Adjuvant Treatment for Resectable Non-small Cell Lung Cancer (NSCLC)

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Despite optimal surgical management, 5-year survival rate of resected NSCLC ranges between 73% for pathological stage Ia and 25% for pathological stage IIIa.
In the early 90's, the Medical Research Council and Institut Gustave-Roussy performed a large overview on the role of chemotherapy in NSCLC using updated individual data. 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). 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 platin-based regimens.

A North American Intergroup Trial (**Int 0115**) demonstrated that a combination of 4 cycles of chemotherapy (etoposide-cisplatin) plus concomitant thoracic radiotherapy was not superior to radiotherapy alone given at the same dose in 463 patients with resected stage II and IIIA NSCLC. Additionally, there was no impact of the p53 and k-ras modifications on the outcome of patients.

In the **ALPI** trial, patients with resected stage I-IIIa NSCLC were randomly allocated to receive either 3 courses of MVP (Mitomycin 8 mg/m2 day 1; Vindesine 3mg/m2 day 1 and 8; Cisplatin 100 mg/m2 day 1 every 3 weeks for 3 cycles) or no adjuvant treatment after complete resection. Overall 1209 patients were enrolled into the study, 606 in the chemotherapy arm and 603 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 1088 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 even if the difference was borderline significant for stage II disease.

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 (CT) 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. There were 932 pts allocated to CT and 67% received at least 300 mg/m² of cisplatin. The drug combined with cisplatin was etoposide (56%), vinorelbine (27%), vinblastine (11%) and vindesine (6%). There were 935 pts in the control arm. After a median follow-up of 56 months, 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 (HR=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 (HR=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. Nevertheless, the effect was no longer significant at 90 months (HR=0.91 [0.81 to 1.02], p=0.10 due to a higher rate of non-cancer related deaths in the chemotherapy arm. ERCC1 was immunohistochemically evaluated in 761 tumor specimens of patients in the **IALT-Bio** program. ERCC1 expression was positive in 44% and negative in 56%. A benefit from 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 not heterogeneous in particular concerning the quality of the resection, and the compliance to chemotherapy was poor.

A Japanese randomized study compared adjuvant **UFT** for 2 years to no treatment in patients with completely resected stage I NSCLC. Among 979 eligible patients, there was a significant advantage in favor 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 to control in 2003 patients (p<0.001).

The NCI-Canada conducted a phase III trial (**JBR 10**) comparing surgery alone to surgery followed by adjuvant chemotherapy with cisplatin and vinorelbine in 459 eligible patients with stage Ib and II resected NSCLC. They showed a 15% benefit at 5 years (p=0.012). The benefit was restricted to stage II patients.

The CALGB also conducted a randomized trial in 344 patients with stage Ib NSCLC (**CALGB 9633**). The initial benefit at 4 years reported with adjuvant Paclitaxel-Carboplatin compared to no adjuvant treatment was not confirmed with a longer follow-up and the benefit is only 3% at 5 years (p=0.10).

In the **ANITA 1** 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/m² weekly compared to a control

arm. A total of 831 patients were included from October 1994 to December 2000. There were 35% stage I, 30% stage II and 35% stage III. Again, there was a survival advantage for adjuvant chemotherapy. Survival rates were 68%, 51%and 45% at 2, 5 and 7 years in the chemotherapy arm vs 63%, 43% and 37% respectively. RR was 0.80 [0.66-0.96] with a p value of 0.017.

The **LACE meta-analysis** reported at ASCO 2006 included a total of 4584 patients accrued in the 5 recent cisplatin-based adjuvant trials. It confirmed the benefit of adjuvant chemotherapy with a 5.3% improvement of survival at 5 years (p=0.0043). Disease-free survival was also improved (5.2% at 5 years, p<0.0001).

Looking at the pathological stage, 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 analyzed, the risk reduction was 20% for Vinorelbine, 7% for other biotherapies and 2% for tritherapies.

In the 1888 patients who received the combination of vinorelbine and cisplatin, the 5-year absolute benefit was 9% and the hazard ratio was 0.95 (0.76-1.20) for stage I vs 0.68 (0.56-0.83) and 0.62 (0.50-0.76) for stage II and III respectively. Finally, the **Individual-data-based meta-analysis** was updated in2007 with a total of over 10,000 patients. It confirmed the significant effect of postoperative chemotherapy, with or without postoperative radiotherapy, with an overall benefit of 4% at 5 years.

In conclusion, the results of the recently reported large randomized studies of adjuvant chemotherapy suggest a 4 to 5% improvement of survival at 5 years. The LACE pooled analysis of the new generation of trials and, more recently, the update of the MRC-IGR meta-anlysis confirmed the role of adjuvant chemotherapy in resected NSCLC except for stage Ia patients. The combination of vinorelbine in combination with cisplatin looks superior to older combinations. The results of the IALT-Bio program suggest to evaluate the expression of ERCC1 in order to determine which patients are more likely to benefit from chemotherapy. If these results are confirmed, we will enter the era of tailored therapy for resected NSCLC.

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