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Current Perspective

Adjuvant chemotherapy for non-small cell lung cancer: Ready for clinical practice?

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ABSTRACT

Radical surgery remains the only treatment with curative potential for patients with operable non-small cell lung cancer (NSCLC). However, despite complete surgical resection, long-term survival is still disappointing with an average 5-year survival rate lower than 60%. Thoracic post-operative radiotherapy trials demonstrated a possible impact in reducing loco-regional recurrence but not overall survival. Moreover, the majority of post-surgical failures are represented by distant metastases, indicating a possible role for adjuvant systemic therapies. The role of adjuvant chemotherapy has now been clearly established in many solid tumors and the role of last generation platinum-based chemotherapy has now being considered as standard of care in advanced NSCLC. However, the role of adjuvant chemotherapy for completely resected NSCLC remains highly controversial. After the meta-analysis published in 1995, which showed a non-statistically significant 5% improvement in 5-year survival with second generation platinum-based adjuvant chemotherapy, several randomized clinical trials addressing the role of last generation adjuvant chemotherapy in patients with completely resected stage I, II and IIIA NSCLC have been completed with conflicting results. The available scientific evidence is reviewed and strengths/weaknesses of each trial are discussed in this article. Although most of the available evidence points to a possible survival benefit in long-term survival improvement ranging from 4% to 15%, the introduction of adjuvant chemotherapy as standard of care in the treatment of resected NSCLC is still a matter of debate. Practical issues and clinical aspects which may help clinicians in the decision making process about prescription of adjuvant treatment are also discussed.

1. Introduction

1.1. Background and rational

Lung cancer is the leading cause of cancer death throughout the world. Non-small cell lung cancer (NSCLC) constitutes 75–80% of lung cancer cases and accounts for approximately 1.2 million new cases worldwide each year [1,2]. Surgery remains the only treatment with curative potential but, unfortunately, only less than one third of all NSCLC patients are suitable for radical surgery at the time of diagnosis. Hence, the long-term survival rate even after complete resection is

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rather disappointing, with a 5-year survival rate for stage IB–IIIA below 60%, since a considerable proportion of patients will eventually develop either local or distant disease recurrence [3].

1.2. *Natural history*

In radically resected NSCLC recurrences occur in more than 80% of cases within 2 years from the time of surgery and are more frequent in distant sites (7–17%, 23–30%, 22–39% and 52–61% in stage IA, IB, II and IIIA, respectively) than loco-regional (5–9%, 6–11%, 9–28% and 13–17% in stage IA, IB, II and IIIA, respectively) with great differences between squamous and non-squamous histologies. Adenocarcinoma, nowadays the predominant histological subtype, has a higher propensity for distant spread. The most common site of metastatic relapse is the brain, followed by bone, lung, liver and adrenals [4–7].

1.3. *Role of adjuvant thoracic irradiation*

For a long period of time, post-operative thoracic radiotherapy has been the preferred adjuvant treatment. Results regarding its potential role have been reported from a number of studies and from PORT (Post-Operative RadioTherapy) meta-analysis [8]. This meta-analysis showed that post-operative chest radiotherapy has, overall, a detrimental effect on survival with a 21% relative increase in the risk of death [hazard ratio (HR) 1.21 (95% CI 1.08–1.34)], equivalent to an absolute detriment of 7% at 2 years, reducing overall survival rate from 55% to 48%. Subgroups analyses suggest that this adverse effect is greatest in patients with stage I and II whereas, for those with stage III (N2), there is no clear evidence of either a positive or a negative effect. Some data, nevertheless, suggest that thoracic irradiation may improve local control in patients with resected N2 disease, especially in the case of squamous-cell histology [9]. This observation reinforces the concept that controlling systemic disease is essential for aiming at an improved survival outcome in completely resected NSCLC.

1.4. *Role of adjuvant chemotherapy in solid tumors*

After complete resection there are, in theory, several circumstances favouring the cytotoxic effect of chemotherapeutic agents. The tumour load is minimal, micrometastatic disease foci should contain few chemotherapy-resistant clones and their growth fraction and the relative chemotherapy fractional cell kill should be the highest [10]. This theory has now been proven as true for most solid tumours including some that are known to be relatively chemoresistant such as colorectal, pancreatic and gastric cancers [11].

1.5. *Role of chemotherapy in advanced non-small cell lung cancer*

The role of platinum-based chemotherapy has now been clearly established in advanced stage NSCLC. In fact, the available scientific evidence indicates that chemotherapy is able to improve survival in patients with stage IV disease, as compared to BSC (Best Supportive Care), in patients with inoperable stage III when combined with thoracic radiation compared to radiation alone and, finally, in patients with stage IIIA (N2) when given before radical surgery as compared to surgery alone [12,13].

With this background, a possible role of chemotherapy in prolonging survival of completely resected NSCLC patients, when used as adjuvant treatment, would seem highly plausible.

2. Study results

2.1. *From first trials to the 1995 meta-analysis*

The study of adjuvant chemotherapy in resected NSCLC started in the early 1960s with earlier trials testing alkylating and immunotherapic agents which failed to demonstrate any survival benefit and, occasionally, produced even a detrimental effect [14]. Subsequently, the role of cisplatin-based combinations was extensively tested in several trials [15]. The great majority of these studies failed to show any improvement in median and long-term survival of adjuvant treatment respect to surgery alone. Common drawbacks in these studies were the overestimation of the potential benefit of adjuvant chemotherapy in the calculation of the sample size, the imbalance in patient and treatment characteristics, the impossibility of reaching the planned accrual and, finally, the low compliance with most chemotherapy regimens used. In 1995, a meta-analysis of adjuvant chemotherapy trials performed between 1965 and 1991 was published. In this meta-analysis, cisplatin-based chemotherapy (8 trials in 1394 patients) revealed a 13% reduction of the risk of death [hazard ratio (HR) 0.87 (95% CI 0.74–1.02)], corresponding to an overall 5% improvement in the 5-year survival rate, which was close to statistical significance ($P = 0.08$) [16].

2.2. *Trials after the 1995 meta-analysis*

The small non-statistically significant benefit in 5-year survival reported in the meta-analysis generated enough enthusiasm to prompt the set up of several other randomized clinical trials addressing the role of second and third generation chemotherapy in patients with completely resected stage I, II and IIIA NSCLC (Tables 1 and 2).

2.3. *US Intergroup trial*

In 2000 Keller and colleagues [17] published the results of INT 0115 study, a randomized trial where 488 completed resected stage II–IIIA patients were randomized to receive radiotherapy alone (50.4 Gy) or radiotherapy plus concurrent chemotherapy (4 cycles of cisplatin 60 mg/m^2 on day 1 and etoposide 120 mg/m^2 on days 1–3 every 4 weeks). After 44 months of median follow-up, the median survival was 39 months in the group given radiotherapy alone and 38 months in chemo-radiotherapy group ($P = 0.56$). Although the results of this trial appear to support the conclusion that concurrent chemo-radiation is not superior to radiation alone as adjuvant treatment of NSCLC, the strength of this conclusion is mitigated by some methodological flaws. First, this study was underpowered to detect any plausible

Table 1 – Meta-analysis and clinical trials of adjuvant chemotherapy (CT) in radically resected patients with NSCLC

Trial	Patients enrolled/ planned accrual (*n*)	Stage	CT regimen/ control arm	Compliance to CT (%)	Hazard ratio (HR) of death	Absolute survival benefit at 5 years (%)	*p*	Strengths	Weaknesses
1995 Meta-analysis[16]	1394	I–III	CDDP-based/ observation	–	0.87	5	0.08	• Individual patient data meta-analysis	• Limited sample size • Old CT regimen
INT 0115[17]	488/–	II–IIIA	CDDP+VP16/TRT	69	0.93	–6[b]	0.56	• Long survival • Accurate staging	• Limited sample size • Size short follow-up • No surgery-alone arm
ALPI[18]	1209/1300	I–IIIA	MVP/observation	69	0.96	1	0.589	• Sample size • Long follow-up	• Old CT regimen • Poor treatment compliance • Treatment toxicity • TRT in both arms
IALT[20]	1867/3300	I–III	CDDP+VP-16 or Vinca Alk's/ observation	74	0.86	4.1	<0.03	• Sample size • Long follow-up • % 3rd generation CT	• Early closure • CT heterogeneity • TRT in both arms
BLT[21]	381/500	I–III	CDDP-based/ observation	64	1.02	–2[c]	0.90	• % 3rd generation CT	• Limited sample size • Short follow-up • Quality of surgery • CT heterogeneity

JCOG 9304[22]	119/200	IIIA (N2)	CDDP+VIN/ observation	58	–	–7.9[e]	0.89		• Limited sample size • Only pN2 patients
UFT meta-analysis[25]	2003	I–III	UFT/ observation	80[a]	0.77	4.6	0.011	• High compliance • Low toxicity	• Only trials in Japan • 95% stage I • 84% ADK • 45% women
NCIC-JBR 10[27]	482/450	IB-II	CDDP+VNR/ observation	65	0.69	15	0.011	• 3rd generation CT • Selected stage population	• Limited sample size • Low compliance • High toxicity • Higher than expected benefit
CALGB 9633[29]	344/500	IB	Carboplatin+ paclitaxel/ observation	84	0.62	12[f]	0.028	• 3rd Generation CT • Selected stage population • High compliance • Low toxicity	• Limited sample size • Higher than expected benefit
ANITA[30]	840/800	IB–IIIA	CDDP+VNR/ observation	56[d]	0.79	8.6	0.013	• 3rd Generation CT • Long follow-up	• Poor compliance • Slow recruitment

Abbreviations: CT, chemotherapy; CDDP, cisplatin; VP-16, etoposide; TRT, thoracic radiotherapy; MVP, mitomycin C, vindesine, cisplatin; Vinca Alk's, vinca alkaloids; VIN, vindesine; VNR, vinorelbine; ADK, adenocarcinoma. –, data not available.

a Compliance at 6 months in Kato et al. [23] and Nakagawa et al. [24].

b The estimated 5-year survival rates were 39% in the radiotherapy group and 33% in the chemo-radiotherapy group, respectively.

c The estimated 2-year survival rates were 60% in the observation group and 58% in the chemotherapy group, respectively.

d Median % planned dose of vinorelbine.

e The estimated 5-year survival rates were 36.1% in the control arm and 28.2% in the chemotherapy arm, respectively.

f At 4 years.

Table 2 – Patient characteristics in recent randomized clinical trials of adjuvant chemotherapy (CT) in radically resected patients with NSCLC

Trial	Median age	Female (%)	Adenocarcinoma (%)	Stage (%)				Pneumonectomy (%)	Radiotherapy (%)
				IA	IB	II	III		
INT 0115[17]	61	42	53			41	59	32	100
ALPI[18]	61	14	37	39		33	28	25	43
IALT[20]	59	20	40	10	27	24	39	35	30
BLT[21]	61	31	37	27		38	34	–	14
JCOG 9304[22]	62	35	73				100	10	0
UFT meta-analysis[25]	62	45	84	95		3	2	–	0
NCIC-JBR 10[27]	61	35	53		45	55		23	0
CALGB 9633[29]	61	36	51		100			10	0
ANITA[30]	59	14	41[a]		35	30	35	37	25

–, data not available.
a Non-squamous.

chemotherapy effect in this setting. In addition, the chemotherapy regimen used (cisplatin-etoposide) is now regarded as a suboptimal treatment for NSCLC. Finally, given the results of the PORT meta-analysis, thoracic radiotherapy should not be regarded as standard reference treatment in adjuvant trials.

2.4. *ALPI trial*

The Italian/EORTC ALPI (Adjuvant Lung Cancer Project Italy) trial randomly assigned 1209 patients surgically staged as having stage I–IIIA NSCLC to receive either no treatment after surgery or chemotherapy with the MVP triplet (mitomycin 8 mg/m^2 on day 1, vindesine 3 mg/m^2 on days 1, 8 and cisplatin 100 mg/m^2 on day 1 every 3 weeks) for three courses [18,19]. After a median follow-up period of 64.5 months, non-statistically significant difference between the two patient groups in progression-free survival [hazard ratio (HR) 0.89 (95% CI 0.76–1.03); $P = 0.128$] and in overall survival [hazard ratio (HR) 0.96 (95% CI 0.81–1.13); $P = 0.589$] could be found. Moreover, there was no evidence of a significant chemotherapy effect in different stages of disease, even if the hazard ratio (HR) for survival in stage II patients was 0.80.

The ALPI trial was the first large, prospective adjuvant study designed to detect reasonably small difference in survival that were in the range of those detected by the 1995 meta-analysis (powered to detect a 7% improvement in 5-year survival from 50% to 57%). This study enrolled a number of patients with stage I–IIIA similar to that reported in the meta-analysis and very close to that originally planned (1209 out of 1300). Potential criticisms for this trial include the chemotherapy combination used and the inclusion of patients treated with chest radiotherapy. Nine percent of patients never began the MVP treatment and only 69% received the three planned cycles, with or without dose adjustments or omissions. The toxicity of this regimen could have contributed to the higher mortality observed during the first year after randomization in the chemotherapy arm. Indeed, survival curves separate in the first two years in favour of the control arm, then cross each other and separate again from the fourth year in favour of the chemotherapy arm. This observation is further corroborated by the causes of events showing that, while the number of relapses is 20% less in the chemotherapy arm, the number of deaths for any cause remains identical. Finally, the inclusion of patients treated with chest radiotherapy (43%) may have decreased the probability of seeing a difference between the two groups and could also explain the increase in non-cancer related death, especially in the chemotherapy arm.

2.5. *IALT trial*

Like the ALPI study, the International Adjuvant Lung Cancer Trial (IALT), which is the largest randomized clinical trial of post-operative adjuvant chemotherapy so far performed in patients radically resected for stage I–III NSCLC, randomized between surgery alone and surgery followed by cisplatin-based chemotherapy [20]. The choice of sequential chest radiotherapy for patients in both arms of the trial was left to the discretion of the investigator. The trial did not require the use a specific chemotherapy regimen, but investigators were allowed to choose the dose of cisplatin (80–120 mg/m^2) and the second drug among etoposide (56.5%), vinorelbine (26.8%), vindesine (5.8%) or vinblastine (11%). The planned number of patients was 3300 to observe a 5% survival difference at 5 years. The study was initiated in 1995 and closed in December 2000 for slow accrual, after enrolment of 1867 patients. With a median follow-up of 56 months, disease-free survival (39.4 vs. 34.3% at 5 years), with a hazard ratio (HR) of 0.83 (95% CI 0.74–0.94) ($P < 0.003$) and also overall survival (44.5 vs. 40.4% at 5 years) with a hazard ratio (HR) of 0.86 (95% CI 0.76–0.98) ($P < 0.03$) favoured the chemotherapy arm. IALT was the first large randomized trial to show a significant prolongation of survival with the use of adjuvant chemotherapy, with an absolute increase in the 5-year survival rate of 4.1%.

The IALT trial was powered to detect a 5% improvement in 5-year survival as suggested by 1995 meta-analysis results. For this purpose the study was due to enrol 3300 patients but was closed prematurely, at an accrual slightly below 2000 patients. The number of patients in this trial is, however, larger than that of cisplatin-treated patients included in meta-analysis and, furthermore, more events were observed than those anticipated in the study design. Under these circumstances, it is unlikely that a larger sample size would

have led to a negative outcome. The IALT trial used chemotherapy regimens less toxic than the MVP regimen, used in the ALPI trial. The increased chemotherapy delivery (74% of patients received at least 240 mg/m^2 of cisplatin) and the smaller number of non-cancer deaths are consistent with this observation. Other potential weaknesses of this trial could be identified in the use of thoracic radiotherapy in around 30% of patients, with the same problem described for the ALPI trial, and in the open chemotherapy-choice design that introduced additional confounding factors for the interpretation of results obtained with variable doses of cisplatin and different chemotherapy regimens.

2.6. *Big Lung Trial*

Data about the role of adjuvant chemotherapy in a subgroup of surgically resected patients enrolled into the large British Big Lung Trial (BLT) have been recently reported [21]. Three hundred eighty-one NSCLC patients with stage I–III were randomized to receive no adjuvant therapy or chemotherapy with cisplatin-based combination [mitomycin C, ifosfamide and cisplatin (MIC), mitomycin C, vinblastine and cisplatin (MVP), cisplatin and vinblastine or cisplatin and vindesine]. Preliminary results do not show any difference in survival between the two groups [hazard ratio (HR) 1.02 (95% CI 0.77–1.35); $P = 0.90$]. However, the small sample size of this trial, the short follow-up (34.6 months), the variability of chemotherapy regimens used and the quality of surgery (15% incomplete resections) preclude any meaningful conclusion to be drawn.

2.7. *JCOG 9304 trial*

This Japanese study, performed only in completely resected pN2 patients, randomized 119 patients to observation or chemotherapy with cisplatin (80 mg/m^2 on day 1) and vindesine (3 mg/m^2 on days 1 and 8) for 3 courses [22]. There was non-statistically significant difference in survival between adjuvant and surgery-alone groups with a median survival of 36 months for both arms. Again, due to the exceedingly low sample size, this trial does not help to clarify the role of adjuvant chemotherapy in NSCLC.

2.8. *The Japanese trials with UFT and the UFT meta-analysis*

In addition to the above mentioned studies, several Japanese adjuvant trials have evaluated the potential role of oral UFT, a combination of uracil, an inhibitor of dihydropyrimidine dehydrogenase (DPD), and tegafur, a prodrug of 5-fluorouracil (5-FU).

In 2004, Kato and colleagues [23] published the results of a study of Japan Lung Cancer Research Group comparing surgery alone to surgery followed by UFT (250 mg/m^2 per day for two years) in 999 patients with stage I adenocarcinoma. Patients assigned to receive UFT had an improved survival with a 5-year survival rate of 88% in UFT arm vs. 85% in the surgery-alone arm [hazard ratio (HR) 0.71 (95% CI 0.52–0.98); $P = 0.04$]. In a subset analysis, the survival benefit seemed to be confined to patients with T2 tumors (85% vs. 74%, $P = 0.005$).

Very recently, Nakagawa [24] published the results of a randomized clinical trial in patients with completely resected pathological stage I, adenocarcinoma or squamous-cell lung carcinoma. A total of 332 patients were randomized in the surgery alone or treatment group (UFT 400 mg/day for 1 year after surgery). The conclusions of this study were that post-operative UFT administration did not significantly improve post-operative survival of stage I NSCLC patients, but subset analyses suggested that UFT might be effective in pT1N0M0 adenocarcinoma patients.

These two trials have been included, together with other 4 Japanese randomized studies (2 positive and 2 negative) in a specific meta-analysis evaluating the efficacy of UFT alone in NSCLC adjuvant chemotherapy [25]. This meta-analysis of 2003 patients showed that long-term adjuvant treatment with uracil–tegafur improved overall survival, resulting in a benefit of 4.6% at 5-years (77.2% vs. 81.8% for no treatment and UFT, respectively; hazard ratio (HR) 0.77 [95% CI 0.63–0.94]; $P = 0.011$) and of 7% at 7-years (69.5% vs. 76.5% for no treatment and UFT, respectively; hazard ratio (HR) 0.74 [95% CI 0.61–0.88]; $P = 0.001$). It is important to underscore that UFT efficacy is restricted to patients with stage I (95% of patients included in the meta-analysis), in particular with $T > 2$ cm, and with adenocarcinoma histology (84% of patients). It remains difficult to understand why an agent with limited activity in advanced disease [26], at least in the Caucasian population, should work in the adjuvant setting. However, protracted treatment duration, pharmacogenomic specificity of the Japanese population and an antiangiogenetic mechanism of action of prolonged UFT treatment, may account, at least in part, for this unexpected result.

2.9. *NCIC-JBR10 trial*

In the NCIC-JBR10 trial, 482 patients with stage IB and II (excluding T3N0) radically resected NSCLC were randomized to receive either post-surgical therapy with cisplatin (50 mg/m^2 on days 1, 8 every 4 weeks for 4 cycles) and vinorelbine (25 mg/m^2, reduced from 30 mg/m^2 for unacceptable toxicity, weekly for 16 weeks) or no chemotherapy [27]. At 5 years, 69% of patients in the chemotherapy arm were alive compared with 54% in the control arm [hazard ratio (HR) 0.69 (95% CI 0.52–0.92); $P = 0.011$] with an absolute survival benefit of 15% for patients receiving chemotherapy. The size of the adjuvant chemotherapy effect in this trial certainly exceeds the expectation in this setting, based on the results of the meta-analysis and subsequent prospective trials (absolute 5-year benefit of 4–5%) raising the doubt of a possible false positive result. However, superselection of early stage disease in this trial may justify a bigger chemotherapy effect if we hypotheize that early stages are those that derive the highest benefit from adjuvant chemotherapy as suggested also by Japanese trials and CALGB 9633. Hence, this trial is the first in which all patients were treated with a last generation chemotherapy regimen. Unfortunately, it has to be noted that this treatment was associated with a significant, though generally reversible, negative impact on quality of life (QoL) [28]. In fact, the compliance to the chemotherapy was low (65% of patients received 3 or 4 cycles), all patients required at least one dose reduction or

treatment delay and 73% of patients experienced grade 3–4 neutropenia.

2.10. *CALGB 9633 trial*

The CALGB 9633 trial included 344 patients with stage IB disease only randomized to receive either carboplatin (AUC 6 on day 1) plus paclitaxel (200 mg/m^2 on day 1) every 3 weeks for 4 cycles or no chemotherapy [29]. After 4 years, 71% of patients who had received chemotherapy were alive compared with 59% of those who had surgery alone [hazard ratio (HR) 0.62 (95% CI 0.41–0.95); $P = 0.028$] with an absolute survival benefit of 12% for patients receiving chemotherapy. Differently to the NCIC and ANITA trials, adjuvant therapy was well tolerated and treatment compliance was excellent with 85% of patients completing 3 or more cycles of treatment. However, the CALGB results, like those of NCIC trial, are certainly better then expected. This more favourable outcome can be partially explained by a peculiar patient selection (earlier stages of disease, more women [30–35%] and more adenocarcinoma histology [50–55%] compared to ALPI and IALT studies) and different type of treatment (lower percentage of pneumonectomy, use of third generation chemotherapy and lack of thoracic radiotherapy).

2.11. *ANITA trial*

Recently, at the 2005 American Society of Clinical Oncology Meeting, the last completed adjuvant study was presented. In the Adjuvant Navelbine International Trial Association (ANITA) trial, 840 patients with radically resected stage IB–IIIA NSCLC were randomly assigned to chemotherapy (4 cycles of cisplatin 100 mg/m^2 every 4 weeks and 16 cycles of vinorelbine at 30 mg/m^2 weekly) or observation only [30]. At 5 years, 51.2% of patients in the chemotherapy arm were alive compared to 42.6% in the control arm [hazard ratio (HR) 0.79 (95% CI 0.66–0.95); $P = 0.013$] with an absolute survival benefit for patients receiving chemotherapy of 8.6%. A subset analysis supports the conclusion that adjuvant chemotherapy significantly improves survival in stage II and IIIA but not in stage IB.

Although the study had a very slow recruitment with an average yearly accrual per centre of 1.4 patients, this trial confirmed, in a less selected population compared to NCIC and CALGB trials and with a longer follow-up (>70 months), that a third generation chemotherapy regimen is effective in NSCLC adjuvant treatment, with a size effect close to the expectation. Unfortunately, it has to be noted that the chemotherapy schedule used in this trial, with high dose cisplatin combined with weekly vinorelbine, as in the NCIC trial, was associated with important toxicity and poor compliance; in fact, 84.6% of patients experienced grade 3–4 neutropenia, with a 12.5% incidence of febrile neutropenia and the median percentage of delivered/planned total was only 56% and 76% for vinorelbine and cisplatin, respectively.

3. Discussion

Until recently, surgery alone, with or without post-operative thoracic irradiation, has been the standard of care for patients with resectable NSCLC. After the meta-analysis published in 1995 [16], which showed a non-statistically significant 5% improvement in 5-year survival with second generation platinum-based adjuvant chemotherapy, 8 prospective trials addressing the role of adjuvant second and third generation platinum-based chemotherapy have been completed [17,18,20–22,27,29,30]. Four of these trials had a positive outcome (IALT, NCIC-JBR10, CALGB 9633, ANITA) showing a statistically significant reduction in mortality with adjuvant chemotherapy, whereas four others were negative, showing no survival benefit for adjuvant chemotherapy (INT 0115, ALPI, BLT, JCOG 9304). For this reason, the role of adjuvant chemotherapy for radically resected NSCLC remains highly controversial. However, it has to be outlined that 3 of the 4 negative trials were significantly underpowered for detecting the expected benefit of adjuvant chemotherapy in that patient population (INT 0115, BLT, JCOG 9304) and the fourth (ALPI) may have failed to show a statistically significant benefit due to an increased mortality during the first year of follow-up in the chemotherapy arm, possibly due to excessive toxicity associated with the MVP triplet. In addition, a series of Japanese trials addressing the role of UFT treatment have also provided evidence of an improved survival outcome with adjuvant chemotherapy in resected early stage NSCLC [25].

The results of two new meta-analyses, based on abstracted data, have been recently published showing a statistically significant small survival benefit for adjuvant chemotherapy. The two meta-analyses included 7200 and 5716 patients of 19 trials (12 included in 1995 meta-analysis + 7 new) and 11 trials (studies published after 1995 meta-analysis), respectively [31,32]. Although these results must be interpreted with caution, because the 2 meta-analyses were not based on individual patient data (IPD), adjuvant chemotherapy appeared to produce a survival advantage compared to surgery alone. At subset analyses, both cisplatin-based chemotherapy and single agent UFT were found to yield a significant survival benefit. It should be underscored that the hazard ratio (HR) in both recent meta-analyses is 0.87, exactly the same found in the first 1995 meta-analysis.

Bria reported a third meta-analysis only in abstract form; this included 6494 patients entered onto 12 trials (11 trials with cisplatin-based chemotherapy + the 1995 meta-analysis). When data were pooled and plotted, significant differences in favour of chemotherapy were seen in the entire study population (Relative Risk Ratios 0.93, $P = 0.01$) and in sub-populations [33].

Another meta-analysis with single patient data has been planned to further clarify the indications for adjuvant chemotherapy. In the projected Lung Adjuvant Cisplatin Evaluation (LACE) pooled analysis of the new trials aims at a better definition of the role of cisplatin-based chemotherapy in adjuvant setting.

Therefore, most of the data consistently show a small reduction in the rate of lung cancer relapse and mortality with modern adjuvant chemotherapy. The size of the benefit (4–15% 5-year absolute survival improvement) is plausible, based on the biological rational of adjuvant chemotherapy in NSCLC, and is similar to that achieved in other solid tumors. Still, these data do not allow definitive conclusions, about the role of post-operative adjuvant chemotherapy in standard management of NSCLC patients, to be drawn. In

fact, the possible survival advantage is small, even if in the same range as the improvement obtained with adjuvant chemotherapy in patients with breast and colon cancer [34,35] and could be considered insufficient in this particular category of patients characterised by older age, higher rate of comorbidities, with sometimes poor and slow recovery after major thoracic surgery and considering the more aggressive type of chemotherapy needed.

At the moment, considering the available scientific evidence, is it possible at patient's bedside to make a decision about the indication for adjuvant chemotherapy? Is it justified to recommend adjuvant chemotherapy to all resected patients? If yes, which chemotherapy should we be using and for how many cycles? In our opinion, to answer these questions, having in mind the available literature data here reported, clinicians have to take into consideration some clinical aspects that are essential in the decision making process.

The first aspect concerns patient clinical conditions. Age, performance status (PS), presence of comorbidities, time to full recovery after the thoracic surgery are crucial in deciding whether a specific patient can be regarded as a good candidate for adjuvant chemotherapy. In fact, both largest trials, ALPI and IALT, showed a high rate of non-cancer related deaths, grade 3–4 toxicities and suboptimal compliance to adjuvant treatment for reasons possibly related to a suboptimal post-operative clinical status of the patients for being treated with cisplatin-containing chemotherapy.

The median age of NSCLC patients is about 70 years, higher than breast and colorectal patients submitted to adjuvant chemotherapy. Considering the median age of the patients included in randomized trials it is reasonable to recommend adjuvant chemotherapy only for patients younger than 70 years.

The performance status (PS) is a very important factor in the decision making about adjuvant chemotherapy. Since the ability of a patient to tolerate cisplatin-based therapy is influenced by the clinical conditions, most clinical trials recruited patients with good PS (ECOG 0–1). For this reason, after thoracic surgery, only patients with PS ECOG = 0, or possibly 1, should be considered for adjuvant chemotherapy.

NSCLC patients very frequently present comorbidities related both to the previous life-style and tobacco consumption (cardiopulmonary diseases, atherosclerosis) and to their age (diabetes, compromised renal function) that can prevent the physician from giving platinum-based chemotherapy. For these reasons, it is suggested that patients with significant comorbidities are excluded from adjuvant platinum-based chemotherapy.

The ability of an individual to tolerate cisplatin-based therapy is perhaps best assessed based on the patient's time to full recovery after surgery. In fact, after thoracic surgery (particularly pneumonectomy), lung cancer patients are very often compromised by the surgical procedure itself and need a longer time to full recovery compared to breast cancer patients after mastectomy and colorectal cancer patients after colectomy. Clinical experience clearly indicates that tolerability of platinum-based chemotherapy is much less if given post-operatively as compared to pre-operatively. Therefore, only patients with rapid and full recovery without major complications after lung resection should be considered for adjuvant chemotherapy. For these reasons adjuvant chemotherapy could be planned between the first and the second month after surgery.

A second important aspect to be considered in the decision making process is disease stage. The ALPI, IALT, BLT and ANITA studies accrued patients with stage I–IIIA disease and no clear differences by stages were found with the exception of the IALT study in which in the subset analysis of benefit seems to be confined to IIIA stage patients. In the ANITA trial no benefit was observed in stage IB. This is in contrast with the results of Japanese, NCIC-JBR10 and CALGB 9633 studies where only patients with stage IB and II were eligible and were found to benefit from adjuvant chemotherapy. On the basis of these results it appears that decision about adjuvant chemotherapy in resected NSCLC should not be based on stage and that patients with pathological stage IB–IIIA should all be considered as potential candidate for adjuvant chemotherapy. However, it is likely to expect a higher chemotherapy benefit in early stage disease.

Last but not least, patients suitable for adjuvant chemotherapy need to be fully informed and able to accept the therapeutic options on the basis of pros (magnitude of the reduction of the risk of death) and cons (impairment of quality of life during and, possibly, immediately after the chemotherapy, and treatment toxicity).

Finally, if, after thorough discussion with the patient, a decision of starting adjuvant chemotherapy is taken, which chemotherapy regimen should we be using and for how many cycles? Apart from UFT, whose efficacy still need to be verified in Caucasian patients and in stage II–III disease, most of the evidence support the use of a third generation platinum-based doublet, particularly carboplatin-paclitaxel (CALGB 9633) and cisplatin-vinorelbine (IALT, NCIC-JBR10, ANITA), for no more than 4 cycles. Other third generation regimens widely used in advanced disease, such as cisplatin-gemcitabine and cisplatin-docetaxel, are an alternative option even if they have not been properly tested in this specific setting.

In conclusion, we believe that, with the currently available scientific evidence, it is reasonable to offer adjuvant chemotherapy with 4 cycles of a third generation platinum doublet to selected patients with radically resected stage IB–IIIA NSCLC. The patients should be younger than 70 years of age, with very good performance status; have absence of comorbidities, make rapid and complete recovery after thoracic surgery, and be fully informed about the pros and cons of the treatment order to allow active patient participation in the treatment decision.

Conflict of interest statement

None declared.

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