Neoadjuvant chemotherapy in early stage non-small cell lung cancer

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Lung cancer is the leading cause of cancer-related death in Europe. Non-small-cell lung cancer (NSCLC) represents approximately 80% of all lung cancers. Surgery remains the cornerstone of treatment for patients with early-stage NSCLC, and provides the best hope for cure. Operable patients with stages IA through IIIA disease are candidates for complete resection with curative intent. Patients diagnosed with these stages represent approximately 35% of all lung cancer cases. However, despite surgical resection, a large number of patients will relapse after surgery. Five-year survival rates vary from 57 to 67% for stage I and from 39 to 55% for stage II. Patients with completely resected stage IIIA disease have a 5-year survival rate of approximately 25% [1]. The most frequent cause of death for patients after complete resection is the development of distant metastases. Relapse at distant sites is thought to be due to occult micrometastatic disease, undetected at the time of presurgical staging. Eradication of this early metastatic disease by chemotherapy may theoretically translate into a decreased incidence of recurrence in distant sites, and thereby improve survival. This chemotherapy can be administrated before (neoadjuvant or induction) or after (adjuvant) surgery. Several recent randomised trials and meta-analyses have demonstrated an overall survival benefit with adjuvant platinum based chemotherapy in early-stage NSCLC [2–5]. These results have lead to the adoption of surgery and adjuvant chemotherapy as the new standard of care in selected patients. The administration of chemotherapy prior to surgery is an alternate approach to adjuvant chemotherapy.

The term neoadjuvant chemotherapy was introduced by Frei to refer to the specific strategy of using drug treatment at the earliest time possible [6]. Neoadjuvant chemotherapy has claimed some potential advantages over immediate surgery and adjuvant therapy. The most important is the systemic treatment of occult microscopic metastatic disease at the earliest possible time, with an improved progression free and overall survival as compared to a local treatment only. The former is thought to be the result of a better control of the cytokines released by the wound repair, the latter by an improved sterilisation of the occult metastases. Besides its systemic effect, chemotherapy induces cytotoxicity at the mlevel of the primary tumour, resulting in clinical and even pathological remissions. A reduction in the primary tumour mass may theoretically lead to more radical and smaller resections or even render borderline unresectable lesions resectable.

Neoadjuvant chemotherapy is thought to be better tolerated than adjuvant administration, resulting in a higher rate of treatment compliance. Only 45 to 60% of the patients are able to complete the adjuvant chemotherapy without dose reductions or delays, whereas full planned chemotherapy was shown to be administrated in more than 80% of the patients in most phase 2 induction trials [7].

Other potential advantages include in vivo assessment of tumour chemosensitivity, a lower risk of developing drug resistance and the selection of responsive patients, as patients with disease progression on chemotherapy will not benefit from surgery.

The potential disadvantages of neoadjuvant chemotherapy include a delay in potentially curative surgery, less accurate staging – as only clinical staging can be done – and increased surgical morbidity and mortality after chemotherapy.

Enthusiasm for the use of neoadjuvant chemotherapy for treating early stage NSCLC was initially generated by positive survival results from two small randomised studies in patients with stage IIIA [8,9]. In a large phase III trial conducted by Depierre and colleagues, lower rates of distant metastases and improved 4-year survival rates in the chemotherapy plus surgery group were reported compared with the surgery alone group [10]. The feasibility and safety of pre-operative chemotherapy in early stage NSCLC was later established in the Bimodality Lung Oncology Team (BLOT) trial [11]. This prompted the development of a phase III trial evaluating surgery with and without chemotherapy in patients with stage IB to IIIA (T3N1) disease. Its major objective was to determine whether three cycles of pre-operative paclitaxel/carboplatin

improved survival compared to surgery alone. The preliminary results of this trial are available [12]. Three hundred and thirty-five patients were randomised to either pre-operative chemotherapy with the above mentioned regimen or no pre-operative treatment. In July 2004 the study was prematurely closed early after reporting of positive adjuvant data: 77% of patients completed all three cycles of chemotherapy. A radiographic response was observed in 40% of the patients. The major side-effects of chemotherapy were neutropenia and neuropathy with low rates of nausea and vomiting. Three patients died during neoadjuvant chemotherapy. A R0 resection was achieved in 84% of the cases. Pathologic complete response rate was 10%. Seven postoperative deaths occurred in the chemotherapy arm compared with four in the surgery alone group. There was a trend toward better progression free (PFS) and overall survival (OS) for the neoadjuvant treatment that did not reach statistical significance, probably because the study was analysed too early before the required number of deaths had occurred.

In the European Intergroup trial, patients with resectable early stage NSCLC were randomised to either surgery alone or three cycles of platinum based chemotherapy followed by surgery. Preliminary results of the impact of neo-adjuvant chemotherapy in terms of feasibility, toxicity, response rates, downstaging and extent or resection in the first 500 patients have been reported [13]. In the chemotherapy group, 75% received all three prescribed cycles. Response was observed in 47% of the chemotherapy treated patients (3% complete response, 44% partial response), 27% had stable disease and only 2% showed disease progression. The side-effects of the chemotherapy were as expected. The median time from randomisation to surgery was 16 days in the surgery alone group and 15 days from recovery from last chemotherapy cycle to surgery in the combination group. The extent of surgery was similar in both groups. There was no difference in complete resection rates, postoperative complications and number of postoperative nights in the hospital between both treatment arms. The pathological stage of disease was compared with the clinical stage at randomisation. In the surgery alone group, 19% was reported as having downstaging compared with 31% in the neo-adjuvant chemotherapy group. This trial shows that the administration of three cycles of neo-adjuvant chemotherapy is feasible and acceptable for the majority of the patients. Compared with surgery alone, the combination therapy resulted in an additional 10% of the patients with downstaging without higher rates of postoperative complications. The mature results of this trial will be discussed.

Systematic reviews from published summary data of randomised chemotherapy trials in early stage NSCLC have been published. The meta-analysis of Berghmans and colleagues [7] reported six randomised trials, including 590 patients, published between 1990 and 2003. The overall fixed-effect hazard ratio on survival was 0.69 (95% CI 0.57–0.84) in favour of the addition of neoadjuvant chemotherapy to surgery. A less extreme result was seen in individual patient data meta-analysis [14]. Data from seven randomised trials (published between 1990 and 2005), including 988 patients were combined in a systematic review and meta-analysis. Preoperative chemotherapy improved survival with a hazard ratio of 0.82 (95% CI 0.69–0.97), equivalent to an absolute benefit of 6% at 5-years. An updated analysis will be discussed at the meeting.

Conclusions

Which of the theoretical advantages and disadvantages of neoadjuvant therapy in NSCLC have been confirmed? The recent randomised evidence concerning the effect of neoadjuvant chemotherapy on outcome is still premature and only published in abstract form. Nevertheless, some cautious conclusions can be formulated.

The available early outcome data are not entirely in line with the expected gain in survival with neoadjuvant treatment followed by resection and this neither in early nor in locally advanced stages. This can be due to the underpowering of the individual studies or contamination of the outcome by the use of adjuvant therapy in some of them. The data of both systematic reviews on the other hand show an overall effect which is significantly in favour of neoadjuvant treatment. The size of the observed effect is comparable to the one described in a similar meta-analysis in adjuvant chemotherapy [3]. One has, however, to keep in mind that both patient populations are different, as only selected postsurgical patients are offered adjuvant chemotherapy, after pathological staging.

Neoadjuvant chemotherapy results in a clinical downstaging in approximately 40–60% of the patients and a pathological complete response rate in 5–10%. As expected, compliance is better with neoadjuvant chemotherapy compared to adjuvant treatment: more than 70% of the patients are able to complete all three cycles of neoadjuvant chemotherapy whereas full planned adjuvant chemotherapy could be administrated in only 45 to 60% of the cases. The feasibility and safety of pre-operative chemotherapy has been

established in several trials. Neoadjuvant chemotherapy does not delay surgery or result in an increased hospital stay or rate of perioperative complications, when compared to immediate surgery. The addition of radiotherapy to chemotherapy increases the morbidity and mortality of the intervention, certainly if a right pneumonectomy is unavoidable.

With the present status of knowledge, neoadjuvant regimens should be platinum-based and at least three cycles of chemotherapy should be administered. As in advanced NSCLC, a two-drug combination of platinum and a third generation drug seems preferable. The role of non-platinum containing regimens has not been explored up to now and remains an area of future research.

In conclusion, as no trial has shown a formal survival benefit with neoadjuvant chemotherapy preceding resection in otherwise resectable and operable patients with NSCLC, this treatment should not yet be offered outside of clinical trials.

We have to keep in mind, however, that a similar caution with regard to neoadjuvant chemotherapy was, till recently, voiced towards adjuvant chemotherapy. The latter has since moved to standard therapy. In case neoadjuvant chemotherapy shows an outcome benefit over immediate surgery in resectable patients, its next challenge will be the randomised comparison with adjuvant chemotherapy.

Conflict of interest statement

None declared.

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