Adjuvant or neoadjuvant chemotherapy for NSCLC

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Abstract: In functionally fit patients with localized disease surgical resection remains the treatment of choice. There is also good evidence to support the use of chemotherapy in stages II-III. However, whether to use neoadjuvant or adjuvant therapy has been the topic of much debate. With its strong evidence base, adjuvant chemotherapy has been adopted in the European Society of Medical Oncology clinical practice guidelines for early and locally advanced stages II-III non-small-cell lung cancer (NSCLC), with consideration of adjuvant therapy in those with stage IB but with tumours >4 cm in size. There are fewer trials comparing neoadjuvant therapy plus surgery with surgery alone. Even less has been carried out directly comparing neoadjuvant with adjuvant therapy. The NATCH trial demonstrated no difference in survival between adjuvant and neoadjuvant arms, whilst others have yet to be completed. Meta-analysis also demonstrates no appreciable difference between the two methods. With such a strong body of evidence, however, postoperative delivery of chemotherapy remains the timing of choice in NSCLC.

Keywords: Lung cancer; chemotherapy; adjuvant; neoadjuvant therapy

Background

Each year 1.5 million new cases of lung cancer are diagnosed worldwide (1). The incidence of lung cancer in Europe is 52.5/100,000 per year (2). Approximately 80% of these cases are non-small-cell lung cancer (NSCLC) (2). In functionally fit patients with localized disease surgical resection remains the treatment of choice (2). There is also good evidence to support the use of chemotherapy in stages II-III (3). Use of chemotherapy in stage IB remains controversial, with no overall survival benefit except in patients with large tumours (3). Both neoadjuvant and adjuvant therapies have been investigated but which is most beneficial remains the topic of much debate.

Adjuvant chemotherapy

The evidence supporting the use of adjuvant chemotherapy in stage II and III is broad. It has become the standard treatment for patients with completely resected stage II or III NSCLC (4). A total of 23 randomized trials between 1992 and 2005 and five further meta-analyses have shown that adjuvant chemotherapy improves survival in patients with completely resected stage II and stage III disease.

The CALGB 9633 study sought to provide clarity over the use of adjuvant chemotherapy in stage IB disease (5). A total of 340 patients were randomly assigned to adjuvant chemotherapy or observation. There was no significant difference in survival (HR 0.83, 95% CI: 064-1.08, P=0.12) between the two groups. However exploratory analysis demonstrated a survival advantage in the adjuvant chemotherapy group amongst those who had tumours greater than or equal to 4 cm in diameter (HR 0.69, 95% CI: 0.48-0.99, P=0.43). Adjuvant chemotherapy was not recommended for all stage IB disease based on these findings. However, the trial group supported consideration of adjuvant chemotherapy for large IB tumours based on their exploratory analysis.

A separate study, the JBR10 trial, showed similar results for stage IB disease. In this study patients with tumours

measuring >5 cm in diameter had a survival advantage when treated with adjuvant chemotherapy (3).

The LACE Collaborative Group published a meta-analysis of five cisplatin-based trials in 2008 (6). It included a total of 4,584 patients and demonstrated a 5.3% improvement in survival at 5 years with adjuvant chemotherapy (P=0.0043). There was also an improvement in disease-free survival of 5.2% at 5 years (P<0.0001). The LACE meta-analysis also demonstrated that there was no association between chemotherapy effect and sex, age, histology, type of surgery, planned radiotherapy or planned total dose of cisplatin.

With its strong evidence base, adjuvant chemotherapy has been adopted in the European Society of Medical Oncology clinical practice guidelines for early and locally advanced stages II-III NSCLC, with consideration of adjuvant therapy in those with stage IB but with tumours >4 cm in size (3).

Neoadjuvant chemotherapy

Whilst the weight of evidence has supported the use of adjuvant chemotherapy in patients with operable lung cancer, the question of timing of administration was reviewed with the publication of the results of LU22/NALVT/EORTC (7) and updated results from SWOG 9900 (8). The former was a randomized trial of surgery alone versus neoadjuvant chemotherapy followed by surgery in 519 patients from 70 centres across the UK, Netherlands, Germany and Belgium. It demonstrated that neoadjuvant chemotherapy was feasible, had a good response rate of 49% (95% CI: 43-55%) and had no effect on the post-operative complication rate. The overall survival, however, between the two groups remained similar with a HR of 1.02 (95% CI: 0.80-1.31, P=0.86).

The SWOG 9900 trial (8) also compared surgery alone versus neoadjuvant chemotherapy followed by surgery. It recruited 354 patients and the disease-free survival HR between the two groups was reported as 0.80 (95% CI: 0.61-1.04, P=0.10). The median overall survival was 41 months (95% CI: 34-55 months) in the surgery alone arm and 62 months (95% CI: 40-76 months) in the neoadjuvant chemotherapy plus surgery arm. The trial closed early after evidence was published that demonstrated survival benefit from adjuvant therapy.

The Chemotherapy in Early stages NSCLC Trial (ChEST) compared neoadjuvant gemcitabine/cisplatin before surgery with surgery alone in patients with stages IB-IIIA NSCLC (9). The progression-free survival hazard ratio was 0.70 (95% CI: 0.50-0.97, P=0.003) and the overall

survival hazard ratio was 0.63 (95% CI: 0.43-0.92; P=0.02), both in favor of preoperative chemotherapy before surgery. However, like SWOG 9900 it also closed early, recruiting fewer than half of the planned 700 patients.

In comparison to adjuvant therapy there are much fewer trials comparing neoadjuvant therapy plus surgery with surgery alone. However, the evidence suggests that neoadjuvant chemotherapy is thought to convey a number of benefits (10):

(I)   Reduction in tumour size;
(II)   Increased operability;
(III) Eradication or prevention of micro-metastases;
(IV)   Better tolerability;
(V)   The possibility that it is more effective when the blood supply remains intact prior to surgery;
(VI)   Better compliance with medication in the preoperative period.

Theoretical disadvantages of the administration of neoadjuvant chemotherapy include:

(I)   A delay in surgical resection;
(II)   The possibility that the tumour may be rendered unresectable after the chemotherapy course;
(III) Increased toxicity.

A recent meta-analysis by the NSCLC Meta-analysis Collaborative Group pooled results from 15 randomized trials comparing neoadjuvant chemotherapy plus surgery with surgery alone (10). A total of 2,385 patients were included. It concluded that pre-operative chemotherapy had a significant effect on survival, with 13% reduction in the relative risk of death. No particular subgroup of patients (including age and stage amongst others) benefited more or less from preoperative chemotherapy. Toxic effects could not be assessed in the analysis.

Neoadjuvant therapy requires a broader evidence base before it could be introduced as a standard treatment option.

Preoperative *vs.* postoperative chemotherapy: randomized trials

A large number of trials have evaluated the impact of post-operative (adjuvant) chemotherapy on survival. Fewer have investigated the impact of pre-operative (induction or neoadjuvant) chemotherapy on survival after surgical resection (11).

However, even less have compared neoadjuvant plus surgery with surgery plus adjuvant chemotherapy in NSCLC.

A randomized phase III trial, the NATCH trial (12), had three arms: (I) preoperative chemotherapy (paclitaxel/

cisplatin) and surgery; (II) surgery alone; (III) surgery and postoperative chemotherapy. The trial demonstrated no difference in disease-free survival between the groups. The HR for disease progression or death in the neoadjuvant group compared with the surgery alone group was 0.92 (95% CI: 0.81-1.04, P=0.176) and the HR for progression or death in the adjuvant group compared with the surgery alone was 0.96 (95% CI: 0.75-1.22, P=0.74). The 5-year overall survival rates were 34.5% in the surgery alone arm, 41.3% preoperative arm and 36.6% in the postoperative arm. The results, however, were nonsignificant. Interestingly, the NATCH trial demonstrated that 90% of the patients assigned to neoadjuvant chemotherapy received three cycles of chemotherapy. This added weight to the argument that neoadjuvant therapy increased the percentage of patients receiving chemotherapy without affecting the percentage undergoing surgery. The trial was criticized for containing a large proportion of stage I disease and for lacking statistical power to show small but potentially important clinical differences.

Initial results from a further randomized trial sponsored by the Chinese Society of Lung Cancer (NCT00321334) were presented at the American Society of Clinical Oncology conference in 2013 (13). It compared survival between adjuvant versus neoadjuvant docetaxel/carboplatin chemotherapy in patients with resectable stage IB to IIIA disease. Recruitment is not complete (with 198 patients recruited out of a planned sample size of 410) and overall survival data is not yet available. The initial 3-year disease free survival for those recruited is similar: 45% in the neoadjuvant arm and 53% in the adjuvant arm, HR =0.88 (0.58-1.33), P=0.54. However, the neoadjuvant arm had significantly more patients who received chemotherapy (100% *vs*. 85.1% in the adjuvant arm, P<0.001) and significantly more who completed three cycles (91.8% *vs*. 82.6% in the adjuvant arm, P=0.061) (13).

Further studies comparing pre-operative and post-operative chemotherapy are yet to be published. Among them are trials sponsored by The National Cancer Centre in Korea (NCT 00398385) and The Samsung Medical Centre and Eli Lilly (NCT 00329472) (11).

Preoperative *vs.* postoperative chemotherapy: meta-analysis

Whilst there have been relatively few head-to-head trials comparing pre-operative chemotherapy and post-operative chemotherapy in NSCLC, meta-analyses have been used to compare the two approaches.

In 2009 Lim *et al*. published an indirect comparison meta-analysis to obtain the relative hazards of post-operative to pre-operative administration of chemotherapy on survival (11). Data from 32 randomized trials involving 10,000 participants were included. There were more trials in the postoperative group (n=22) compared to the preoperative group (n=10) demonstrating the weight of evidence in existence for postoperative chemotherapy. For overall survival, the relative hazard ratio of postoperative compared to preoperative chemotherapy was 0.99 (95% CI: 0.81-1.21, P=0.91). For disease free survival the findings were similar with a relative hazard ratio of 0.96 (95% CI: 0.77-1.20, P=0.70).

Conclusions

The evidence demonstrates that chemotherapy conveys a survival benefit in patients with resectable lung cancer. Less clear is whether the timing of administration of chemotherapy-preoperative or postoperative-affects survival. At present there appears to be no difference in overall and disease free survival between the two groups. Given the broad evidence base and consistent results in support of adjuvant chemotherapy, however, it remains the timing of choice.

Acknowledgements

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. D'Addario G, Felip E; ESMO Guidelines Working Group. Non-small-cell lung cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20 Suppl 4:68-70.
3. Vansteenkiste J, De Ruysscher D, Eberhardt WE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi89-98.
4. 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.
5. Strauss GM, Herndon JE 2nd, Maddaus MA, et al.

Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-51.

6. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.

7. 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.

8. Ball D, Mitchell A, Giroux D, et al. Effect of tumor size on prognosis in patients treated with radical radiotherapy or chemoradiotherapy for non-small cell lung cancer. An analysis of the staging project database of the International Association for the Study of Lung Cancer. J Thorac Oncol 2013;8:315-21.

9. 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.

10. NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-71.

11. Lim E, Harris G, Patel A, et al. Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials. J Thorac Oncol 2009;4:1380-8.

12. 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.

13. Chaft JE, Rusch V, Ginsberg MS, et al. Phase II trial of neoadjuvant bevacizumab plus chemotherapy and adjuvant bevacizumab in patients with resectable nonsquamous non-small-cell lung cancers. J Thorac Oncol 2013;8:1084-90.