Locally advanced non-small cell lung cancer: role of induction chemotherapy in resectable N2 disease

M. R. Migliorino1, L. De Petris1, S. De Santis1, A. Cipri1, R. Belli1, S. Condò1, O. Ariganello1, M. Di Molfetta1, A. Saponiero1 & F. de Marinis1,2*

15th Pneumo-Oncology Unit, Department of Lung Diseases, San Camillo-Forlanini Hospitals, Rome; 2Fo.R.O. (Oncological Research Foundation), Rome, Italy

Patients with resectable stage IIIA-N2 non-small cell lung cancer should receive induction chemotherapy before surgery. The aim is to early control systemic disease, eventually cure the mediastinal tumor spread and improve patients' survival. A recent metanalysis of randomized trials with second-generation platinum-based combinations has reinforced the evidence concerning the benefit of induction chemotherapy followed by surgery versus surgery alone in resectable disease. Moreover a large number of phase II trials have explored the activity and feasibility of platinum-based combinations with third-generation drugs in the same setting. Still opened questions to address with current clinical research are the eventual role of radiotherapy as induction treatment, the impact of definite chemoradiation versus induction treatment followed by surgical resection on local control and survival and finally the non-easy choice between neo-adjuvant and adjuvant chemotherapy.

**Key words:** neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, NSCLC, stage IIIA, N2

**introduction**

Non-small cell lung cancer (NSCLC) that has a T-stage between T1 and T3 and has spread to the ipsilateral mediastinal lymphnodes is defined as stage IIIA-N2. Patients diagnosed at this stage represent approximately 20% of all lung cancer patients. Nevertheless, within the same stage, patients' outcome and management highly depends on the extension of mediastinal involvement, and on other additional factors that are not actually included in the currently used international staging system. In fact, in technically resectable N2 disease, minimal or clinical involvement has different survival impact [1], while in the so-called N2-bulky disease (multistation, fixed or extracapsular spread) the total volume of primary tumor and metastasis burden have an inverse correlation with survival [2]. Moreover, if N2-bulky disease is treated together with patients with stage IIIB NSCLC, with a combination of chemo- and radiotherapy, the current management of clinical, technically resectable, N2 disease is still debated.

In this latter group of patients, induction chemotherapy has several end-points. It aims to shrink the tumor volume, reach a complete response at the mediastinal level and thus allow a curative surgical resection. Moreover, the systemic treatment before surgery aims to control distant micrometastasis and thus improve patients overall survival. Nevertheless, the evidence towards the benefit of this approach for patients who could receive surgery as the primary intervention is not conclusive, and this is due to several considerations. The proper staging of the mediastinum with invasive intervention, such as mediastinoscopy or trans-bronchial biopsy, at diagnosis and eventually for the assessment of response after induction treatment; the eventual role of non-invasive procedures, such as the positron emission tomography (PET), for the same purpose; the role of adjuvant radiotherapy, that in early stages of disease is detrimental [3], but whose role in stage IIIA is still controversial; finally, the stronger evidence that post-operative chemotherapy has gained in the last years, and its demonstrated improvement in survival compared to surgery alone in very large phase III trials on radically resected patients [4]. On the other hand, pre-operative chemotherapy with cisplatin and third-generation drugs combinations has demonstrated to be active and extremely well tolerable. Response rate ranges from 50% till 70%, much higher than in advanced disease, with a complete response rate of 5–15%; the toxicity is low and manageable, the compliance to treatment is high, due to the lower burden of tumor-related symptoms, and surgery-related mortality after neoadjuvant chemotherapy is not increased.

**randomised trials of induction chemotherapy**

The role of neoadjuvant chemotherapy versus surgery alone was explored in the early 90s by two phase III trials, that were prematurely stopped due to the striking improvement in survival for the study arm versus the control arm (approximately 20 months vs. 10 months, respectively) [5, 6]. Updated reports of these trials demonstrated how the benefit of this approach could be long-lasting [7, 8] (Table 1).
Table 1. Phase III randomized trials of neoadjuvant chemotherapy followed by surgery vs surgery alone in patients with resectable NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>No. of patients</th>
<th>Neoadjuvant treatment</th>
<th>Pre-treatment surgical assessment of mediastinal lymph-node status</th>
<th>Median survival time (months)</th>
<th>3-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosell et al.</td>
<td>IIIA</td>
<td>30</td>
<td>Mitomycin, Ifosfamide, Cisplatin</td>
<td>Only in pts with cN2 disease</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>IIIA</td>
<td>30</td>
<td>None</td>
<td></td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Roth et al.</td>
<td>IIIA</td>
<td>28</td>
<td>Etoposide, Cyclophosphamide, Cisplatin'</td>
<td>Only in pts with cN2 disease</td>
<td>21</td>
<td>43</td>
</tr>
<tr>
<td>Nagai et al.</td>
<td>IIIA-N2</td>
<td>31</td>
<td>Vindesine, Cisplatin</td>
<td>In all pts</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Depierre et al.</td>
<td>IB-IIIA</td>
<td>176</td>
<td>Optional</td>
<td></td>
<td>37</td>
<td>51.6</td>
</tr>
</tbody>
</table>

Supplement 2

f84% of responding patients received further 2 cycles of adjuvant chemotherapy.

c81% of responding patients received further 3 cycles of adjuvant chemotherapy.

dTrial stopped prematurely for too slow accrual.

eDifference non-statistically significant.

Unfortunately, these results were not confirmed by other two trials [9, 10]. The major limitations of these studies were a small sample size (an average of 30 patients per study arm in three trials, while one trial enrolled 170 patients per arm [10]), an often non-rigorous pre-treatment surgical assessment of mediastinal spread, a mixture of patients at different stages (from IB to IIIA), the non-standardized use of post-operative chemo- and radiotherapy and the use of second generation platinum-based combination treatments.

Despite the heterogeneity of these studies, in a recent meta-analysis [11] the advantage of neoadjuvant chemotherapy followed by surgical resection versus surgery alone in patients with resectable disease has been clearly defined, even in the subset of patients with N2 disease (HR 0.66 [95% CI 0.48–0.93]).

**new induction regimens: platinum-based doublets and triplets**

With the advent of third-generation drugs i.e., gemcitabine, vinorelbine, taxanes, the interest towards induction chemotherapy increased, and this lead to several phase II trials with third-generation drugs combined with platinum.

The EORTC 08941 trial is a phase III study that randomized patients with pN2 NSCLC to surgery or radiotherapy after a partial response to induction chemotherapy. Final results are awaited, but from this study three separate phase II trials to report the results of induction chemotherapy alone with cisplatin-gemcitabine [12], cisplatin-docetaxel [13] or carboplatin-paclitaxel [14] have been already published. Induction chemotherapy was well tolerated, and response rate was 40–70%. Among all patients randomized to the surgery arm, radical resection was obtained in 49.7% of cases, while a pathological downstaging to N0 or N1 disease was achieved in 40.9% of patients [15].

Cisplatin combined with docetaxel or gemcitabine was administered as induction chemotherapy in patients with N2 disease in other 2 studies [16, 17]. Again, though one of these studies included only resectable-N2 disease [16], while our trial included also selected non-N3 stage IIIB patients [17], response rates were similar (approximately 60%). Nevertheless, the percentage of pathological clearance of mediastinal lymphnodes was 60% in the first study, while only 20% in our study that enrolled also non-resectable disease.

In order to improve the activity of induction chemotherapy in patients with N2 disease, we added a third drug (paclitaxel) to the combination of cisplatin and gemcitabine [18]. All 49 patients enrolled in this phase II study had a biopsy-proven mediastinal disease; response rate was 73.5%, radical surgery after induction chemotherapy was performed in 55% of patients, while in 35% of all patients (17/49) mediastinal lymphnodes were found tumor-free at surgery. Median survival time was 23 months. Moreover, the triplet was very well tolerated, with grade 3–4 neutropenia recorded in 30% of patients.

A Spanish trial [19] assessed the activity of another triplet with cisplatin, vinorelbine, gemcitabine, as induction treatment in locally advanced disease. This regimen reached a response rate of 52%, and a median survival time of 12.5 months. Compared to the CGP combination, these results seem disappointing. Though, the patient population selected in the Spanish trial was at worse prognosis compared to the previous Italian trial (76% of patients with stage IIIB vs. 0% in the De Marinis et al. [18] trial). This could have lead to a lower probability of down-staging after induction chemotherapy, a less possibility of performing radical surgery, and thus to a shorter overall survival (Table 2).

**platinum-free induction combinations**

Another phase II trial has explored the activity of platinum-free combination of gemcitabine and vinorelbine as induction treatment in 62 patients with resectable NSCLC, including stage I-IIIA (N2) [20]. In the overall population, response rate
was 37%, and among 11 patients who at initial staging had N2 disease, and underwent surgery, mediastinal lymphnodes were negative only in two patients. Thus, though indirectly, this combination shows less activity in this setting than combinations that include platinum.

**role of radiotherapy as induction combination treatment**

Concerning the role of radiotherapy in this setting, besides the EORTC 08941 trial, it has been explored by other studies. In a phase II trial [21], patients with N2 disease (either resectable or bulky) were non-randomly treated with platinum-based either chemotherapy or chemoradiation as neoadjuvant therapy, followed by surgical resection. If in both groups the percentage of R0-resection and postoperative mortality following induction treatment was similar (approximately 90% and 3%, respectively), patients treated with induction chemoradiation had a higher pathological mediastinal downstaging (78% versus 61%). In a earlier phase III trial [22], 73 patients with pN2 disease (again either bulky or resectable) were randomized to radiotherapy or surgery following induction chemotherapy with a second-generation cisplatin-based triplet. No differences in survival were demonstrated between the two arms, and complete surgical resection was achieved in 73% of patients undergoing thoracotomy. Finally, the second interim analysis of the most important phase III trial in this setting, designed to better clarify the role of radiotherapy as induction or definitive treatment, has been recently published [23]. In this trial, 429 patients with resectable pN2 disease, after an induction treatment with chemoradiation, have been randomized to complete chemoradiation till full dose, or to undergo surgical resection. In both arm further adjuvant/consolidation chemotherapy has been administered. Preliminary results show a higher incidence of esophagitis for the full-dose chemoradiation arm, but a non-significant difference in survival between the two arms ($P = 0.24$).

**open questions**

Finally, though neoadjuvant chemotherapy is considered a standard of care in patients with resectable disease in the updated guidelines of the European Society of Medical Oncology [25], several issues still remain to be assessed for the proper management of stage IIIA-N2 NSCLC. Among other factors, the optimal regimen to use as induction treatment has not yet been established. Possible neoadjuvant strategies might be to give induction chemotherapy alone to patients with minimal mediastinal involvement, while to treat with a more aggressive combination of chemo- and radiotherapy those patients with a higher tumor burden. In this latter case, then, a fast and effective revaluation would address patients to surgical resection or definite local treatment with the same induction schedule at full doses. In the future a phase III trial properly powered to detect differences in survival should challenge pre-operative versus post-operative chemotherapy. A similar trial is ongoing (NATCH trial) but unfortunately its target is limited to patients with stage I-IIIA (N1) disease.
references


