# Adjuvant chemotherapy of non-small-cell lung cancer

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## 1. Introduction

Adjuvant use of chemotherapy has established efficacy in several solid human tumours – breast, colon and lung cancers being among the most frequent. The role of adjuvant treatment – either locoregionally or systemically after local treatment, allowing a complete resection of the primary tumour and locoregional lymph nodes – is to improve cure rates. The goal of adjuvant chemotherapy is to eradicate micrometastases that may already be established but are undetectable as well as to destroy possible circulating tumour cells. The benefit, however, is hypothetical, and patients are generally selected on the basis of the pTNM staging obtained at surgery. One has to keep in mind that most of the patients who will be disease-free at 5 years have already been cured by surgery. The benefit of adjuvant chemotherapy is always limited in terms of magnitude to low percentages, and the risk/benefit ratio for a given patient is low. In addition, adjuvant chemotherapy has its own toxicity that may be acute but also long-lasting even after termination. Taking these considerations into account, the use of chemotherapy and the choice of cytotoxic agents should be based on properly conducted clinical trials, with a well-defined population and a follow-up long enough to assure a real benefit with time. Data from efficacy in metastatic settings should not simply be applied to adjuvant use without results of randomised trials in this situation and a proven level of evidence. Tumour cell biology shows that a given tumour evolves with time, and that metastatic disease is quite a different disease from the adjuvant setting.

The purpose of this Educational Lecture is:

- To review the data on adjuvant chemotherapy for NSCLC.
- To analyse how the concept has evolved with time.
- To present the results of meta-analysis.
- To provide an update on the most recent trials.
- To examine the impact on special populations.
- To look at possible prognostic/predictive biomarkers.
- To provide recommendations for routine practice.

## 2. The first signal of a possible effect of adjuvant chemotherapy in resected NSCLC

During the last 4 decades of the 20th century, numerous trials of various sample sizes and chemotherapy combinations have been performed in various settings worldwide. Despite an effort to accrue about 10,000 patients in 50 clinical trials, none of them individually has been convincing enough to establish adjuvant chemotherapy as a standard of care. In 1995, the Non-Small Cell Lung Cancer Collaborative Group under the joint auspices of the Medical Research Council (MRC) in the United Kingdom, Institut Gustave Roussy in France and Istituto Mario Negri in Italy published a meta-analysis looking at the impact of adjuvant chemotherapy in resected non-small-cell lung cancer (NSCLC) [1]. They reviewed updated data on individual patients from randomised trials performed between 1965 and 1991. All types of treatment were analysed, including adjuvant chemotherapy, radiation therapy and advanced disease. Among these trials, 14 – including a total of 4357 patients – were performed in the postoperative setting and compared surgery to surgery + chemotherapy. The drugs used were heterogeneous, as were the doses, and overall no benefit on overall survival was shown. The analysis was refined on the basis of the heterogeneity between categories of regimen used, and that was statistically significant. Therefore, chemotherapy regimens were grouped into three categories: (1) long-term alkylating agents, (2) other drugs, and (3) cisplatin-based. No heterogeneity was found within each category, and a separate meta-analysis was performed for each of the three groups. The hazard ratios (HRs) of death showed differences among the groups, already suggesting that the choice of chemotherapy was important: (1) long-term alkylating agents: HR 1.15 (1.04–2.20), *P* 0.005; (2) other drugs: HR 0.89 (0.72–1.11) *P* 0.30; and (3) cisplatin-based: HR 0.87 (0.74–1.02) *P* 0.08.

These initial results showed a highly significant detrimental effect of long-term alkylating agents, with a 15% increase in the risk of death from alkylating agents. On the contrary, in the cisplatin-containing regimen group, the benefit, although

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not significant, showed a 13% reduction in the risk of death, translating into an improved 5% survival at 5 years; however, this survival benefit was not significant, and in practice cisplatin-based adjuvant chemotherapy is not a standard of care for resected NSCLC at this time.

Based on the results of the meta-analysis, further randomised trials were performed taking advantage of the "signal" seen earlier with cisplatin-based chemotherapy.

## 3. Evolution of the concept of adjuvant chemotherapy for resected NSCLC

After the initial meta-analysis of adjuvant chemotherapy in resected NSCLC by the Non-Small Cell Lung Cancer Collaborative Group, additional randomised trials were performed and meta-analysed by Hotta and other Japanese investigators [2]. This second meta-analysis included 11 trials with a total of 5716 patients, performed in Japan but also in the rest of the world. Among these randomised trials six had UFT, an oral fluoropyrimidine widely used in Japan, either as a single agent or in combination with cisplatin. The remaining five were more in agreement with what is used in the western world, including etoposide, mitomycin C, vindesine, vinorelbine or vinblastine in combination with cisplatin. Sample sizes were sometime small, trials having 100 patients or fewer. Most of these trials individually showed no significant benefit on the 5-year survival rate, but overall the meta-analysis obtained an HR of 0.87 at a significant *P* value of 0.001. When only the cisplatin-containing regimens were considered, the HR was 0.89 with a *P* value of 0.012. In Japanese patients treated in UFT single-agent trials, the risk of death was reduced by 20% (HR 0.799, *P* value 0.015).

Additional trials based on platinum-containing regimens have also been performed in the western world and will be summarised individually below.

### 3.1. *IALT*

The International Adjuvant Lung Cancer Trial (IALT) Collaborative Group [3,4] conducted a pragmatic randomised trial, started in 1995, evaluating the impact of a cisplatin-based chemotherapy in resected NSCLC (stages I–III according to the 1986 AJCC classification). The experimental arm offered three or four cycles of various cisplatin-containing regimens to be compared by observation. Companion drugs associated with cisplatin included one of four drugs (vindesine, vinblastine, vinorelbine or etoposide), the dose of cisplatin was left to the discretion of each centre (ranging from 80 to 120 mg/m$^2$), as was the number of cycles (three or four) or the use of adjuvant radiotherapy. A total of 14 regimens were therefore possible. The trial was planned for 3300 patients, but it discontinued early with 1867 patients because of low accrual due to the emergence and recent results of neoadjuvant chemotherapy. The most frequent chemotherapy regimens used (in 76% of patients) were cisplatin–etoposide and cisplatin–vinorelbine. Additional radiation was delivered in 20–25% of patients. The patient population included 36% stage I (10% IA), 24% stage II and 40% stage III. At the date of publication [3], after a median follow-up of 56 months, a significant overall survival benefit was seen with a 14% reduction in the risk of death and a *P* value of 0.03, translating into a 4.1% survival benefit at 5 years. No subgroup analysis was reported, but G. Strauss [4] in a separate paper concluded that only stage III patients were benefiting from adjuvant chemotherapy.

The results of IALT were later updated in 2010 [5]. The initial benefit seen with a median follow-up of 56 months was not confirmed when more events were observed after a median of 7.5 years of follow-up. The HR for overall survival moved up from 0.86 to 0.91, with a no-longer-significant *P* value of 0.10. The analysis of the cause of death showed a slight increase in non-cancer-related death in the chemotherapy arm, possibly reflecting long-term adverse effects of adjuvant chemotherapy (HR 1.36, *P* value 0.06), the incidence of local recurrences or distant metastases remaining lower in the adjuvant chemotherapy population. This emphasises the need for a sufficiently long follow-up for adjuvant trials.

### 3.2. *Big Lung Trial*

The Big Lung Trial [5,6] was a pragmatic, UK-based trial to evaluate the impact of cisplatin-containing chemotherapy in NSCLC in all settings: early, locally advanced and metastatic.

In the adjuvant situation, cisplatin could be combined with several drugs, including mitomycin–ifosfamide (MIC), mitomycin–vinblastine (MVP), vindesine (CV) or vinorelbine (NP). The trial started in 1995 and stopped in 2001. It accrued in the surgical setting only 381 patients out of 1394 planned. It is therefore difficult to draw conclusions from such a small sample size. With a median follow-up of 35 months the HR of 1.02 (*P* value 0.90) showed no benefit at all.

### 3.3. *ALPI*

The Adjuvant Lung Project Italy (ALPI) [6] along with the European Organisation for Research and Treatment of Cancer (EORTC) performed an adjuvant chemotherapy trial in resected stages I, II and III (UICC/AJCC 1986) NSCLC. Surgery followed by adjuvant chemotherapy with mitomycin, vindesine and cisplatin (MVP) was compared with surgery alone. Three cycles of chemotherapy were planned after randomisation. The study accrued 1209 patients between January 1994 and January 1999. After a median follow-up of 65 months, the overall survival HR was 0.96 ($P = 0.589$), showing no benefit from adjuvant chemotherapy. This negative trial had several weaknesses: 108 patients from a single centre were excluded from the analysis, only 69% of randomised patients received the three planned cycles of chemotherapy and half of them required dose reduction. The toxicity of MVP was prohibitive with an excess of toxic death during the first year. However, even though the study was negative, the 3.4% overall survival benefit at 5 years was not that different from that of the IALT (4.1%).

### 3.4. *CALGB 9633*

In the United States, CALGB 9633 [7,8] evaluated the use of three or four cycles of paclitaxel–carboplatin in the adjuvant setting for resected stage IB only (T2N0 TNM 6 classification). This study planned to accrue 500 patients starting in Septem-

ber 1995, but stopped at 344 in November 2003. Results were presented first at ASCO 2004 [7] with 34 months of follow-up, and full mature data were published in 2008 [8] with a median follow-up of 74 months. At the initial ASCO 2004 presentation, the outcome was in favour of adjuvant paclitaxel–carboplatin, with an overall survival HR of 0.62 ($P = 0.028$) and a 4-year survival rate of 71% versus 59% in the control arm. This was the first study to demonstrate a benefit in early stage IB. However, the updated publication with a much longer follow-up did not confirm the initial, preliminary results. With time and more events, the overall survival HR went up to 0.83 ($P = 0.12$), a 2% improvement on the 5 year-survival rate. Similarly, as seen in the IALT discussed above, in CALGB 9633 the benefit of adjuvant faded with time and emphasised the need for prolonged follow-up to establish the proof of benefit in adjuvant setting.

Interestingly enough, a subgroup exploratory analysis was performed in CALGB 9633 according to tumour size $\geqslant$ or <4 cm [8]. In the updated analysis with a 74 month follow-up the overall survival in stage IB was not improved in the intent-to-treat population, but an overall survival benefit was seen for patients with a tumour $\geqslant$4 cm with an HR of death = 0.69 and a $P$ value = 0.043, a median overall survival of 99 months compared with 77 months in the surgery only arm. On disease-free survival the magnitude of the benefit was similar for tumours $\geqslant$4 cm. These data support the adjuvant use of paclitaxel–carboplatin in patients with resected stage pIB $\geqslant$4 cm NSCLC.

### 3.5. *NCIC JBR 10*

From July 1994 to April 2001, the National Cancer Institute of the Canada Clinical Trials Group (NCIC-CTG) [9,10] accrued 482 NSCLC patients in the JBR-10 phase III randomised trial of adjuvant cisplatin–vinorelbine versus surgery alone for R0 resected stages pIB (45%) and pII (except T3N0, TNM 6 classification). Patients were randomised to receive four cycles of cisplatin–vinorelbine over 16 weeks in the chemotherapy arm versus observation in the control arm. The results were published after median follow-up of 5.1 years [9] and updated after 9.3 years.

Overall survival was improved after 5 years of follow-up with an HR of death of 0.69, $P = 0.009$, reflecting a 15% benefit at 5 years (69 versus 54%) and medians of 94 versus 73 months. Similarly, disease-free survival was extended in the chemotherapy group (HR 0.60, $P < 0.001$). The updated survival data after 9.3 years showed that the benefit was preserved with time with an HR of death = 0.78 ($P = 0.04$) [10]. Subgroup analysis according to stage IB versus II did not show a statistically significant benefit in stage IB. The benefit was restricted to stage II (HR 0.59, $P = 0.004$). In the updated analysis with 9.3 years of follow-up, similar findings were reported. Based on the tumour size effect reported in CALGB 9633, this parameter was examined in JBR-10 with a cut-off value of 4 cm in stage IB. Similarly, in JBR-10 a difference was noted, with a potential detrimental effect of adjuvant cisplatin–vinorelbine in stage IB <4 cm (HR 1.73, $P = 0.56$) and a potential benefit in tumours $\geqslant$4 cm (HR 0.66, $P = 0.133$).

In an attempt to find a predictive biomarker of efficacy, the RAS mutational status (including H, N and KRAS) was evaluated in 451/482 patients. Ras mutational status was not associated with a differential effect of chemotherapy.

Chemotherapy compliance in JBR-10 showed that 45% of patients randomised to cisplatin–vinorelbine received the planned four cycles, 55% three cycles and 64% two cycles. The median number of delivered cycles was three. The most frequent adverse event was neutropenia. Dose of vinorelbine was reduced from 30 to 25 mg/m$^2$ weekly after 18 patients were treated initially.

The JBR-10 trial established the benefit of adjuvant cisplatin–vinorelbine (the first third-generation drug combined with cisplatin) in stage II R0 resected NSCLC, and possibly in stage IB $\geqslant$4 cm.

### 3.6. *ANITA 1*

ANITA (Adjuvant Navelbine International Trialists Association) [11] is an international randomised phase III trial evaluating on overall survival the benefit of 4 cycles of cisplatin–vinorelbine in R0 resected p stages IB (T2N0), II and IIIA NSCLC (TNM 6). From December 1994 to December 2000, a total of 840 patients were accrued, with 407 randomised to chemotherapy. The use of adjuvant radiation therapy – after surgery in the control arm or after chemotherapy in the experimental arm – was allowed, neither randomised nor mandatory but left to the decision of the investigators.

With a median follow-up of 70 months, the primary overall survival end-point was met on the intent-to-treat population (HR of death 0.79, $P = 0.013$), a benefit of 8.6% at 5 years confirmed at 7 years. Relapse-free survival was also significantly improved (HR of relapse 0.76, $P = 0.002$). No difference was seen with the surgery alone arm in stage IB (62% versus 64% survival at 5 years). The benefit was actually restricted to stages II and IIIA. In stage II, the 5-year survival rates were 52% versus 39% in the chemotherapy arm versus control arm respectively (HR of death 0.71), in stage IIIA 42% versus 26% (HR of death 0.69). These results do not allow a definitive conclusion, however, since the test of interaction was not significant and no $P$ values were calculated. The impact of the N stage was reported independently of T stage: for pN0 patients median overall survival was 99.6 versus 95.5 months in the control arm and chemotherapy arm respectively. In patients with pN1 disease, median overall survivals were respectively 31.2 versus 65.7 months in favour of adjuvant chemotherapy and 20 versus 32.6 months in patients with pN2 stages. No conclusion can be reached from adjuvant radiation since its use was not randomised, but it showed a potential detrimental effect in pN1 disease after adjuvant chemotherapy and a benefit in pN2 disease [12]. This will have to be confirmed in a clinical trial, presently ongoing, and will be discussed elsewhere.

Chemotherapy compliance, similar to the results of JBR10, showed that 73% of patients received two cycles, 61% three cycles and 50% the planned four cycles, with a relative dose intensity of 59% for vinorelbine and 89% for cisplatin, reflecting the toxicity of the regimen with 85% grade 3–4 neutropenia and 9% febrile neutropenia.

The ANITA trial established the value of adjuvant cisplatin–vinorelbine (the first third-generation drug combined with cisplatin) in stage II and IIIA R0 resected NSCLC.

Within the LACE, a subgroup analysis was performed on patients who received the vinorelbine–cisplatin chemotherapy in the adjuvant setting from JBR 10, ANITA, IALT and BLT, for a total of 1888 patients [13]. Overall, the survival benefit was 8.9% at 5 years (HR of death 0.80, $P < 0.001$). Stage was a significant predictor of efficacy on 5-year survival: 14.7% in stage III, 11.6% in stage II and only 1.8% in stage I. These results were significantly superior to other cisplatin-based combination chemotherapy regimens used in the LACE meta-analysis ($P = 0.04$).

## 4. The impact of adjuvant chemotherapy on special populations

### 4.1. *Adjuvant chemotherapy in elderly patients*

The use of adjuvant chemotherapy may be an issue in clinical practice since the life expectancy is increasing and medical progress allows resection in the elderly population, including for NSCLC.

The JBR.10 investigators have reported the results of their trial on elderly patients, with a cut-off age set at ⩾65 years, and compared with patients <65 years old [14]. The two groups differed significantly in terms of histology (more adenocarcinoma in the younger group) and performance status (more PS = 0 in the younger group). The benefit of adjuvant cisplatin–vinorelbine on overall survival, reported for the overall population, was also seen in the elderly, ⩾65 years old (HR of death 0.61, $P = 0.04$). Elderly patients significantly received fewer doses of cisplatin and vinorelbine, and the dose intensity was significantly reduced as well. No differences in toxicity were observed. According to this analysis, adjuvant cisplatin–vinorelbine seems feasible in patients ⩾65 years old.

Addressing the same question of the effect of age on cisplatin-based adjuvant chemotherapy, the LACE group compared the overall survival of three groups according to age (<65, 65–69, >70 years old) [15]. The HRs of death were 0.86 for <65-year-olds, 1.01 for the mid category (65–69 years old), and 0.90 in the oldest patients (>70). The test for trend was not significant and the LACE concluded that "chemotherapy should not be withheld from the elderly purely on the basis of age". Similar to JBR.10, lower doses of cisplatin and fewer cycles were delivered in the elderly. No differences in toxicity were observed.

Based on these two reports, adjuvant cisplatin-based chemotherapy seems feasible in elderly patients and provides a survival benefit with acceptable tolerance.

Age is not the only parameter to consider in practice, however, and patients from clinical trials with strict inclusion criteria are not always reflecting the general practice population. Decisions should also take into account performance status, comorbidities, compliance issues and patient willingness.

### 4.2. *Japanese population*

In Japan, as opposed to the Western world or other Asian countries, fluoropyrimidines are widely used to treat NSCLC. UFT, an oral fluoropyrimidine – either as a single agent or in combination with cisplatin – has been evaluated in randomised clinical trials for the adjuvant treatment of resected NSCLC versus surgery alone. Those trials have been meta-analysed. In the meta-analysis by Hamada et al. [16], individual patient data were collected. Among nine trials, six compared surgery versus surgery + UFT; two had a third arm with cisplatin-containing chemotherapy, but the patients for the third arm were not meta-analysed. Most of the patients presented with adenocarcinoma and early stage I disease. They were treated for a period of 1–2 years with oral UFT. In this selected population of 2003 patients, the use of UFT postoperatively showed a significant benefit at 5 and 7 years compared with surgery alone (respectively +4.3% and +7%) with an HR of death of 0.74 ($P = 0.001$).

Another Japanese meta-analysis – based on published data of adjuvant trials performed worldwide since 1995 – included 11 trials among which six were UFT-based [2]. A separate analysis of the UFT-containing regimen was provided. Most of the trials were not statistically significant due to small sample sizes. The use of UFT as a single agent on 1751 patients showed a significant benefit with an HR of death of 0.799 ($P = 0.015$). In the UFT-containing regimen trials the use of UFT was prolonged to 1 or 2 years.

The benefit of UFT in adjuvant chemotherapy is so far limited to Japanese patients since the drug is not used for this indication outside Japan.

## 5. Predictive biomarkers of chemotherapy efficacy in the adjuvant setting

The benefit of adjuvant chemotherapy in NSCLC is still recent. Very few trials have looked at predictive biomarkers that would allow better patient selection. The available data are from retrospective studies with the limitations associated with such an approach.

### 5.1. *ERCC 1*

In 2006, the IALT group reported that the level of expression of ERCC 1 (excision repair cross-complementation group 1) by immunohistochemistry was both predictive for the efficacy of cisplatin-based chemotherapy on survival and prognostic [17]. In a subsequent study from the LACE biology, looking at the four protein isoforms of ERCC 1 in the entire population of the LACE group, with additional antibodies mapping ERCC 1, the predictive effect of ERCC 1 was not validated [18]. Based on these results, ERCC 1 cannot be recommended at the present time to select patients for adjuvant cisplatin-containing chemotherapy.

### 5.2. *KRAS*

In the JBR10 trial [10], KRAS mutational status was assessed for its potential value as a predictive factor of resistance to chemotherapy. No differential benefit on overall survival was noticed between KRAS wild-type and mutant patients. However, a trend towards a benefit was observed for disease-specific survival (DSS) with adjuvant cisplatin–vinorelbine in the KRAS wild-type patients (HR of DSS 0.72, $P = 0.06$), with no benefit in mutant patients.

The LACE Bio group retrospectively analysed 1543 patients for their KRAS mutational status on codons 12, 13 and 14 [19]. Overall, KRAS has no prognostic value according to the survival in the surgery-alone arm. There was also no significant difference in overall survival according to the KRAS mutational status between the control arm and the adjuvant chemotherapy arm. Looking more specifically at the mutation type, there is much variability in the effect of adjuvant chemotherapy among the patients harbouring a codon 12 mutation, none of them being significant due to the size of the samples. The codon 13 mutation was associated with a detrimental effect of adjuvant chemotherapy (HR of death 5.78, $P = 0.002$), but this information would require validation from a larger sample.

At the present time, KRAS should not be used for the decision for adjuvant chemotherapy in NSCLC.

### 5.3. *Other biomarkers*

The LACE Bio group has undertaken an extensive analysis of biomarkers that could potentially act as predictive factors of adjuvant chemotherapy efficacy. In addition to ERCC 1 and KRAS that have been already reported, this search includes beta-tubuline, mucine, P53, P27, P16, cyclin E, Bax, EGFR mutation as well as histology and lymphocytic infiltration.

Another approach undertaken by several groups is to look for a gene signature that would be associated with improved survival and efficacy of chemotherapy. Several sets of genes have been identified in retrospective studies, but none so far has implications in clinical practice.

At the present time, no predictive biomarker has been identified which could be used in clinical practice. Much hope, however, is placed on such tools to better define selected patients who would benefit from adjuvant chemotherapy.

## 6. Conclusion

As in other human solid tumours, adjuvant chemotherapy for resected NSCLC is now part of the standard of care.

It should be offered at all ages in fit patients resected with stage II and III disease. Stage IB might be discussed, mainly with tumours of >4 cm in diameter.

Adjuvant chemotherapy in Western countries should be cisplatin based. Among the companion drugs to be combined with cisplatin, vinorelbine is the only third-generation drug that has been evaluated and that has demonstrated durable long-term efficacy. All the other drugs tested – including etoposide, vindesine, vinblastine and paclitaxel (combined with carboplatin) – have finally failed to demonstrate a definitive efficacy. The other third-generation drugs docetaxel, gemcitabine and pemetrexed have never been evaluated in proper randomised trials with overall survival as the primary endpoint. Therefore, the only combination to be used in an adjuvant setting for resected NSCLC, on evidence-based medicine, is vinorelbine–cisplatin. Other compounds – including targeted agents – with proven efficacy in metastatic settings have not been evaluated in the adjuvant setting. Anti-EGFR tyrosine kinase inhibitors have failed to demonstrate a benefit in the adjuvant setting of EGFR-mutated NSCLC in the JBR 19 randomised trial. They cannot be recommended for such use.

Metastatic stages and early or locally advanced diseases have different behaviours. It is known that in other tumour types, such as colon cancer, regimens with similar efficacy in stage IV do not translate into similar benefit in earlier stages. Considering the possibility of cure in the majority of patients with surgery alone, and the limited benefit of adjuvant chemotherapy in terms of improved 5-year survival, no added risk should be taken for the patients in a situation where the risk/benefit ratio is rather small.

## Conflict of interest statement

The author has no conflicts of interest relating to this article.

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