Management of early-stage non-small-cell lung cancer (NSCLC)

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Approximately 1.5 million new cases of lung cancer are diagnosed annually worldwide. Around 85% of these tumours are non-small-cell lung cancer (NSCLC). The optimal treatment for early-stage NSCLC (i.e. clinical stages I and II) is surgery, mostly lobectomy. In patients with functional limitations, an alternative to surgical resection is radiotherapy, and stereotactic irradiation may play a greater role in the future.

Despite optimal local management, five-year survival rate of resected NSCLC ranges between 73% for pathological stage Ia and 25% for pathological stage IIIa. In the early 1990s, a large overview of the role of chemotherapy in NSCLC using updated individual data showed a 13% reduction in the risk of death with adjuvant chemotherapy at five years ($P = 0.08$), suggesting an absolute benefit of 5% [1]. These results constituted the rationale for a new generation of randomised studies with cisplatin-based regimens.

The ALPI trial included patients with resected stage I-IIIa NSCLC. They were randomly allocated to receive either three courses of mitomycin (8 mg/m^2 day 1); vindesine (3 mg/m^2 days 1 and 8); cisplatin 100 mg/m^2 day 1 every three weeks or no adjuvant treatment after complete resection [2]. Overall 1209 patients were enrolled into the study; 1088 patients were analysed with a median follow-up of 63 months. The hazard ratio (HR) was 0.94 for overall survival and 0.89 for disease-free survival. No statistically significant difference was observed even if the difference was borderline significant for stage II disease.

The IALT was a large worldwide randomised study whose aim was to determine the impact on overall survival of three to four cycles of a cisplatin-based chemotherapy (CT) after complete surgical resection in patients with stages I–III NSCLC [3]. Thoracic radiotherapy may be given according to the preregistration policy of each centre. There were 932 patients allocated to CT and 935 patients in the control arm. After a median follow-up of 56 months, there was a significant difference in overall survival between the two arms (HR = 0.86 [0.76–0.98], $P < 0.03$). Disease-free survival was also significantly different (HR = 0.83 [0.74–0.94], $P < 0.003$). The effect was no longer significant at 90 months (HR = 0.91 [0.81–1.02], $P = 0.10$) owing to a higher rate of non-cancer-related deaths in the chemotherapy arm. ERCC1 was evaluated by immunohistochemistry in 761 tumour specimens of patients in the IALT-Bio programme [4]. ERCC1 expression was positive in 44% and negative in 56%. A benefit of cisplatin-based adjuvant chemotherapy was associated with the negative expression of ERCC1 (test for interaction, $P = 0.009$).

In the post-operative subgroup of the Big Lung Trial, no benefit from adjuvant chemotherapy was observed among 381 patients, but the population was heterogeneous, in particular concerning the quality of the resection and the compliance with chemotherapy [5].

A Japanese randomised study compared adjuvant tegafur-uracil (UFT) for two years with no treatment in patients with completely resected stage I NSCLC [6]. Among 979 eligible patients, there was a significant advantage in favour of UFT ($P = 0.036$), but the benefit was restricted to the 27% of patients with T2N0 NSCLC. At the 2004 ASCO meeting, the Japanese adjuvant UFT meta-analysis confirmed a significant advantage of the drug compared with controls in 2003 patients ($P < 0.001$).

The NCI-Canada conducted a phase III trial (JBR 10) comparing surgery alone with surgery followed by adjuvant chemotherapy with cisplatin and vinorelbine in 459 eligible patients with stage Ib and II resected NSCLC [7]. They showed a 15% benefit at five years ($P = 0.012$). The benefit was restricted to stage II patients.

In the ANITA 1 trial, which also concerned patients with completely resected NSCLC, chemotherapy consisted of four cycles of cisplatin-vinorelbine [8]. A total of 831 patients were included. Again, there was a survival advantage for adjuvant chemotherapy (HR: 0.80 [0.66–0.96], $P = 0.017$).

The LACE meta-analysis reported at ASCO 2006 included a total of 4584 patients accrued in the five recent cisplatin-based adjuvant trials [9]. It confirmed the benefit of adjuvant chemotherapy with a 5.3% improvement in survival at five years ($P = 0.0043$). Disease-free survival was also improved (5.2% at five years, $P < 0.0001$). There was a negative effect of adjuvant chemotherapy for stage Ia. The risk reduction was 8% for stage Ib, 17% for stages II and III. The effect of chemotherapy did not vary according to age, gender, PS, type of surgery and histology. When the drug combined with cisplatin was analysed, the risk reduction was 20% for vinorelbine, 7% for other bitherapies and 2% for tritherapies [10].

Finally, the meta-analysis based on individual data was updated in 2007 with a total of over 10,000 patients [11]. It confirmed the significant effect of postoperative chemotherapy, with or without postoperative radiotherapy, with an overall benefit of 4% at five years.

In conclusion, recent randomised studies of adjuvant chemotherapy for NSCLC suggest a 4–5% improvement in survival at five years except for stage Ia patients. The combination of vinorelbine in combination with cisplatin looks superior to older combinations. Tailored chemotherapy is still under evaluation at the moment.

Conflict of interest statement

The author has no conflict of interest to report.

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