Debate

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Adjuvant chemotherapy should not be given in NSCLC.

N. Thatcher. *Christie Hospital NHS Trust, Medical Oncology Dept., MAnchester, United Kingdom*

The large majority of patients develop distant recurrence following a complete resection - post-operative (adjuvant) chemotherapy is therefore an attractive proposition [Wagner, Chest 2000]. However, a large meta-analyses of 16 adjuvant trials of 4457 patients showed no survival benefit for post-operative chemotherapy. Indeed with alkylating agents there was survival detriment of 5% at 5 years, p=0.005 and there was no statistical difference HR 0.87, p=0.08 with cisplatin chemotherapy. In a further six trials of 668 patients cisplatin added no benefit to surgery plus radiotherapy HR 0.94, p=0.46 [NSCLC Collaborative Group, Br Med J 1995].

A surprising result was seen in a three arm Japanese study of 323 patients where oral Tegafur was associated with a projected 5-year survival increase from 49 to 64.1% (p=0.02). However, Tegafur plus a cisplatin regimen was not significant in this and a subsequent Japanese trial [Wada J Clin Oncol 1996, Chubu, Eur J Surg Oncol 1995].

The most recent (IALT) study of cisplatin based chemotherapy versus no chemotherapy in 1867 patients showed a small survival advantage of 5% projected at 5 years compared with the no chemotherapy control arm (HR 0.86, p<0.03) [Le Chevalier ASCO 2003]. However, the intended target accrual in this trial was 3300 patients and more (14%) post-operative radiotherapy (PORT) was given to the control patients. The PORT meta analysis of 2128 patients demonstrated a survival detriment of 7% at 2 years (HR 1.21, p=0.001) [Lancet 1998]. Three other recent randomised trials of adjuvant cisplatin based chemotherapy failed to show a survival benefit over no chemotherapy, HR 0.93, p=0.56, [Keller et al., N Engl J Med 2000], HR 0.96, p=0.58 [Tonato ASCO 2002], HR 1.0, p=0.98 [Waller ASCO 2003].

Therefore a large body of evidence (17 trials vs one, the IALT) demonstrates no survival advantage with the use of adjuvant cisplatin based chemotherapy. Given the additional chemotherapy toxicity there is no compelling evidence for the use of adjuvant chemotherapy following complete resection in NSCLC.

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Adjuvant chemotherapy as part of the curative treatment of operable Non-Small Cell Lung Cancer

T. Le Chevalier. *Institut Gustave Roussy, Dept of Oncology, Villejuif, France*

Surgery is the main curative treatment for early stage NSCLC. Nevertheless, more than 50% of patients will die of tumor progression after complete surgical resection. This matter deserves the use of adjuvant treatments.

The first chemotherapeutic agents widely studied in NSCLC were alkylating agents. From 1980, cisplatin was part of most chemotherapy regimens. In the early 90's, the Medical Research Council and Institut Gustave-Roussy decided to perform a large overview on the role of chemotherapy in NSCLC using updated individual data. In the group comparing surgery alone to surgery followed by adjuvant chemotherapy, 14 trials were recorded with an overall accrual of 4357 patients. The results of the 5 trials which used long-term alkylating agents showed a 15% increase in the risk of death which corresponds to a 5% absolute negative effect of chemotherapy on survival at 5years (p=0.005). In the 8 trials which used a cisplatin-based regimen, a 13% reduction in the risk of death was observed, suggesting an absolute benefit of 5% with adjuvant chemotherapy at 5 years (p=0.08). Chemotherapy was randomly added to surgery and radiotherapy in a total of 807 patients. This led to a 6% reduction in the risk of death with cisplatin-based regimen, suggesting a 2% absolute benefit at 5years. Sex, performance status, age and histologic subtype had no impact on this effect. These results constituted the rationale for a new generation of randomized studies with cisplatin-based regimens.

The first was the ALPI trial in which, after surgery, patients with stage I, II and IIIa NSCLC were randomly allocated to receive either 3 courses of MVP (Mitomycin 8 mg/m^2 day 1; Vindesine 3mg/m^2 day 1 and 8; Cisplatin 100 mg/m^2 day 1 every 3 weeks for 3 cycles) or no adjuvant treatment. Overall 1197 patients were enrolled into the study, 592 in the chemotherapy arm and 587 in the control arm. In the chemotherapy arm, 69% of patients completed the treatment but half of them had treament modifications. Radiotherapy was delivered in 482 patients. A total of 1076 patients were analysed with a median follow-up of 63 months. H.R. was 0.94 for overall survival and 0.89 for disease-free survival. No statistically significant difference was observed. The IALT was a large worldwide randomized study whose aim was to determine the impact on overall survival of 3 to 4 cycles of a cisplatin-based chemotherapy regimen after complete surgical resection in patients with stage I-III NSCLC. Thoracic radiotherapy might be given according to the preregistration policy of each centre. A total of 1867 patients were included and the study was closed for inclusions on December 31, 2000. Median follow-up is 56 months. There were 935 pts allocated to CT and 67% received at least 300 mg/m* of cisplatin. The drug combined with cisplatin was etoposide (56%), vinorelbine (27%), vinblastine (11%) and vindesine (6%). There were 932 pts in the control arm. Overall survival was significantly different between the 2 arms: 2 and 5-yr survival rates were 70% and 45% in the CT arm vs 67% and 40% in the control arm respectively (RR=0.86 [0.76-0.98], p<0.03). Disease-free survival was also significantly different: 61% and 39% in the CT arm vs 55% and 34% in the control arm at 2 and 5 yrs respectively (RR=0.83 [0.74-0.94], p<0.003). No significant interaction was observed with age, gender, PS, type of surgery, pStage, histology, cisplatin dose, combined drug, radiotherapy.

The NCI-Canada also conducted a phase III trial comparing surgery alone to surgery followed by adjuvant chemotherapy with cisplatin and vinorelbine in 482 patients with resected NSCLC. Results are expected in 2004. In the ANITA1 trial, which also concerned patients with completely resected NSCLC, chemotherapy consisted of 4 cycles of cisplatin at 100 mg/m2 every 4 weeks and 16 cycles of vinorelbine at 30 mg/m^2 weekly compared to a control arm. A total of 831 patients were included from October 1994 to December 2000 and the analysis is planned next year. ANITA2 was started at the same time for patients unable to receive cisplatin and who are randomized to receive either vinorelbine alone (30 mg/m^2 weekly for a total of 16 administrations) or to be in the control arm. Finally adjuvant chemotherapy is part of the Big Lung Trial led by the Medical Research Council.

In conclusion, the results of the recently reported large randomized studies of adjuvant chemotherapy, and particularly the IALT study, suggest a 4-5% improvement of survival at 5 years, a benefit comparable to that observed in breast and colon cancer. The planned LACE pooled analysis of the recent adjuvant trials will add information on the optimal use of post-operative chemotherapy and the IALT biology program will explore potential predictive test to better identify patients in whom adjuvant chemotherapy can be indicated and tailored