Pre-operative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage nonsmall cell lung cancer

Several randomised controlled trials and meta-analyses have shown that adding adjuvant cisplatin-based chemotherapy to surgical resection improves disease-free survival and overall survival in patients with early-stage nonsmall cell lung cancer (NSCLC). Compliance with post-operative chemotherapy is far from optimal, leading to incomplete treatment in many patients. Delivery of pre-operative or neoadjuvant chemotherapy was more feasible in several trials, but has been studied far less extensively than adjuvant therapy. This study reports the results of a phase III trial comparing pre-operative chemotherapy plus surgery, surgery plus adjuvant chemotherapy, or surgery alone in resectable NSCLC.

**Patients and methods**

A total of 624 patients with resectable early-stage NSCLC (stages IA >2 cm, IB, II or T3N1) were randomly assigned to surgery alone (212 patients), three cycles of pre-operative carboplatin-paclitaxel (CP) followed by surgery (201 patients) or surgery followed by three cycles of adjuvant CP (211 patients). The primary end-point was disease-free survival (DFS), secondary objectives were overall survival, and the assessment of chemotherapy delivery and adverse events.

**Results**

In the pre-operative arm, 97% of patients started the planned chemotherapy, 90% completed all three planned cycles, 9% had dose reductions at some point and 11% required one or more dose delays. Radiological response rate was 53%. In the adjuvant arm, 66% of the patients were able to start chemotherapy, only 61% received three cycles, 11% had at least one dose reduction and 16% required one or more dose delays.

94% of the patients underwent surgery: 95% in the surgery arm, 91% in the neo-adjuvant arm and 96% in the adjuvant arm. Surgical procedures and postoperative mortality were similar across the three arms.

Patients in the pre-operative arm had a non-significant trend toward longer DFS than those assigned to surgery alone (5-yr DFS 38% versus 34%, hazard ratio (HR) 0.92; p=0.176). 5-yr DFS rates were 37% in the adjuvant arm versus 34% in the surgery arm (HR 0.96; p=0.74).

Subgroup analyses (stage II–T3N1) showed 5-yr DFS rates of 25%, 37% and 31% in the surgery-alone group, the pre-operative group and the adjuvant group, respectively. 5-yr overall survival rates were 44%, 47% and 46%, respectively. For the stage II–T3N1 subgroup, they were 35%, 41% and 37%, respectively.

**Conclusion**

In early-stage patients, no statistically significant differences in DFS were found with the addition of pre-operative or adjuvant chemotherapy to surgery. In this trial, in which the treatment decision was made before surgery, more patients were able to receive pre-operative than adjuvant treatment.

**References**

Editorial comment

At first glance, the results of this study may look surprising, and in contrast with our knowledge that surgery plus adjuvant chemotherapy does better than surgery alone. However, the lack of statistical differences in this study may have several explanations. First, our data on adjuvant chemotherapy come from thousands of patients, and a three-arm study with —200 patients per arm does not have enough statistical power to show or exclude significant survival differences in this setting. Second, the chemotherapy regimen used is not the best choice, as cisplatin is definitely a more active drug than carboplatin in NSCLC [1]. Thirdly, and perhaps most importantly, 75% of the patients were in clinical stage I (10.7% stage IA), and 58% pathological stage I. The benefits of adjuvant chemotherapy are mainly documented for stages II and II A, and perhaps for some stage IB patients with lager sized primary tumours [2]. In summary, the potential survival differences were diluted by suboptimal chemotherapy and less appropriately chosen stages in a study that was underpowered from the start.

The merit of this study is that it demonstrates in a randomised controlled manner that delivery of pre-operative chemotherapy is much more feasible, both in terms of proportion of patients or number of cycles, than postoperative administration. Moreover, this leads to better outcome data for neoadjuvant versus adjuvant, be it nonsignificant in a study with a 200 patients per arm.

Current treatment guidelines recommend adjuvant administration of chemotherapy. A recent systematic review of neoadjuvant trials [3], with no evidence of a difference in outcome between the timing of administration of chemotherapy, and this trial indicate that pre-operative chemotherapy needs further evaluation.

S. Derijcke, J. Vansteenkiste, Leuven, Belgium