Review Article

Neoadjuvant chemotherapy in early-stage non-small cell lung cancer

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Abstract: Surgical resection followed by adjuvant chemotherapy is the standard of care for completely resected stages II and III non-small cell lung cancer (NSCLC) patients. In order to improve survival in patients with early-stage NSCLC, efforts have been focused on the use of chemotherapy and radiotherapy before surgery with the aim of reducing the risk of relapse. Neoadjuvant chemotherapy is an attractive treatment option which is employed in different tumors and may well be associated with certain advantages in NSCLC patients such as being effective in treating occult microscopic systemic disease, downstaging mediastinal lymph node and improving the success of surgery by tumor reduction. Furthermore, chemotherapy compliance prior to surgery is generally better than after surgery. The potential disadvantages are treatment-related toxicities and the delay of surgery. At present, neoadjuvant chemotherapy is still considered an experimental treatment modality in early-stage disease and its role should be more clearly defined.

Key Words: Neoadjuvant; early-stage; non-small cell lung cancer (NSCLC)

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Introduction

Current standard care for treating early stage non-small cell lung cancer (NSCLC) is surgical resection, when feasible, followed by adjuvant chemotherapy in stages II and III. However, chemotherapy compliance in the post-surgery setting is relatively poor and other strategies, such as neoadjuvant chemotherapy, have been addressed in clinical trials.

The role of neoadjuvant or induction chemotherapy in non-metastatic NSCLC has been evaluated in non-randomized and randomized clinical trials since neoadjuvant or induction therapy in resectable patients carries several theoretical advantages including locoregional cytoreduction, control of distant micrometastases, and a higher preoperative chemotherapy compliance compared with chemotherapy compliance after surgery. When this neoadjuvant approach was first discussed, the main potential disadvantages were treatment-associated toxicities and a delay in the surgical procedure, although at present, these drawbacks are considered barely relevant.

Studies analyzing neoadjuvant chemotherapy, and neoadjuvant chemoradiotherapy

In the 1990s, two small randomized trials comparing neoadjuvant platinum-based chemotherapy followed by surgery *versus* surgery alone in stage IIIA NSCLC had a profound impact because they demonstrated a survival benefit in patients receiving preoperative chemotherapy. Rosell *et al*. (1) compared resection and post-operative radiation (50 Gy) *versus* induction chemotherapy with three courses of cisplatin, mitomycin C and ifosfamide followed by resection and post-operative radiation in 60 patients with stage IIIA NSCLC. A three-fold survival advantage was seen in those patients who received induction chemotherapy (26 *versus* 8 months, P<0.001). Roth *et al*. (2) reported the results of a similar clinical trial in which 60 patients with stage IIIAN2 disease were randomly assigned to receive induction chemotherapy with three cycles of cyclophosphamide, etoposide and cisplatin followed by resection *versus* surgical resection alone. Radiation was

administered to more than half the patients in both groups. Induction chemotherapy was associated with a six-fold increase in median survival (64 *versus* 11 months, P<0.008).

Updated analyses of both studies continue to favor survival in the neoadjuvant chemotherapy arms. Long-term results of Rosell *et al*. study (3) confirmed a statistically significant survival difference (22 *versus* 10 months, P=0.005). In the long-term report of the Roth *et al*. (4) study with a follow-up of 82 months, 32% of patients who underwent neoadjuvant chemotherapy remained alive *versus* 16% of those who had undergone surgery alone (P=0.056).

The results of these two studies were discussed extensively as the survival advantages for the neoadjuvant chemotherapy groups were far greater than could be reasonably expected (5) and because both studies have a number of weaknesses in their design. These include variable prescription of adjuvant radiotherapy, the use of older drugs, and the application of the 1986 staging classification, in which stage III is even more heterogeneous than in the present one. Furthermore, in the Rosell *et al*. study there was a poor outcome in the surgery-alone group, which may be attributable to an imbalance of biological prognostic factors.

Since these early studies, several groups have evaluated neoadjuvant chemotherapy combinations prior to surgery in patients with early-stage disease.

In 2001, the French Thoracic Cooperative Group reported the results of a phase III study including 355 patients with stage IB, II and IIIA disease randomized to receive neoadjuvant chemotherapy (two courses of mitomycin C, ifosfamide and cisplatin) followed by surgery *versus* surgery alone (6). In both arms, patients with pT3 or pN2 disease received adjuvant thoracic radiotherapy, and responding patients received two additional cycles of adjuvant chemotherapy. Overall response to induction chemotherapy was 64%. The median survival was 37 months for the combined arm *versus* 26 months for the surgical arm (P=0.15). Interestingly, a survival benefit was observed in patients with stage I or II (P=0.027), but not in patients with stage IIIA (P=0.85). A major limitation of this study was the chemotherapy regimen employed, which resulted in poor compliance and an excess of toxicity in the initial phases of the trial.

The role of induction chemotherapy in stages IB to T3N1 NSCLC has also been evaluated by the Biomodality Lung Oncology Team (BLOT) trial in a phase II study in order to assess the feasibility of this approach. A total of 94 patients with early-stage NSCLC were scheduled to receive two courses of paclitaxel and carboplatin administered every three weeks followed by surgery and then, 3 cycles of adjuvant chemotherapy with the same agents for patients undergoing complete resection (7). Ninety-two patients completed preoperative chemotherapy, 59% of major responses were observed, and 82% underwent complete resection. However, only 45% of the patients received the planned adjuvant chemotherapy. In this trial, the 5-year survival rate was 42%. Based on this study, the Southwest Oncology Group (SWOG) 9900 trial randomly assigned 354 patients with stages IB, II or IIIA (excluding superior sulcus tumors and N2 disease) NSCLC to either three cycles of induction chemotherapy with paclitaxel and carboplatin followed by surgery *versus* surgery alone (8). This trial was closed to accrual early, owing to the data available in 2004 showing that adjuvant therapy improved survival after surgery. In the study, a response rate of 41% was seen in the neoadjuvant chemotherapy arm. In both arms of the trial, 84% of the patients underwent complete resection. The median overall survival was 62 months for neoadjuvant chemotherapy arm *versus* 41 months for the surgery alone arm, with a 19% reduction in the risk of death in favor of induction chemotherapy. However, this difference did not achieve statistical significance (HR 0.80, P=0.10).

The Medical Research Council LU22/NVALT 2/EORTC 08012 trial evaluated the role of induction chemotherapy with one of six platinum-based combinations followed by surgery *versus* surgery alone in 519 patients with stages IA to III NSCLC (9). The study was negative with regard to overall survival (HR 1.02, P=0.86). Subgroup analyses were not reported.

The Spanish Lung Cancer Group led the NATCH (Neo-adjuvant *Versus* Adjuvant Taxol/Carbo Hope) trial which included 624 patients with stages IA (size >2 cm), IB, II, T3N1 NSCLC (10). It was a three-arm study in which participants were randomly assigned to receive induction chemotherapy followed by surgery, surgery followed by adjuvant chemotherapy or surgery alone. The chemotherapy regimen was paclitaxel and carboplatin. Although a trend for improved 5-year disease-free survival rates with neoadjuvant therapy was observed (38.3% with neoadjuvant chemotherapy, 36.6% with adjuvant chemotherapy, and 34.1% with surgery alone), there were no statistical differences (P=0.71) among the three arms; it is noteworthy that the majority of patients had stage I disease. In this trial, in the subgroup of patients with stage II-T3N1, the 5-year disease-free survival rates favored the neoadjuvant arm (36.6% in the neoadjuvant group, 31%

in the adjuvant arm, and 25% in the surgery group). A greater proportion (90%) of patients in the neoadjuvant group received the planned three cycles of neoadjuvant chemotherapy compared with the adjuvant group in which only 66% of the patients started adjuvant treatment.

Recently, the CHEST (Chemotherapy for Early Stages Trial) has reported surprisingly different results (11). This study randomly assigned 270 patients with stages IB, II and IIIA NSCLC to three cycles of induction chemotherapy with cisplatin and gemcitabine followed by surgery *versus* surgery alone. Overall, a significant advantage for induction chemotherapy was found with regard to progression-free survival (HR 0.70, P=0.003) and overall survival (HR 0.63, P=0.02), the study being positive in its primary end point (progression-free survival). However, the benefit of induction chemotherapy in progression-free survival was limited only to the subgroup of patients with stages IIB or IIIA disease (92% were IIB); progression-free survival at 3 years was 23% better in the chemotherapy group (P=0.002). The risk of death was reduced by almost 60% among patients with stage IIB/IIIA disease who were randomly assigned to receive induction chemotherapy (P<0.001, HR 0.42). In contrast, in the stage IB/IIA subgroup (93% were IB) there were no differences in progression-free survival (P=0.83, HR 1.06) or overall survival (P=0.94, HR 1.02). Interestingly, in this study, slightly more patients in the surgery alone arm (25%) required pneumonectomy compared with 17% of patients in the chemotherapy arm.

Meta-analyses from data of randomized trials addressing the role of neoadjuvant chemotherapy in early-stage NSCLC are of interest. Berghmans *et al*. reported data from six randomized trials, published between 1990 and 2003, including 590 patients (12). The addition of neoadjuvant chemotherapy to surgery was associated with a non-significant improvement in overall survival (HR 0.65, CI, 0.41-1.04).

Burdett *et al*. examined data from seven randomized trials including 988 patients, published between 1990 and 2005. Neoadjuvant chemotherapy improved survival (HR 0.82, CI, 0.69-0.97), with an absolute benefit of 6% at 5 years (13).

In the CHEST trial results, Scagliotti *et al*. reported the results of a meta-analysis including 10 randomized clinical trials with a total of 2,188 patients comparing neoadjuvant chemotherapy followed by surgery *versus* surgery alone (including NATCH trial and CHEST data). This meta-analysis did show a significant survival advantage for those patients randomly assigned to receive induction chemotherapy (HR 0.89, P=0.02) (11).

Finally, preliminary results from a systematic review and meta-analysis of individual patient data from 13 randomized trials reported that neoadjuvant chemotherapy was associated with an improvement in survival in operable patients with 5% absolute benefit at 5 years (HR 0.88, P=0.025) (14).

Another strategy is the addition of thoracic radiotherapy to chemotherapy in the preoperative setting, which may improve local control and help sterilize mediastinal disease. The principal drawback of preoperative chemoradiotherapy is that it can lead to an increase in surgical complications, principally bronchopleural fistula and post-pneumectomy mortality. Neoadjuvant chemoradiotherapy has been analyzed mainly in stage III disease. The phase III randomized North American Intergroup Trial (Intergroup 0139 trial) addresses the role of surgery after neoadjuvant chemoradiation in resectable stage III NSCLC; 429 potentially resectable patients with biopsy-proven stage IIIA N2 NSCLC were randomly assigned to concurrent chemoradiotherapy (two cycles of cisplatin and etoposide plus radiotherapy up to 45 Gy) followed by surgical resection or further radiation to a definitive dose of 61 Gy (15). Consolidation chemotherapy with cisplatin/etoposide was given to patients in both arms (15). The 5-year disease-free survival rate was 22% for the surgical group and 11.1% for the definitive radiation group. However, the two groups did not differ in their median overall survival (23.6 *versus* 22.2 months, respectively, HR 0.87, P=0.24). The mortality rate observed in the surgical arm was 7.9%, compared with 2.1% in the definitive radiation arm. After neoadjuvant chemoradiotherapy, postoperative mortality was 26% for those patients who underwent pneumonectomy compared with only 1% in patients who had a lobectomy. In an exploratory unplanned, matched subgroup analysis, patients treated with a lobectomy after induction concurrent chemoradiotherapy had a significantly better survival than those who underwent a pneumonectomy or were treated non-surgically.

Two randomized studies address the potentially favorable contribution of adding thoracic radiotherapy to chemotherapy before surgery in patients with stage III disease. The German Lung Cancer Cooperative Group conducted a clinical trial including 558 stage III NSCLC patients, all of whom received three cycles of cisplatin and etoposide; the control group then underwent surgery followed by post-operative radiotherapy while the investigational arm received further chemotherapy

with hyperfractionated radiotherapy (1,5 Gy twice daily to 45 Gy) followed by surgery (16). Although the addition of radiotherapy in the preoperative setting increased the rate of mediastinal clearance (46% *versus* 29%) and decreased the rate of positive surgical margins (8% *versus* 14%), no differences were observed in progression-free survival or overall survival between the two groups. The risk of bronchopleural fistula (5% *versus* 1%) and post-pneumectomy mortality (14% *versus* 6%) was higher in patients receiving preoperative radiotherapy.

At the ASCO-2013 meeting the results of a Swiss trial analyzing neoadjuvant chemotherapy with or without preoperative irradiation in stage IIIAN2 disease (SAKK trial 16/00) were presented (17). Patients with resectable stage IIIAN2 were randomized to receive 3 cycles of neoadjuvant cisplatin and docetaxel followed by accelerated boost radiotherapy or neoadjuvant chemotherapy alone with subsequent surgery for all patients. They reported the results of a planned interim analysis on data of the first 219 patients. In this study, preoperative radiotherapy did not improve median event-free survival (12.8 months for the preoperative chemotherapy followed by radiotherapy arm *versus* 11.8 months for the preoperative chemotherapy alone arm) or survival (27.1 months for the preoperative chemotherapy followed by radiotherapy arm *versus* 26.2 months for the preoperative chemotherapy alone arm).

Overall, these two randomized studies (16,17) suggest that the addition of preoperative radiotherapy seems not to improve overall survival.

Summary and conclusions

In the light of available data, there is, at present, clearer evidence favoring adjuvant strategies when compared with neoadjuvant strategies in early-stage NSCLC. Overall, neoadjuvant approaches are less well studied than adjuvant strategies and the majority of neoadjuvant trials have closed early and have been small in size. Some advantages are associated with neoadjuvant chemotherapy. The compliance with neoadjuvant chemotherapy is better; in the NATCH trial, in which patients were randomized before surgery, a considerable number of patients were unable to receive adjuvant chemotherapy due to slow recovery from surgery. There are subgroups of NSCLC patients who clearly benefit from neoadjuvant strategies, such as those with pathologic complete response at surgery (18), but there are no markers to identify those patients at diagnosis. In our opinion, in the light of the NATCH and CHEST trial results, neoadjuvant strategies may be considered for patients with more advanced disease (T3N1, and patients with multiple N1 regions involved in the preoperative staging) and for those in whom we believe adjuvant chemotherapy could be difficult to administer.

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References

1. Rosell R, Gómez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. N Engl J Med 1994;330:153-8.
2. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst 1994;86:673-80.
3. Schirren J, Eberlein M, Fischer A, et al. The role of sleeve resections in advanced nodal disease. Eur J Cardiothorac Surg 2011;40:1157-63.
4. Roth JA, Atkinson EN, Fossella F, et al. Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. Lung Cancer 1998;21:1-6.
5. Johnson DH, Piantadosi S. Chemotherapy for resectable stage III non-small-cell lung cancer--can that dog hunt? J Natl Cancer Inst 1994;86:650-1.
6. Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. J Clin Oncol 2002;20:247-53.
7. Pisters KM, Ginsberg RJ, Giroux DJ, et al. Induction chemotherapy before surgery for early-stage lung cancer: A novel approach. Bimodality Lung Oncology Team. J Thorac Cardiovasc Surg 2000;119:429-39.
8. Pisters KM, Vallières E, Crowley JJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. J Clin Oncol 2010;28:1843-9.
9. Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/

EORTC 08012 multicentre randomised trial and update of systematic review. Lancet 2007;369:1929-37.
10. Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010;28:3138-45.
11. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIA non-small-cell lung cancer. J Clin Oncol 2012;30:172-8.
12. Berghmans T, Paesmans M, Meert AP, et al. Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. Lung Cancer 2005;49:13-23.
13. Burdett SS, Stewart LA, Rydzewska L. Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. Cochrane Database Syst Rev 2007;(3):CD006157.
14. Burdett S, Rydzewska LH, Tierney JF on behalf of the NSCLC Meta-analyses Collaborative Group. Pre-operative chemotherapy improves survival and reduces recurrence in operable non-small cell lung cancer: preliminary results of a systematic review and meta-analysis of individual patient data from 13 randomised trials. 14th World Conference on Lung Cancer, July 3-7, 2011 Amsterdam, The Netherlands (abstract O23.01).
15. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86.
16. Thomas M, Rübe C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. Lancet Oncol 2008;9:636-48.
17. Pless M, Stupp R, Ris HB, et al. Neoadjuvant chemotherapy with or without preoperative irradiation in stage IIIA/N2 non-small cell lung cancer (NSCLC): A randomized phase III trial by the Swiss Group for Clinical Cancer Research (SAKK trial 16/00). J Clin Oncol 2013;31:abstr 7503.
18. Mouillet G, Monnet E, Milleron B, et al. Pathologic complete response to preoperative chemotherapy predicts cure in early-stage non-small-cell lung cancer: combined analysis of two IFCT randomized trials. J Thorac Oncol 2012;7:841-9.

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