Editorial

Pre-operative chemotherapy for non-small cell lung carcinoma

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Abstract: The roll by the cytotoxic chemotherapy and its efficacy in the treatment of non-small cell carcinoma (NSCLC) was not clearly identified until the 1980s when studies showed that cisplatin was beneficial in the treatment of NSCLC. The first randomized controlled trial (RCT) to evaluate the efficacy of post-operative (adjuvant) chemotherapy using the cisplatin regimen for resectable NSCLC was reported in 1988. Since then, an increasing number of RCTs have been carried out to evaluate post-operative chemotherapy. Pre-operative (neo-adjuvant) chemotherapy is a relatively new treatment strategy, as its name indicates. Compared with post-operative chemotherapy, fewer RCTs have been carried out to evaluate pre-operative chemotherapy. Given the inconsistency of the results from the RCTs, at least 12 meta-analyses have been published. Most of these meta-analyses reported overall survival (OS) benefit with hazard ratios (HRs) in the range of 0.81 to 0.89 in favor of pre-operative chemotherapy. An individual patient data meta-analysis by Burdett in 2014 indicates that the option of pre-operative chemotherapy + surgery is associated with better OS (HR 0.87, 95% CI, 0.78-0.96, P=0.007) and recurrence-free survival (RFS) (HR 0.85, 95% CI, 0.76-0.94, P=0.002) survival for operable NSCLC when compared with treatment with surgery alone. Although the current consensus recommends the use of post-operative chemotherapy, pre-operative chemotherapy has equivalent efficacy. Both strategies should be regarded as the first choice treatment options. Despite Burdett's comment, indication of pre-operative chemotherapy for stage IA disease should be judged carefully.

Keywords: Adenocarcinoma; adjuvant chemotherapy; meta-analysis; randomized controlled trial (RCT); survival; systematic review

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Introduction

Primary lung carcinoma is currently the most common malignancy worldwide. Carcinoma from lung and bronchus is the leading cause of cancer death and new cancer cases for men. After breast cancer, it is also the most common cause of cancer death for women and the fourth highest cause of new cancer cases (1). In this article, we discuss treatments for non-small cell carcinoma (NSCLC) focusing on pre-operative chemotherapy.

The introduction of diagnostic immunohistochemical staining techniques and the establishment of examinations for genetic variants have led to huge changes in the classification scheme and subsequent treatment of NSCLC, since the publication World Health Organization pathologic criteria in 2004. Awareness of these changes in diagnostic criteria is essential to understand the evidence for peri-operative chemotherapy. First, the existence of two gene types is of considerable clinical importance for cases with adenocarcinoma as this predicts an excellent response to peri-oral molecular targeting therapies: the epidermal growth factor receptor (EGFR) mutations and the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) translocation (2). Second, the classification of adenocarcinoma by the International Association for the Study of Lung

Carcinoma provides new recommendations especially for adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA). AIS and MIA were both formerly named bronchioloalveolar carcinoma (3). If a patient with AIS or MIA undergoes curative resection, the patient has 100% or near 100% disease-specific survival (3).

Theoretical rationales relating to peri-operative chemotherapy

There are two options when conducting peri-operative chemotherapy: post-operative chemotherapy (adjuvant chemotherapy) or *t* pre-operative chemotherapy (neo-adjuvant chemotherapy) (4-13).

Patients with stage I, II, or IIIA NSCLC have substantial risk for recurrence even after complete curative surgical resection. This is mainly due to micrometastasis, which cannot be detected despite strenuous imaging studies preceding the surgery. The main purpose of both pre- and the post-operative chemotherapy is to eradicate micrometastasis. In addition, each of the peri-operative chemotherapies has its own particular theoretical rationales.

Post-operative chemotherapy

Only immediate surgery without pre-operative chemotherapy can provide precise pathological staging, because tumor shrinkage by pre-operative chemotherapy may result in underestimating the disease stage. Patients who undergo immediate surgery with post-operative chemotherapy have more chance to undergo surgery safely compared with enfeebled patients due to the pre-operative chemotherapy. If preoperative-chemotherapy is ineffective or only minimally effective, the delay in surgery can lead to the disease spreading (4-7).

Pre-operative chemotherapy

Cancer shrinkage of primary site and lymph node by pre-operative chemotherapy may make surgical resection easier. Pre-operative chemotherapy combined with radiotherapy might make possible the complete resection of a locally advanced cancer (i.e., down staging of stage IIIA-N2 and IIIB disease). Pre-operative chemotherapy may also prevent the spread of cancer cells during the surgery. Patients who undergo pre-operative chemotherapy have more chance of a safe outcome from systemic chemotherapy compared with patients who have already undergone surgery. Responsiveness to chemotherapy can be evaluated before surgery. In clinical settings, it may quicker to arrange chemotherapy than to arrange surgery. Therefore, arranging the operation during pre-operative chemotherapy is a reasonable choice to avoid possible delay of treatment (4,5,8,9).

Historical backgrounds of the peri-operative chemotherapy

Post-operative chemotherapy

The roll by the cytotoxic chemotherapy and its efficacy in the treatment of NSCLC was not clearly identified until the 1980s. Most first and second generation anti-cancer drugs evaluated in more than 20 randomized controlled trials (RCTs) did not contribute to the overall survival (OS) benefit. These medications frequently had trend toward harm especially when used for post-operative chemotherapy. However, the results of RCTs carried out in the 1980s constantly suggested benefit in the treatment of NSCLC from the use of cisplatin, the first platinum agent (6).

To our knowledge, the first RCT to evaluate the efficacy of post-operative chemotherapy using the cisplatin regimen for resectable NSCLC was reported by Sawamura in 1988 (10). Since 1988, increasing numbers of RCTs have been performed to evaluate the possible therapeutic value of post-operative chemotherapy using cisplatin. Although most of these studies did not show a statistically significant benefit individual study basis, the majority of the studies suggested trend toward benefit from the addition of post-operative chemotherapy to curative surgery (5-7).

Two very sizable RCTs, reported in 2004, had a considerable impact on the consensus for the treatment of resectable NSCLC (11,12). The largest trial ever conducted by Arriagada with 1,867 NSCLC patients concluded that cisplatin-based post-operative chemotherapy improved OS among patients with completely resected NSCLC with a hazard ratio (HR) of 0.86 [95% confidence interval (CI), 0.76-0.98, P<0.03] (11). In the same year, Kato published results of a RCT with 979 stage I adenocarcinoma cases. Post-operative chemotherapy with uracil-tegafur improved OS among patients with completely resected pathological stage I adenocarcinoma of the lung with HR of 0.71 (95% CI, 0.52-0.98, P=0.04). The subgroup analysis of Kato's study indicated that post-operative chemotherapy was not beneficial in T1N0M0 (tumor size <3 cm, stage IA according to tumor nodule metastasis classification 7th

edition) cases, but was of the great benefit in T2N0M0 cases (12). After the landmark publications by Arriagada and Kato, post-operative chemotherapy was accepted as part of the standard treatment for resectable NSCLC.

Further solid evidence supporting post-operative chemotherapy was provided by the Lung Adjuvant Cisplaitn Evaluation published in 2008 by Pignon (7). This individual patient data meta-analysis used data from five large-scale RCTs that compared surgery alone with the surgery plus cisplatin-based post-operative chemotherapy. In the meta-analysis of 4,584 patients with a median follow-up of 5.2 years, post-operative chemotherapy was associated with an improved OS with HR of 0.89 (95% CI, 0.82-0.96, P=0.005). Notably, this study suggested that post-operative chemotherapy might lead to a deterioration in the OS of stage IA (tumor size <3 cm) cases (HR 1.40, 95% CI, 0.95-2.06), although the treatment looked to be effective for stage IB-IIIA cases (7). The fact that post-operative chemotherapy was shown to have less benefit for stage IA disease (tumor size <3 cm) than stage IB disease is compatible with the observation in Kato's RCT (12). These observations are reasonable because cases with earlier stage NSCLC have a lower risk of micrometastasis and recurrence (7,12).

Pre-operative chemotherapy

Pre-operative chemotherapy is a relatively newer treatment strategy, as the word "neo-adjuvant (pre-operative)" chemotherapy clearly indicates in contrast with "adjuvant (post-operative)" chemotherapy. Compared with post-operative chemotherapy, fewer RCTs were conducted to evaluate the pre-operative chemotherapy (5,8,9). Some of these studies have suggested promising results. However, once the RCTs by Arriagada and Kato in 2004 had confirmed the benefit of post-operative chemotherapy, treatment by surgery alone was no longer ethically acceptable. As a result, two large scale RCTs were closed prematurely, these being the Southwest Oncology Group Trial S9900 (Pisters *et al.*) and Chest Investigators (Scagliotti *et al.*) (5,8,9). It should be emphasized that the two RCTs were not stopped because of any perceived ineffectiveness of pre-operative chemotherapy, but because surgery alone was seen as inferior to surgery plus post-operative chemotherapy. No clear evidence has suggested that pre-operative chemotherapy is inferior to post-operative chemotherapy.

Thereafter, to our knowledge, no new RCTs have been carried out to compare the surgery alone and the surgery plus pre-operative chemotherapy. However, the long-term follow-up results have been sporadically reported since 2004 (5,8,9). In addition, meta-analyses that evaluated survival benefits from the pre-operative chemotherapy have been reported almost annually since 2005 (8).

At least 12 meta-analyses have been published since the first one by Berghmans in 2005 (5,8). Most of these meta-analyses reported HRs for OS in the range of 0.81 to 0.89 in favor of pre-operative chemotherapy (5,8,9). Cumulative meta-analysis indicates that pre-operative chemotherapy plus surgery could provide OS benefit with HRs of around 0.85 since 2003 (8). Though the total sample size was has almost tripled from 1,312 by 2003 to 3,728 by 2012, RCTs after 2003 did not largely change the pooled HR (8).

Meta-analysis by Burdett [2014]

Burdett has reported four meta-analyses relating to pre-operative chemotherapy (8,9). Here we review the most recent meta-analysis published in 2014. This new meta-analysis confirmed the efficacy of pre-operative chemotherapy as suggested by the previous meta-analyses. However, this analysis has additional strengths. In particular, this is the only individual patient data meta-analysis and can therefore provide more solid evidence than an aggregate (summary data) meta-analysis (9).

The meta-analysis includes RCTs comparing the pre-operative chemotherapy plus surgery arm and the surgery-alone arm for resectable stage I-III NSCLC. RCTs that had planned to use post-operative radiotherapy in both arms, and/or post-operative chemotherapy in pre-operative arms were also considered eligible. Unpublished RCTs were also sought. No language restrictions were set.

The primary outcome was defined as the OS. The secondary outcomes included the recurrence-free survival (RFS), time to loco-regional recurrence, time to distant recurrence, complete resection rates, and short-time (six months) mortality. All analyses were done on an intention-to-treat basis. A two-stage fixed model was used for the meta-analysis (9).

The researchers identified 19 eligible RCTs, of which 17 were published and two were unpublished. After scrutinizing the 19 RCTs, 15 RCTs consisting of 2,385 patients were finally included for the analysis. Ten trials gave only pre-operative chemotherapy and five trials also used post-operative chemotherapy only for responders to pre-operative chemotherapy. Fourteen out of the 15 RCTs used

platinum-based chemotherapy; one used docetaxel alone. Eight RCTs used post-operative radiotherapy in both arms. Among the included patients with a median age of 62 years, 80% were men, 93% had stage IB-IIIA NSCLC, 50% had squamous cell carcinoma and 29% had adenocarcinoma. The median follow-up duration was six years. During the follow-up period, 1,427 deaths were observed (9).

The analysis indicated that patients treated with pre-operative chemotherapy had good OS with HR of 0.87 (95% CI, 0.78-0.96, P=0.007), which was almost equivalent to the improvement of the five year OS rate from 40% to 45%. Patients in every category were shown to gain a similar benefit from pre-operative chemotherapy. There was no clear interaction for improvement in OS with number of pre-operative chemotherapy cycles, the type of chemotherapy regimen, age, performance status, clinical stage, histological type, sex, or whether the chemotherapy was given only pre-operatively or both pre-operatively and post-operatively. However, adding post-operative chemotherapy for the responders might improve the survival (HR 0.78, 95% CI, 0.64-0.95, P=0.02). There was also no clear evidence of difference in effect of chemotherapy on survival by whether postoperative radiotherapy was used (interaction P=0.87) (9).

Pre-operative chemotherapy did not affect the six-month mortality rate (OR 0.88, 95% CI, 0.67-1.14, P=0.33) or the complete resection rate (OR 0.88, 95% CI, 0.68-1.14, P=0.33). There was a benefit from pre-operative chemotherapy for the RFS (HR 0.85, 95% CI, 0.76-0.94, P=0.002) and time to the distant recurrence (HR 0.69, 95% CI, 0.58-0.82, P<0.001). But no effect for the time to the loco-regional recurrence was clearly identified (HR 0.88, 95% CI, 0.73-1.07, P=0.20).

Discussion

Burdett's meta-analysis [2014] together with previously reported RCTs and meta-analyses has confirmed that pre-operative chemotherapy is an acceptable strategy for operable NSCLC (5-9). Nonetheless, we still have some unsolved problems relating to pre-operative chemotherapy.

Comparison between pre-operative and post-operative chemotherapy

A large number of trials have evaluated the efficacy of adding post-operative or pre-operative chemotherapy to radical resection for NSCLC, but there is limited data directly comparing pre- and post-operative chemotherapy. In a phase III trial by Felip, 624 patients with IB-IIIA NSCLC diseases were assigned to one of the three treatments: surgery alone, pre-operative chemotherapy plus surgery, or surgery plus post-operative chemotherapy, wherein the chemotherapy regimen was carboplatin paclitaxel. However, no difference in OS and disease-free survival (DFS) were seen (13).

In 2009, Lim conducted a systematic review and meta-analysis of RCTs to evaluate OS and indirectly compared the pooled HR for OS by both pre- and post-operative chemotherapy. The data were abstracted from 32 RCTs involving more than 10,000 participants. Twenty two trials administered post-operative and ten trials administered pre-operative chemotherapy. No differences were observed in OS and DFS between pre- and post-operative chemotherapy (5).

The individual patient data meta-analysis provided the most reliable evidence for this issue. As we commented in the previous section, Burdett's in 2014 meta-analysis indicated the benefit from pre-operative chemotherapy on OS with HR of 0.87 (95% CI, 0.78-0.96, P=0.007) and on RFS with HR of 0.85 (95% CI, 0.76-1.0.94, P=0.002) (9). Pignon also conducted an individual patient data meta-analysis. The results favored post-operative chemotherapy with HR for OS of 0.89 (95% CI, 0.82-0.96, P=0.005) and HR for DFS of 0.84 (95% CI, 0.78-0.91, P<0.001) (7). The two individual patient data meta-analyses yielded almost compatible HRs.

Even though post-operative chemotherapy is currently considered the standard treatment option for operable NSCLC, we believe that both pre-operative and post-operative chemotherapy should be the first choice options, as pre-operative chemotherapy can provide similar benefits for both OS and RFS/DFS. The head-to-head large-scale comparison to detect the OS difference between pre-operative and post-operative chemotherapy is interesting. But, it is practicable to detect such a small difference in a RCT.

Efficacy of pre-operative chemotherapy for stage IA NSCLC

Burdett stated that there was no interaction between the disease stage and the impact of pre-operative chemotherapy, and that pre-operative chemotherapy is applicable for operable NSCLC at any stage. However, we should consider carefully whether pre-operative chemotherapy is uniformly helpful for stage IA NSCLC cases. First of all, although Burdett's meta-analysis in 2014 tried to include

stage IA to IIIA NSCLC patients, only 134 out of 2,385 (6%) cases had stage IA disease (9). Thus internal validity for stage IA patients is questionable. In addition, most of the patients in the meta-analysis were recruited 10 to 20 years ago. Since then, there had been many developments concerning imaging, surgery procedures, and understanding of the pathology of early stage adenocarcinoma.

Recent advances in imaging and the surgery procedures have largely reduced the risk of post-operative recurrence. The necessity of pre-operative chemotherapy for stage IA disease may have decreased in line with this. Fluorodeoxyglucose positron emission tomography (FDG-PET), which was not usually available in the last century, is now easily available for daily clinical practice and provides more accurate clinical staging. FDG-PET is highly sensitive for both lymph node metastasis and distant metastasis (14). Therefore, appropriate use of FDG-PET preceding the surgery can almost prevent under-staging. Controversy surrounded the standard surgery procedure for stage IA NSCLC until the 1990s. In the era, surgeons tried to conduct a curative segmentectomy instead of a lobectomy. However, the current consensus is that the lobectomy is superior to the segmentectomy to control recurrence. This is because a lobectomy can decrease the risk of positive resection margins and because surgeons can approach N1 lymph node during the lobectomy (4,15). The appropriate selection of a lobectomy has also reduced the risk of recurrence in the stage IA disease.

Another problem is the heterogeneity of stage IA disease. Recent consensus is that stage IA (tumor size <3 cm with N0M0) NSCLC is not a uniform category in view of tumor size. Chang observed 10,761 stage IA NSCLC cases that underwent curative surgical resection. Patients with small tumor size (<2 cm) had better OS with HR of 0.83 when compared with patients with larger tumor size (2.1-3.0 cm) (16). Tumor, nodule, and metastasis classification 7th edition, adopted in 2009, subdivided the T_1 category into T1a (tumor size ≤2 cm) and T1b (tumor size >2 cm). T_{1a} cases may have less chance to benefit from pre-operative chemotherapy because they have less probability for recurrence. Stage IA adenocarcinoma is also heterogeneous in terms of histopathology. AIS and MIA were new categories added in International Association for the Study of Lung Carcinoma classification in 2009. They were formerly referred to as bronchioloalveolar carcinoma in the third edition of the World Health Organization classification (3). The number of patients diagnosed with these diseases is increasing due to lung cancer screening with computed tomography scans. AIS is defined as a small (≤3.0 cm) solitary adenocarcinoma with pure lepidic growth, lacking any invasion. If completely resected, patients with AIS have 100% disease-specific survival (3). Post-operative chemotherapy may be a choice for cases with ground glass nodules, if the histopathological examination of the surgical specimen suggests invasive adenocarcinoma. However, there is no reason to conduct pre-operative chemotherapy for patients with a small ground glass nodule that may be AIS.

The Lung Adjuvant Cisplatin Evaluation meta-analysis (Pignon *et al.*) and Kato's RCT suggested that cases with stage IA (tumor size <3 cm) NSCLC are less likely to benefit from post-operative chemotherapy (7,12). In general, the impact of pre-operative chemotherapy is equivalent to that of post-operative chemotherapy (5-9). The key advantage of pre-operative chemotherapy is the pre-operative tumor shrinkage that leads to better resectability (5,8,9). However, the stage IA disease is already easily resectable and patients have little to gain from pre-operative tumor shrinkage. Therefore, it is not easy to explain that only pre-operative chemotherapy is beneficial for stage IA disease.

The best chemotherapy regimen

The best chemotherapy regimen for pre-operative chemotherapy has not been clarified. Burdett's meta-analysis in 2014 did not find any difference in OS according to the chemotherapy regimen used (9). Furthermore, recently developed and excellent medications such as pemetrexed and bevacizmab were not evaluated (17), because the recruitment for the original RCTs included in the meta-analysis started prior to 2000.

The recommended regimen for post-operative chemotherapy may suggest hints for the regimen selection for a pre-operative chemotherapy regimen. The current consensus is that cisplatin should be included in post-operative chemotherapy regimen, but the best cisplatin regimen has not identified (4,6,7). For post-operative chemotherapy, the cisplatin plus vinorelbine regimen has the most sold evidence of being beneficial (7). However, no RCT has compared the efficacy of the different platinum-based chemotherapy regimens for post-operative chemotherapy. The efficacy of the third generation cytotoxic agent for inoperable advanced cases makes it plausible that the platinum-based doublet with one of the third generation cytotoxic agents is effective for peri-operative chemotherapy (17). Experts have different opinions for choice of regimen. While guidelines from the American Society of Clinical Oncology recommend a cisplatin

plus vinorelbine regimen (18), guidelines from the National Comprehensive Cancer Network recommend the use of the cisplatin-based doublet with one of the third generation cytotoxic agents (17). Some molecular targeted drug therapies were proved to aid survival in advanced inoperable adenocarcinoma. These include gefitinib, erlotinib, and afatinib for cases with the EGFR mutation positive NSCLC cases; and crizotinib for cases with EML4-ALK translocation (2,17). Thus, it may seem a reasonable option to use these molecular targeted drugs for peri-operative chemotherapy. Goss conducted a placebo-controlled RCT to evaluate the survival benefit of adding post-operative treatment with 250 mg gefitinib for completely resected stage IB, II or IIIA NSCLC cases (19). In the subgroup of 15 patients with positive EGFR mutation, the post-operative use of gefitinib was associated with trend for poor OS with HR of 3.16 (95% CI, 0.61-16.45, P=0.15) (19). It was surprising that post-operative treatment with gefitinib was related to a harmful trend even in the EGFR mutation-positive patients, though not conclusive due to very limited sample size. One possibility is that the EGFR pathway plays a less important role in early stage NSCLC (19). A phase III placebo-controlled RCT to evaluate the administration of erlotinib as the post-operative chemotherapy for 1,252 NSCLC cases is still ongoing. However, interim analysis did not indicate a promising result (20). Even in a subgroup of 161 EGFR mutation-positive patients, the post-operative use of erlotinib was not associated with improvement of OS (HR 1.09, 95% CI, 0.545-2.161, P=0.815) (20). The efficacy of using tyrosine kinase inhibitors for post-operative chemotherapy is not yet clear. However, very limited evidence by case report suggested the possibility that gefitinib may useful for preoperative down staging of bulky N2 cases (21).

To date, the best regimen for pre-operative chemotherapy is the cisplatin-based doublet with one of the third generation cytotoxic agents, even for EGFR mutation-positive cases. But further investigation of the regimen is anticipated. Studies focusing on pre-operative chemotherapy for non-squamous, or adenocarcinoma, are especially anticipated as recently developed agents were more effective for non-squamous diseases.

Conclusions

We reviewed an individual patient data meta-analysis by Burdett in 2014. This indicated that pre-operative chemotherapy improves OS (HR 0.87, 95% CI, 0.78-0.96, P=0.007) and RFS (HR 0.85, 95% CI, 0.76-0.94, P=0.002) for operable NSCLC compared with surgery alone. Although the current consensus recommends the use of post-operative chemotherapy, both strategies should be regarded as the first choice treatment options.

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