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REVIEW ARTICLE

Preoperative chemotherapy in early-stage (stage IB-IIIA) resectable non small cell lung cancer. Is it justified?

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Summary

Only 20-30% of patients with non small cell lung cancer (NSCLC) present with early-stage disease at the time of diagnosis and may benefit by surgical resection. Five-year survival in early-stage disease varies from 38 to 57% for stage IB and from 13 to 23% for stage IIIA according to the clinical and pathological assessment of the patients. Occult micrometastatic disease already present in many patients with resectable NSCLC at the time of diagnosis and surgical treatment leads to local and distant disease recurrence. Therefore a more systemic approach should be considered in early-stage disease. The role of adjuvant chemotherapy has already been established in this field. Within the past decade attention has been focused on the possible beneficial effects of preoperative chemotherapy considering that patients' compliance to the induction treatment can be very high with eventual eradication of micrometastatic disease and primary tumor downstaging.

In this review we present the currently available data on induction chemotherapy followed by surgery in early-stage (stages IB-IIIA) NSCLC with a fundamental question to be answered: is this approach justified in current clinical practice?

Key words: chemotherapy, induction treatment, lung cancer, resectable lung cancer

Background

Lung cancer remains the primary cause of cancer-related death in Europe and USA [1]. Surgery continues to be the standard of care in the treatment or early-stage NSCLC (stage I-IIIA). Unfortunately only 20-30% of the patients with lung cancer present with early-stage disease at the time of diagnosis and may benefit by a potentially curative resection. Five-year survival rates vary from 38 to 57% for stage IB and from 13 to 25% for stage IIIA [2] according to the clinical and pathological assessment of the patients, with an overall 5-year survival of 14% across all disease stages [3]. Local or distant disease recurrence is the most common cause of death in these patients. Recurrence is most probably the result of occult micrometastatic disease already present at the time of diagnosis. Several reports support the hypothesis of an already disseminated disease at the time of diagnosis and/or surgical treatment of patients with early-stage NSCLC. Ahrendt and colleagues have documented mediastinal nodal involvement by molecular techniques in 28% of patients with stage I disease [4]. In the report by D'Cunha et al. 38% of patients with clinical stage I disease were upstaged after the application of molecular markers of micrometastatic disease in mediastinal lymph nodes [5]. Finally Sher et al. detected, by molecular techniques, cancer cells in the venous blood in up to 70% of patients with NSCLC with cancer cell load (Lc) highly correlated to survival even in operable early-stage patients [6]. The eradication of such micrometastatic disease makes necessary a multimodality approach to lung cancer patients, including those in early stages. A well-documented metaanalysis of 52 randomized trials in 1995 reported some data of a potentially more favorable outcome in lung cancer patients receiving chemotherapy after surgery [7]. Recent randomized trials have demonstrated a survival benefit of adjuvant chemotherapy in resect-

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able lung cancer patients (Table 1) [8-13]. Within the past decade attention has been focused to the use of chemotherapy in the preoperative setting of patients with resectable NSCLC.

In this review we present the currently available data on the eventual beneficial effects of neoadjuvant chemotherapy in patients with early-stage resectable NSCLC.

The concept of neoadjuvant/induction chemotherapy

The concept of preoperative chemotherapy based on the Goldie and Coldman hypothesis (the less the tumor size, the more the tumor response and the fewer the chemoresistant cells) was introduced by Frei in 1982 [14].

Preoperative drug treatment at an early phase of patients' management may eradicate occult micrometastatic disease with improved survival compared to the local disease control offered by primary surgery. Since chemotherapy is also cytotoxic at the level of the primary tumor, a reduction of its size (T downstaging) could lead to improved resectability rates or lesser resections. Neoadjuvant chemotherapy is better tolerated by the patients. While only 45-60% of the patients receive the planned chemotherapy in the adjuvant setting, eventually with lower doses and delays, trials on preoperative chemotherapy report compliance rates of more than 80% [15]. Other benefits by the use of neoadjuvant chemotherapy could be a lower risk of drug resistance and *in vivo* testing of tumor's chemosensitivity.

The major disadvantage of preoperative chemotherapy is the inability to perform an accurate staging of the patients, since only clinical staging can be carried out. Delay in surgical treatment and eventually increased risks of perioperative mortality and morbidity

Table 1. Adjuvant chemotherapy in early-stage non small cell lung cancer

Study [reference]	*Number of patients*	*Patient groups*	*Overall survival+/- Median survival*		*Disease free survival*
IALT trial [8]	1867	S→ OBS (935 pts)	S→ OBS: 66.7% (2 yrs) and 40.5% (5 yrs)		S→OBS: 34.3% (5 yrs)
		S→ po-CT (932 pts): Cisplatin + Etoposide or Vinorelbine or Vinblastine or Vindesine	S→ po-CT: 70.3 (2 yrs) and 44.5% (5 yrs)		S→ po-CT: 39.4% (5 yrs)
			HR for death 0.86 (in favor of po-CT), p<0.03		HR 0.83 (in favor of CT) p <0.003
Winton et al. [9]	482	S→OBS (240 pts)	S→ OBS: 54% (5 yrs)		S→OBS: 49% (5 yrs)
		S→ po-CT (242 pts): Cisplatin+Vinorelbine	S→ po-CT: 69% (5 yrs), p= 0.03		S→po-CT: 61% (5 yrs), p=0.08
			Median survival: 73 months vs. 94 months (HR 0.69, p=0.04)		Median DFS not yet reached for S→po-CT
ANITA trial [10,11]	840	S→OBS (433 pts)	S→OBS: 63% (2 yrs), 39% (5 yrs), 26% (7 yrs)		Median DFS: 20.7 months for S→OBS vs. 36.3% for S→ po-CT (HR 0.76, p=0.002)
		S→po-CT (407 pts): Cisplatin+ Vinorelbine	S→ po-CT: 68% (2 yrs), 51% (5 yrs), 45% (7 yrs)		
			Median survival: 47.3 months vs. 65.7 months (HR 0.80, p= 0.017)		DFS benefit for S→ po-CT: 9% (6 months), 9.5% (1 yr), 9.6% (2 yrs), 8.7% (5 yrs), 5.5% (7 yrs)
			Survival benefit for S→po-CT: 2.8% (1 yr), 4.7% (2 yrs), 8.6% (5 yrs), 8.4% (7 yrs)		
CALGB 9633 trial [12,13]	344		*Preliminary [12]*	*Update [13]*	
		S→OBS (171 pts)	S→OBS: 59% (4 yrs)	S→ OBS: 70% (3 yrs), 57% (5 yrs)	Improvement in DFS favoring adjuvant CT p= 0.035 [12] p= 0.027 [13]
		S→po-CT (173 pts): Paclitaxel+Carboplatin	S→po-CT: 71% (4 yrs), p<0.05	S→ po-CT: 79% (3 yrs), 60% (5 yrs), p= 0.035 (3 yrs), p= 0.32 (5 yrs)	

S: surgery, OBS: observation, po-CT: postoperative chemotherapy, DFS: disease free survival, HR: hazard ratio, yrs: years

after preoperative chemotherapy, although reported as potential problems, require further evaluation based on the results of the trials published on induction chemotherapy.

Neoadjuvant chemotherapy in early-stage (stage I-IIIA) NSCLC - Currently available data

The use of neoadjuvant chemotherapy in resectable NSCLC was primarily triggered by the beneficial effects of preoperative chemotherapy reported in small randomized trials of patients with stage IIIA disease (Table 2). In 1992 Pass et al. presented the results of a randomized trial on preoperative chemotherapy. The trial included 27 patients with stage IIIA N2 NSCLC: 13 were assigned to chemotherapy (etoposide+platinum)-surgery-chemotherapy, and 14 to surgery followed by mediastinal radiotherapy. Median survival, although better in the chemotherapy arm (29 vs. 16 months) wasn't statistically significant (p=0.095). Three-year survival rate also favored the chemotherapy group of patients (42 vs. 12%; p >0.05) [16]. Rosell et al. studied 60 patients with stage IIIA NSCLC. Those patients were randomly assigned to surgery or to a combined treatment consisting of 3 cycles of mitomycin C (6 mg/m^2), ifosfamide (3 g/m^2) and cisplatin (50 mg/m^2), followed by surgery. A statistically significant difference was reported in median survival between the two arms of the trial. In the first publication in 1994 a median survival of 8 months was reported for the surgical arm vs. 26 months in the chemotherapy group (p < 0.001) [17]. The difference remained statistically significant in the second publication of the results of this trial 4 years later with median survival of 10 months in the surgery group and 22 months in the chemotherapy group (p=0.005). Five-year survival rates were 0% and 17%, respectively [18]. Similar results were reported by Roth and colleagues in a phase III trial also including 60 patients with stage IIIA-N2 disease randomly assigned to surgery alone or to chemotherapy (3 cycles of cisplatin, etoposide, cyclophosphamide) followed by surgery and 3 additional courses of chemotherapy in the presence of an objective response. A median survival of 11 months for the surgical arm was significantly lower than the one of 64 months for the combined treatment group of patients (p=0.008) [19]. Four years later this difference continued to exist but it reached marginal statistical significance (14 vs. 21 months; p=0.053). Five-year survival rates were 15% and 36%, respectively (p=0.048, Breslow-Gehan-Wilkcoxon test) [20].

Phase II trials (Table 3)

Since 1985 investigators have attempted to evaluate the role of neoadjuvant chemotherapy in the subgroup of early-stage (stage IB-IIIA) resectable NSCLC considering the high incidence of disease recurrence in these patients after surgical resection.

In a phase II study carried out by Dautzenberg and colleagues to assess the role of perioperative polychemotherapy (cisplatin 100 mg/m^2, cyclophosphamide 600 mg/m^2, vindesine 3 mg/m^2) in resectable NSCLC (stage I-III) 26 patients were randomized into 2 groups: 13 patients received 2 cycles of preoperative chemotherapy and 2 additional cycles of postoperative chemotherapy, while the other 13 patients underwent surgical resection only. The study was closed prematurely because of a high rate of disease progression in the preoperative chemotherapy arm group (36%) leading to cancellation of the surgical resection planned [21].

In the Bimodality Lung Oncology Trial 94 patients underwent surgery after 2 cycles of paclitaxel and

Table 2. Phase III trials of preoperative (± postoperative) chemotherapy in stage IIIA non small cell lung cancer

Study [reference]	*Number of patients*	*Study groups*	*Median survival (months)*		*Overall survival*
Pass et al. [16]	27	p-CT (etoposide+ platinum)→S→ po-CT S→ Med RT	29 16 p= 0.095		42% (3 yrs) 12% (3 yrs) p>0.05
Rosell et al. [17,18]	60	S p-CT (cisplatin+mitomycin+ifosfamide)→ S	8 26 p<0.001	10 22 p= 0.005	0% (5 yrs) 17% (5 yrs) p=0.005
Roth et al. [19,20]	60	p-CT (cisplatin + etoposide + cyclophosphamide) x 3→ S ± po-CT	64 11 p=0.008	21 14 p=0.053	36% (5 yrs) 15% (5 yrs) p=0.048

S: surgery, p-CT: preoperative chemotherapy, po-CT: postoperative chemotherapy, Med: mediastinal, RT: radiotherapy, yrs: years

Table 3. Phase II trials of preoperative (± postoperative) chemotherapy in early-stage non small cell lung cancer

Study [reference]	*Number of patients*	*Treatment*	*Results*
Dautzenberg et al. [21]	26	p-CT (cisplatin+cyclophosphamide+vindesine) x 2→ S→ po-CT x 2: 13 pts S: 13 pts	Compliance 84.6% (11/13) Tumor response 45% (5/11) Disease progression in combined treatment 36% (4/11)
BLOT trial [22]	94	p-CT (paclitaxel+ carboplatin) x2→ S	Major objective response 56% (53/94) Surgery after CT 94% (88/94) Radical resection 86% (81/94) Compliance to p-CT 96% (90/94) 1- and 2- year survival 85% and 56%
De Boer et al. [23]	22	p-CT (cisplatin+mitomycin+vinblastine) x 3→ S	Compliance 100% Objective tumor response 55% (12/22) Minor response 27% (6/22) Partial pathologic response 50% (11/22)

S: surgery, p-CT: preoperative chemotherapy, po-CT: postoperative chemotherapy

carboplatin. After induction chemotherapy 53/94 (56%) patients presented a major objective response, 88 (94%) patients underwent surgical exploration and in 81 (86%) patients a complete resection of the tumor was achieved. Ninety (96%) patients completed the preoperative chemotherapeutic protocol and only 45% of the patients received the planned postoperative chemotherapy. There was one death during induction chemotherapy due to cerebrovascular accident and 2 postoperative deaths due to postoperative pneumonia and pulmonary embolus. Chemotherapy and surgery-related morbidity remained within acceptable levels. One-and 2-year survival was 85% and 56%, respectively [22].

British investigators also presented promising results in a phase II study of 22 patients with early-stage (stage IB, II and IIIA) resectable NSCLC receiving 3 cycles of preoperative chemotherapy with mitomycin, vinblastine and cisplatin. An objective tumor response was observed in 56% and a minor response in 27% of the patients. Half of the patients showed a partial pathologic response. There was no significant toxicity or quality of life deterioration during the induction treatment [23]. Both the Bimodality Lung Oncology Trial and the British report by De Boer and colleagues were evolved into large phase III trials.

Phase III trials (Table 4)

The Southwestern Oncology Group 9900 trial represents the evolution of the Bimodality Lung Oncology Trial. Although planned to recruit 600 patients the trial was closed in July 2004 with encouraging preliminary results presented in 2005. Three hundred and fifty-four patients were enrolled in this trial. They were assigned to receive either immediate surgery (174 patients) or chemotherapy with paclitaxel and carboplatin prior to surgical treatment (180 patients). There was a high compliance to the induction treatment with 77% of the patients in the chemotherapy group receiving all 3 cycles of the induction therapy. The clinical response rate after neoadjuvant chemotherapy was 41%, while pathologic complete response was only 10%. In both arms of the study a R0 resection was achieved in 84% of the patients. The most common side effects of chemotherapy included neutropenia and neuropathy. Three (1.7%) patients died during the induction treatment. One patient presented hemoptysis, one CMV pneumonia and the last one a rapid deterioration of his precarious cardiopulmonary function. There have been 7 (4%) postoperative deaths in the chemotherapy arm and 4 (2.4%) in the surgical one. The causes of death were not reported. Although the median progression free survival and median overall survival were higher in the neoadjuvant treatment arm (31 vs. 20 months, and 47 vs. 40 months) neither of them reached statistical significance [24]. In a more recent report in the 2007 ASCO annual meeting progression free survival was 33 months for the induction treatment arm and 21 months for surgery alone arm (hazard ratio / HR=0.77, p=0.07), the median overall survival was 75 and 46 months, respectively, and survival rates at 1, 3 and 5 years were 82%, 62% and 50% for the induction chemotherapy arm and 79%, 57% and 43% for surgery alone (HR=0.81, p=0.19). Although the differences between the two groups of the trial did not reach statistical significance, both progression free survival and overall survival continue to favor the induction chemotherapy arm [25].

In the MRC LU22/NVALT-2/EORCT 08012 trial 519 patients were randomly assigned to receive 3 cycles

Table 4. Phase III trials of preoperative chemotherapy vs. surgery alone in early-stage/resectable non small cell lung cancer

Study [reference]	*Number of patients*	*Study groups*	*Results*			
			Response to induction	*Median survival*	*Overall survival*	*DFS or PFS*
SWOG trial 9900 [24, 25]	354	p-CTX (paclitaxel+carboplatin) x3→S (180 pts). Compliance to induction 77% S (174 pts)	Clinical response 41% Pathologic complete response 10%	42 vs. 40 months in favor of p-CT; p=0.32 [24] 75 vs. 46 months in favor of p-CT; p=0.19 [25]	1, 3 and 5-year survival [25]: 82%, 62%, 50% (p-CT) 79%, 57%, 43% (S) HR 0.81, p=0.19	PFS 31 vs. 20 months in favor of p-CT; p=0.14 [24] 33 vs. 21 months in favor of p-CT. 5-yr PFS: 42 vs. 32% HR 0.77, p=0.07 [25]
MRC LU22/NVALT 2/EORTC 08012 trial [26]	519	p-CT (platinum-based) x3→S (258 pts). Compliance to induction 75% S (261 pts)	Response 49% Downstaging 31%	55 months for both study groups	5-year survival: 44% (p-CT) 45% (S)	
Depierre et al. [27]	373	p-CT (mitomycin+ifosfamide+ carboplatin) x 2→ S (179 pts). Compliance to induction 77% S (176)	Response to p-CT 64%	p-CT: 37 months S: 26 months, p= 0.15	1, 2, 3 and 4 year survival: 77.1%, 59.2%, 51.6%, 43.9% (p-CT) 73.3%, 53.3%, 41.2%, 35.3% (S) p=NR	Median DFS 26.7 months (p-CT) 12.9 months (S); p=0.033 DFS at 3 years 44% (p-CT) 33% (S) p=NR
Sorensen et al. [29]	100	p-CT (paclitaxel+ carboplatin) x 3→ S (44 pts) S (46 pts)	Response to p-CT 46%	p-CT: 34.4 months S: 22.5 months p>0.05	5-year survival: 36% (p-CT) 24% (S) p> 0.05	
ChEST trial [30] - preliminary results at 10 months	267	p-CT (gemcitabine+cisplatin) x 3→S (126 pts). Compliance to induction 79.4% S (141 pts)	Response to p–CT 32.5%			PFS at 6 months 89.1% (p-CT) 79.6% (S) p=NR
NATCH trial				Results awaited		

S: surgery, p-CT: preoperative chemotherapy, DFS: disease free survival, PFS: progression free survival, NR: not reported

of platinum-based chemotherapy prior to surgery (CT-S group, 258 patients) or to undergo immediate surgery (S group, 261 patients). Neoadjuvant chemotherapy was feasible, with 75% of the patients of the chemotherapy arm completing the preoperative treatment. Chemotherapy resulted in a good response rate of 49% and a higher downstaging rate of 31%, compared to 19% downstaging reported in the surgical group. There was no difference in the surgical resection required, postoperative complications and quality of life of the patients between the two arms of the trial. Median survival and 5-year survival rates were almost identical between CT-S and S alone groups (55 months and 44% for CT-S group and 55 months and 45% for S group) [26].

From 1991 to 1997 Depierre et al. conducted another large phase III trial on the role of preoperative chemotherapy in stage I (except T1,N0), II and IIIA NSCLC. Three hundred and seventy-three patients were assigned to receive 2 cycles of chemotherapy (mitomycin C, ifosfamide and cisplatin) prior to surgery or to proceed to immediate surgery. Two additional cycles of chemotherapy were delivered to chemotherapy responders after the surgical treatment. All patients with N2 or T3 disease underwent postoperative radiotherapy. There were 2 chemotherapy-related deaths and the postsurgical mortality was similar between the two groups of patients. A high response rate to preoperative chemotherapy was reported (64%). Median survival was 37 months in the combined (CT-S) treatment arm and 26 months for the surgery-alone (S) arm (p=0.15). Difference in survival rates was minimal at 1 year (S-arm 73.3%, CT-S arm 77.1%), but increased across the years reaching 6.9% at 2 years (52.3% vs. 59.2%), 10.4% at 3 years (41.2% vs. 51.6%) and 8.6% at 4 years (S-arm 35.3%, CT-S arm 43.9%). It was also observed that the benefit of preoperative chemotherapy was limited to stage I and II disease with higher relative risk (RR) of death in stage IIIA (RR of death 0.68 in N0 and N1 disease and 1.04 in N2 disease). Finally, disease free survival was significantly better in the group of patients receiving preoperative chemotherapy. This trial concluded that the combined treatment is associated with a survival benefit more evident after the first 2 years and mostly for stage I and II disease [27]. Similar to the results to Depierre et al. on the role of neoadjuvant chemotherapy in stage IIIA disease were reported by the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group, although in a small phase III study of 62 patients with stage IIIA-N2 disease and limited statistical power [28].

In 2005 Sorensen et al. presented at the ASCO annual meeting another randomized trial of 100 patients (stages IB, II and IIIA-T3) assigned in two groups: treatment A included 44 patients who underwent 3 courses of paclitaxel and carboplatin followed by surgery, and treatment B included 46 patients who underwent primary surgery. Although this trial was terminated prematurely because of slow recruitment, it resulted in increased median survival by one year and increased 5-year survival by 12% in the combined treatment arm of the study [29].

At the moment the results of 2 more trials are expected. The chemotherapy for early stages trial (ChEST) was closed in 2004 with 267 patients assigned to surgery alone or 3 cycles of preoperative cisplatin and gemcitabine. The preliminary data of this trial were presented at the ASCO 2005 annual meeting. At 10 months of median follow up the patients' compliance to induction treatment was 79.4%, the response to neoadjuvant chemotherapy 32.5% and the progression free survival at 6 months 89.1% for the combined treatment group and 79.6% for the primary surgery group (p-value not reported). Initial data indicate an advantage by the addition of preoperative chemotherapy. The trial is still ongoing in its follow up and definitive data will be published after a median follow up of 3 years is reached [30].

The Neoadjuvant Carboplatin/Taxol Hope (NATCH) trial was designed to compare surgery alone, preoperative chemotherapy (carboplatin+paclitaxel) and postoperative chemotherapy (carboplatin+paclitaxel). This last trial is still ongoing.

Reviews and metaanalyses

Reviews and metaanalyses of previously published data of randomized neoadjuvant chemotherapy trials in early-stage NSCLC show a survival benefit for the combined treatment. Berghmans and colleagues presented a metaanalysis of 6 randomized trials with a total of 590 patients. Patients with stage III disease only were included in 4 trials, while early-stage disease was confined in two. The overall HR for the induction chemotherapy followed by surgery was 0.66, supporting the addition of chemotherapy in the preoperative setting [15]. In the metaanalysis by Burdett and colleagues included were 7 randomized trials of preoperative chemotherapy with a total of 988 patients. A survival benefit was also reported by the addition of preoperative chemotherapy to the surgical resection with a HR of 0.82 translated to a 5-year survival improvement of 6% (from 14% to 20%) [31]. Incorporating the data of the MRC LU22/NVALT-2/EORCT 08012 trial to the Burdett's metaanalysis resulted in a 12% relative survival benefit for the combined approach with a HR of 0.88, corresponding to a 5-year survival benefit of 5% [24].

Conclusions

Except stage IA NSCLC, where surgery alone is considered the treatment of choice, patients with stages IB-IIIA will probably present a relapse of disease, likely due to the presence of systemic micrometastatic disease at the time of diagnosis and therapy. This makes clear the need for a systemic therapeutic approach, combining chemotherapy to the surgical resection. Recent randomized trials and metaanalyses have confirmed a clear survival benefit with the use of chemotherapy after surgical resection. Randomized trials in stage III NSCLC have documented a survival benefit in patients receiving preoperative chemotherapy, triggering attention to combined modality treatments in patients with early-stage NSCLC. The available data on preoperative chemotherapy in stage IB-IIIA NSCLC are clearly incoherent to the awaited survival improvement in these patients, probably as a result of the heterogeneity of the various trials and the eventual interference of postoperative chemotherapy in the results of some of them. Nevertheless, 2 recent metaanalyses presented by Berghmans et al. [15] and Burdett et al. [31], including the last one's revision with the addition of the results of the MRC LU22/NVALT-2/EORCT 08012 trial, demonstrated a significant improvement in survival with the use of neoadjuvant chemotherapy. Neoadjuvant chemotherapy is feasible and safe with over 70% of the patients completing the induction treatment. As already shown by the presentation of the various trials, preoperative chemotherapy is not related with delay in surgery and/or increased rates of perioperative complications compared to primary surgery. Even in stage IIIA with mediastinal nodal involvement, where preoperative chemoradiation is the induction treatment of choice in the attempt to achieve better resectability rates and survival improvement, the risks for perioperative mortality and morbidity are within acceptable levels with the possible exclusion of the right pneumonectomy as already shown in a previously published review [32]. Induction chemotherapy is related to a clinical tumor downstaging in 40-60% of the patients and to a complete pathologic response in 5-10% of them. It should be platinum-based with at least 3 courses. Although neoadjuvant chemotherapy seems to improve survival in patients with early-stage NSCLC the available data are preliminary and insufficient to justify its use outside of clinical trials.

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