



Induction systemic therapy followed by surgery for stages II–III non-small cell lung cancer: steady efforts

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Lung cancer is the leading cause of mortality worldwide with 1.6 million deaths in 2012. The prognosis of lung cancer remains very poor (1). For most countries, the age-standardized 5-year survival rate ranges from 10% to 20% for most countries (2). Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung malignant tumors. The first-line treatment for NSCLC is determined on the principles according to the TNM stage, which is the most reliable prognostic factor for this disease. Even patients with a localized tumor (stage I and stage II), as well as those with a resectable, locally advanced tumor (stage IIIA), have a poor prognosis when they are treated with surgery alone. In a Japanese study, the 5-year survival rate for pathological stages IB, IIA, IIB, and IIIA (categorized following the UICC-TNM staging system version 6) were 60–66%, 59–60%, 42–47%, and 28–33%, respectively (3).

Since about 80% of recurrences are distant metastases (4) and many patients developed micrometastases at the time of surgery (5–7), chemotherapy has been added as a treatment postoperatively (adjuvant chemotherapy) or preoperatively (induction or neoadjuvant chemotherapy). The results of adjuvant chemotherapy in the controlled randomized trials are excellent; the first large-scale meta-analysis using individual data (lung adjuvant cisplatin evaluation, $n=4,584$) showed that 76% of patients received 3 to 4 cycles of chemotherapy, and the hazard ratio [95% confidence interval (CI)] was 0.89 (0.82–0.96), corresponding to a 5-year absolute benefit of 5.4% from chemotherapy (8).

The second meta-analysis ($n=8,447$) and its follow-up data confirmed the results, with a hazard ratio (95% CI) of 0.86 (0.81–0.92) and a 5-year absolute benefit of 4% (9,10). However, these results from clinical trials should be interpreted with caution, because only the selected patients were included for the adjuvant clinical trials. For example, patients with pathological stage IIIB, incomplete resection, and unfavorable clinical course after surgery were all excluded from these trials. In other words, the advantages of the adjuvant approaches is the ability to select patients who are the good candidates for chemotherapy after surgery, and to predict the prognosis of patients based on an accurate pathological TNM stage.

Compared with adjuvant chemotherapy, induction chemotherapy has been less frequently tried because of the excellent advantages of adjuvant chemotherapy mentioned above. Induction chemotherapy; however, may have the following potential advantages: (I) increased compliance to chemotherapy; (II) better delivery of chemotherapy to the tumor tissue through an intact vasculature; (III) systemic treatment of occult microscopic metastases at the earliest possible time; (IV) assessment of tumor chemosensitivity in patients; and (V) reduction of the primary tumor mass that can lead to an increase in resectability. The potential disadvantages of this approach are as follows: (I) delay in surgery; (II) decreased percentages of patients who receive a potentially curative surgery; (III) increased surgical mortality and morbidity; and (IV) less accurate staging (11–13).

Table 1 Main randomized trials of neoadjuvant chemotherapy followed by surgery vs. surgery alone published in 2000

Authors [years]	Clinical stage	Treatment*	Total N of patients	Planned CT performed, %	N [%] of resection	N [%] of complete resection	N [%] of surgical death	Endpoint evaluation	Results, %	P value	HR for OS (95% CI)	Name of clinical Trial
Depierre [2002] (14)	IB-IIIA	Surgery alone	176	–	166 [94]	149 [85]	8 [4.8]	OS at 4 years	35	0.15	0.74 (0.56–0.99)	MIP-9 trial
		CDDP + IFO + MMC f/b surgery	179	90	163 [91]	154 [86]	12 [7.4]		44			
Nagai [2003] (15)	IIIA	Surgery alone	31	–	29 [94]	24 [77]	0	OS at 3 years	26	0.53	NR	JCOG 9209
		CDDP + VDS f/b surgery	31	71	23 [74]	20 [65]	0		23			
Gilligan [2007] (12)	IB-IIIA	Surgery alone	261	–	242 [93]	205 [79]	NR	OS at 5 years	45	0.86	1.02 (0.80–1.31)	MRCLU22/ NVALT2/ EPRTC08012
		Platinum-based CT f/b surgery	258	75	231 [90]	205 [79]	NR		44			
Pisters [2010] (16)	IB-IIIA	Surgery alone	168	–	158 [94]	146 [87]	4 [2.5]	OS at 5 years	33	0.11	0.79 (0.60–1.06)	SWOG s9900
		CBDCA + PTX f/b surgery	169	79	147 [87]	142 [84]	7 [4.8]		42			
Felip [2010] (17)	IB-IIIA	Surgery alone	210	–	189 [90]	NR	11 [5.8]	DFS at 5 years	34	0.18	0.96 (0.84–1.10)	NATCH trial
		CBDCA + PTX f/b surgery	199	90	174 [87]	NR	9 [5.2]		38			
Scagliotti [2012] (13)	IB-IIIA	Surgery alone	141	–	136 [96]	114 [81]	5 [3.7]	PFS at 3 years	48	0.03	0.63 (0.43–0.92)	CHEST
		CDDP + GEM f/b surgery	129	84	110 [85]	97 [75]	4 [3.6]		53			

*Treatment: CBDCA, carboplatin; CDDP, cisplatin; GEM, gemcitabine; IFO, ifosfamide; MMC, mitomycin-C; PTX, paclitaxel; VDS, vindesine; CT, chemotherapy; DFS, disease-free survival; HR, hazard ratio; NR, not reported; OS, overall survival; PFS, progression-free survival.

Phase III trials of induction chemotherapy followed by surgery versus surgery alone fully published in 2000 are summarized in *Table 1* (12–17). Although the compliance for induction chemotherapy remains high, either the percentage of resection or that of complete resection is not improved. A recent meta-analysis using individual patient data (n=2,385) showed a hazard ratio (95% CI) of 0.87 (0.78–0.96), corresponding to a 5-year absolute survival benefit of 5% (11). This figure is comparable to the results of adjuvant chemotherapy. A unique phase III trial (17) which compared using induction chemotherapy followed by surgery, surgery following adjuvant chemotherapy, and surgery alone, had revealed that as high as 90% of patients allocated to the induction chemotherapy arm received full cycles of chemotherapy. Whereas, only 61% of patients in the adjuvant chemotherapy arm received full cycles of chemotherapy. Tumor resection was observed in 87% of patients in the induction chemotherapy arm, 90% of patients in the adjuvant chemotherapy arm, and

90% in the surgery alone arm. The 5-year disease-free survival, the primary endpoint of this study, was 38.3%, 36.6%, and 34.1% for the induction chemotherapy arm, adjuvant chemotherapy arm, and surgery alone arm, respectively, with no statistical significance. Thus, induction chemotherapy has potential advantages over surgery alone or even adjuvant chemotherapy following surgery, but this approach is still under investigation and should be performed in the clinical trial settings.

Cascone *et al.* reported a phase II trial of the three cycles of cisplatin (80 mg/m²) and docetaxel (75 mg/m²) induction chemotherapy followed by surgery and adjuvant erlotinib for 1 year in NSCLC patients with clinical stages IB to IIIA (18). Of the 47 eligible patients, 14 had stage IB, 13 had stage IIB, and 18 had stage IIIA. A total of 40 patients received the planned three cycles of chemotherapy, 4 patients received 2 cycles of chemotherapy and 3 patients received 1 cycle of chemotherapy. No cisplatin dose reduction was required in 87% of patients, and the planned

docetaxel dose was maintained in 94% of patients. In spite of these good compliances to the chemotherapy, surgery was performed in only 37 (78.7%) patients. Of them, 35 (74.5%) underwent a complete resection. Adjuvant erlotinib was initiated in 21 (45%) patients, and was completed for 1 year in 12 (26%) patients. The 5-year overall survival rate for patients with pretreatment stages I, II, and III were 51.9%, 55.5%, and 21.1%, respectively. The recurrence pattern was distant metastases in the majority (85%) of cases. Induction cisplatin and docetaxel were well tolerated, but adjuvant erlotinib did not improve the outcomes when it was compared with the historical controls.

Complete tumor resection is the mainstay of treatment for resectable NSCLC without distant metastases. Thus, the percentages of patients who then proceeded to surgery and those who underwent a complete tumor resection are crucial in clinical trials of the induction chemotherapy. The actual resectability in phase II of the study was only 78.7%, although the induction chemotherapy was well tolerated without the chemotherapy dose reduction in nearly 90% of patients. However, the reasons for not proceeding to surgery included an “excessive cardiopulmonary risk” in 4 of 10 patients who then gave up surgery as an option. This phrase, imprecise without a specific name of adverse events, implies that three cycles of cisplatin and docetaxel at full doses may be more exhausting than what was expected for the patients who were planning to undergo surgery, although this dose and schedule are tolerable for most of the patients who had been treated with chemotherapy alone. In this study, the complete resection rate of 74.5% is also disappointing. None of the patients had exhibited a complete radiological response, and only one patient achieved a pathological complete response in the primary tumor. Thus, it is clear that the efficacy of cisplatin and docetaxel, which is one of the most powerful platinum doubles for stage IV disease, is not sufficient for the use of induction chemotherapy.

Another investigational point of this phase II study is adjuvant erlotinib (18). However, the epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors were found to have a very limited role for the unselected patients who did not undergo an EGFR mutation analysis, and this was also demonstrated in adjuvant settings (19).

To date, the standard care of patients with clinical stages II–III NSCLC remains upfront surgery followed by a platinum-based adjuvant chemotherapy, according to the pathological findings in the resected tumor and the general condition of the patients after surgery. Then, is there no

scope for induction drug therapy in these patients? A recent pilot study of two doses of nivolumab followed by surgery in 22 patients with a surgically resectable clinical stage I–IIIA NSCLC showed that the treatment-related adverse events of any grade occurred in only 5 (23%) patients, and grade 3–4 adverse events in 1 (4.5%) patient. All 21 eligible patients who had undergone surgery, had no treatment-related delays and 20 (95%) underwent complete resection. Radiographic evaluation of 21 patients showed 2 (9.5%) partial responses and 18 (86%) stable diseases. In the pathological evaluation of surgical specimens, results showed that 9 (45%) of 20 patients had a major response and 2 (10%) had complete disappearance of viable tumor cells (20). Thus, administration of induction immune checkpoint inhibitors before surgery can be feasible without delaying curative surgery and is highly effective. An experimental model using triple-negative breast cancer-bearing mice showed that paclitaxel was more effective when given after surgery than before surgery, whereas anti-PD-1 antibody was more effective in eradicating disseminated tumors when given before surgery than after surgery (21). These data points suggest that immunotherapy, including immune checkpoint inhibitors, may work better in the induction phase before surgery.

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Footnote

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