Patients with completely resected stage III NSCLC are candidates for postoperative adjuvant chemotherapy with a cisplatin-based doublet, preferably cisplatin plus vinorelbine (2,3). A meta-analysis based on individual data from 4,584 patients from five randomized trials of cisplatin-based chemotherapy demonstrated that adjuvant chemotherapy increases the 5-year survival rate by absolute 5% and that this benefit is greater in patients with stage III disease (3). Patients with mediastinal lymph node involvement at the time of surgery may also be considered for adjuvant radiotherapy in addition to adjuvant chemotherapy. Adjuvant radiotherapy after complete tumor resection improves progression-free survival but its beneficial impact on overall survival remains yet to be proven. The currently ongoing LUNG-ART trial evaluates whether adjuvant radiotherapy improves overall survival of patients with completely resected stage III NSCLC.

Patients with unresectable stage III NSCLC and good performance status receive chemoradiotherapy (1). Chemotherapy consists of a platin-based doublet with cisplatin-based chemotherapy being preferred over carboplatin-based protocols (1). Most studies used cisplatin plus etoposide or cisplatin plus a Vinca alkaloid such as vinorelbine (1). The number of chemotherapy cycles ranges from two to four, although the optimal number of chemotherapy cycles remains unclear. Thoracic radiotherapy is given up to doses of 60–66 Gy (1). Concomitant chemoradiotherapy results in superior survival at the expense of increased toxicity compared to the sequential chemoradiotherapy. In a meta-analysis based on 1,205 patients from six randomized trials, concomitant chemoradiotherapy compared to sequential chemoradiotherapy improved survival of patients with absolute survival benefits at three and five years of 5.7% (from 18.1% to 23.8%) and 4.5% (from 10.6% to 15.1%), respectively (4). This survival benefit of the concomitant approach was primarily due to a better locoregional control but at the cost of increased acute esophageal toxicity.

One of the strategies for improving outcome of patients with locally advanced NSCLC has focussed on improving chemotherapy. This strategy has been studied in the PROCLAIM study which evaluated whether survival of patients with stage IIIA/IIIB unresectable non-squamous cell NSCLC can be increased by cisplatin plus pemetrexed with concurrent thoracic radiotherapy compared to cisplatin plus etoposide concurrent with thoracic radiotherapy (5). Rationales for this study were the improved efficacy and better tolerability of pemetrexed plus cisplatin compared to

cisplatin plus gemcitabine in patients with advanced non-squamous NSCLC (6) and the *in vitro* radiosensitizing effect of pemetrexed. Based on these advantages, cisplatin plus pemetrexed was hoped to improve outcome including overall survival of patients with stage III non-squamous cell NSCLC.

The PROCLAIM study was a randomized phase III trial and aimed at showing superior survival for patients treated with cisplatin plus pemetrexed compared to patients treated with cisplatin plus etoposide. In the cisplatin-plus-pemetrexed arm, patients received three cycles of cisplatin plus pemetrexed and four cycles of pemetrexed consolidation therapy. In the cisplatin-plus-etoposide arm, patients received two cycles of cisplatin plus etoposide and two cycles of consolidation chemotherapy with a platinum-based doublet. The doses of pemetrexed were identical to those usually used in the palliative setting. The pre-planned interim analysis of the PROCLAIM study indicated futility and led to the closure of the trial after enrolment of 598 patients with unresectable non-squamous cell NSCLC. The two treatment arms well balanced in terms of patient characteristics. In the final analysis, the survival of patients between both treatment arms was not different. The hazard ratio was 0.98 (95% confidence interval, 0.79–1.20; P=0.83) and median survival times were 26.8 and 25.0 months, respectively. The trial showed a non-significant and clinically non-relevant improvement in progression-free survival. Toxicity slightly favoured cisplatin plus pemetrexed in terms of drug-related grade 3–4 events (64% *vs.* 76.8%).

Overall, the PROCLAIM study was a well designed phase III study with survival as its primary endpoint. Importantly, the study used cisplatin-based chemotherapy in both treatment arms. Patient enrolment took nearly four years, thereby underscoring the challenge of enrolling lung cancer patients into clinical trials. As its most important finding, the trial failed to demonstrate an improvement in the overall survival of patients treated with cisplatin plus pemetrexed compared to those treated with cisplatin plus etoposide. The trial, therefore, once again stresses the well known difficulty of improving survival of patients with locally advanced NSCLC. The fact that a lack of benefit was seen both for survival and progression-free survival is consistent with a previous report that progression-free survival is a valid surrogate endpoint for overall survival in studies of chemotherapy and radiotherapy for patients with locally advanced lung cancers (7). As a positive finding, the PROCLAIM study demonstrated an acceptable safety profile of pemetrexed plus cisplatin. A lower incidence of any grade 3–4 adverse events including neutropenia was observed, although the incidence of any grade pneumonitis was increased. Therefore, cisplatin plus pemetrexed lends itself as another chemotherapy protocol for patients with locally advanced NSCLC.

Other strategies that have been studied to improve outcome of patients with stage III NSCLC include induction chemotherapy, consolidation chemotherapy, targeted therapies, novel radiotherapy techniques and integration of surgery (1,8-15). Increasing chemotherapy delivery by either induction or consolidation therapy has been studied (8-10). Consolidation chemotherapy with docetaxel failed to increase survival (9). In a pooled analysis based on published studies, consolidation chemotherapy was also shown to provide no significant survival benefit (10). Consolidation therapy with gefitinib compared to placebo following chemoradiotherapy and docetaxel consolidation was even associated with worse survival of patients with locally advanced NSCLC and unselected for EGFR mutation status of their tumors (11). Reasons for this unexpected finding remain unclear. Vaccination with tecemotide in patients who have undergone chemoradiotherapy also failed to improve outcome (12).

The RTOG 0617 study evaluated a high radiotherapy dose (74 Gy) versus a standard dose (60 Gy) and the combination of chemoradiotherapy with cetuximab in patients with unresectable stage III NSCLC (13). The higher radiotherapy dose was associated with worse survival compared to the standard dose and reasons for this unexpected result remain unclear. The combination of chemoradiotherapy with cetuximab did not improve overall survival in the total study population. However, the combined treatment was associated with increased overall survival in patients with high EGFR expression in their tumors. EGFR expression was based on an immunohistochemistry score like in the FLEX trial (16). Thus further evaluation of chemoradiotherapy combined with cetuximab is warranted in patients with high EGFR expression in their tumors.

Finally, the inclusion of surgery as part of a trimodality treatment is another strategy to improve outcome (14,15). Surgery must aim at complete resection of the tumors which also includes systematic mediastinal lymph node exploration and resection (1). Surgery can be considered in selected patients, particularly in those with resectable disease and in those in whom induction therapy has resulted in mediastinal down-staging. Because pneumonectomy after chemoradiotherapy was associated with increased mortality

in a phase III trial (14), pneumonectomies should only be carried out in selected patients in experienced high-volume centres (1). The positive impact of surgery in patients with stage IIIA NSCLC has also been confirmed in a recent meta-analysis which demonstrated that neoadjuvant chemoradiotherapy or chemotherapy followed by surgery is superior to chemoradiation or radiotherapy, particularly in patients undergoing lobectomy (15).

In conclusion, improvements in the survival of patients with locally advanced NSCLC will most likely continue to be difficult to be achieved, although immunotherapy with immune checkpoint inhibitors holds promise for the near future. Thus two strategies will remain most important for decreasing the world-wide burden of lung cancer. Firstly, early detection by means of low-dose computer tomography screening should be implemented in specialized cancer centres based on the mortality reduction observed in the National Lung Screening Trial (17). Secondly, tobacco control measures must be strengthened as the most effective strategy against lung cancer and the most important health measure in this century (18,19).

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Footnote

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