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Current state and prospect of the perioperative strategy for non-small cell lung cancer

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Abstract: This paper provides an overview of perioperative treatment for non-small cell lung cancer (NSCLC), including the current widespread use of cytotoxic anticancer agents, promising molecular targeted agents, and immuno-checkpoint inhibitors. Multiple clinical trials have confirmed that postoperative chemotherapy with cytotoxic anticancer agents should be given for stage IIB to III (according to the 8th edition of the TNM classification for NSCLC) if possible, and preoperative treatment also is recommended for patients with N2 or higher stage. However, advances in concurrent chemoradiotherapy are expected to change the significance of neoadjuvant therapy. Perioperative treatment with molecular targeted agents appears to extend disease-free survival, but there is currently no evidence that it can extend overall survival. Perioperative treatment with immune checkpoint inhibitors requires further evidence but is likely to be effective. Although perioperative treatment of NSCLC could be costly it continues to evolve in hopes of a cure.

***Keywords*:** postoperative, preoperative, chemotherapy, molecular targeted therapy, EGFR-TKI, immune-checkpoint inhibitor

Introduction

Perioperative chemotherapy has been used to improve the cure rate for non-small cell lung cancer (NSCLC) for some time, with many options emerging in recent years from the development of anticancer drugs.

This paper provides an overview of current widely used perioperative chemotherapy treatment (centered on cytotoxic anticancer agents) for NSCLC and the promising development of molecular-targeted drugs and immunotherapies.

Perioperative treatment with cytotoxic anticancer agents

The current common perioperative treatment strategy is chemotherapy with cytotoxic anticancer agents. Surgery is performed for early-stage and surgically resectable NSCLC because recurrent or inoperable NSCLC is quite difficult to cure. Unfortunately, although the 5-year survival rate is 80 to 90% for stage IA1 to IA3 disease in the 8th edition of the TNM staging system, stage IB or higher has a poorer outcome; with 70% for stage IB disease, 50 to 60% for stage II disease, and less than 50% for stage III disease (*1*). These survival rates, as a result of multidisciplinary treatment with cytotoxic anticancer agents, continues to improve. The rationale for these treatments had been tested in clinical trials, which use strategies to increase the possibility for the cure of entirely resectable NSCLC by adding systemic treatment before and after surgery. A typical clinical trial is shown in Table 1. The pooled meta-analysis found chemotherapy to be useful preoperatively and postoperatively (*2,3*); therefore, these are now established as standards of care.

First, we describe the postoperative treatment of chemotherapy with cytotoxic anticancer agents. A meta-analysis in 1995 suggested the use of cisplatin (CDDP) based regimens (*4*), and subsequent clinical trials showed an improvement in disease-free survival (DFS) (*5-7*). Then, a meta-analysis, Lung Adjuvant Cisplatin Evaluation (LACE), based on individual data from 4,584 patients showed that postoperative adjuvant chemotherapy prolonged 5-year survival (hazard ratio (HR) 0.89, 95% confidence interval (CI): 0.82-0.96) and subgroup analyses showed that the therapy was highly efficacious for stage II and stage III (TNM 7th edition, IIB to III in 8th edition) (*8*). Therefore, if possible, postoperative chemotherapy should be performed for stage IIB and stage III. For disease stages lower than IIB, there are still controversial studies showing the efficacy of postoperative chemotherapy. A Japanese clinical trial showed that tegafur/uracil was effective for lower stage disease (*9*), and it is often done as a standard of care in Japan. However, there is no international consensus for lower stage disease.

Table 1. Clinical trials of perioperative therapy using chemotherapy

Authors (*Ref.*)	Abbreviation of trials	Year	Stage*	Adjuvant/NeoAdjuvant	HR (of what)	Regimen
Wada *et al*. (*9*)	(Not applicable)	1996	I to III	Adjuvant	0.55 (OS)	Tegafur/Uracil
Arriagada *et al*. (*5*)	IALT	2004	I to III	Adjuvant	0.86 (OS) 0.83 (DFS)	CDDP base
Winton *et al*. (*6*)	JBR-10	2005	IB to II	Adjuvant	0.69 (OS) 0.60 (DFS)	CDDP + VNR
Douillard *et al*. (*7*)	ANITA	2006	IB to IIIA	Adjuvant	0.80 (OS)	CDDP + VNR
Strauss *et al*. (*12*)	CALGB 9633	2008	IB	Adjuvant	0.83 (OS)§	CBDCA + PTX
Felip *et al*. (*16*)	(Not applicable)	2010	IA to IIB or T3N1	Neoadjuvant	0.92 (DFS)‡ 0.96 (OS)	CBDCA + PTX
Scagliotti *et al*. (*15*)	ChEST	2012	IB to IIIA	Neoadjuvant	0.70 (PFS) 0.63 (OS)	CDDP + GEM

CBDCA, carboplatin; CDDP, cisplatin; DFS, disease-free survival; GEM, gemcitabine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel; VNR, vinorelbine. *Classification according to TNM 7th edition. §HR was not significantly different. However, there were significant differences in the subgroup analysis for tumors 4 cm or larger. ‡HR was not significantly different in both DFS and OS.

Table 2. Clinical trials of perioperative therapy using EGFR-TKI

Authors (*Ref.*)	Phase	Abbreviation of trials	Year	Stage*	HR (of what)	Regimen
Goss *et al*. (*18*)	III	CTSUBR19	2013	IB to IIIA	1.24 (OS)§ 1.22 (DFS)	gefitinib
Kelly *et al*. (*19*)	III	RADIANT	2015	IB to IIIA	0.61 (DFS)‡	erlotinib
Zhong *et al*. (*21*)	III	CTONG1104	2018	II to IIIA (N1-N2)	0.60 (DFS) 0.96 (OS)	gefitinib
Yue *et al*. (*23*)	II	EVAN	2018	IIIA	0.54 (DFS)	erlotinib
Wu *et al*. (*24*)	III	ADAURA	2020	IB to IIIA	0.20 (DFS)	osimertinib

DFS, disease-free survival; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; HR, hazard ratio; OS, overall survival. *Classification according to TNM 7th edition. §Only 15 patients (3.0%) with EGFR mutations were included. ‡A subset analysis of 161 patients (16.5%) with EGFR-positive mutations was provided.

In terms of the regimen of chemotherapy for the postoperative treatment, a subgroup analysis of LACE showed that CDDP + vinorelbine (VNR) was highly effective for 5-year survival benefits (HR 0.80, 95% CI: 0.70-0.91) (*10*). However, various other regimens have been studied, for example, CDDP + docetaxel (DTX) (*11*) and carboplatin (CBDCA) + paclitaxel (PTX) (*12*). Although the CBDCA-based regimen may be appropriate for patients who cannot tolerate CDDP, the risks and benefits of chemotherapy for those patients should be considered. In elderly patients, for example, the effect of postoperative chemotherapy is reduced after five years (*13*).

A meta-analysis of preoperative treatment showed that this prolonged overall survival (OS) compared with surgery alone (*2*). Besides, preoperative chemotherapy and postoperative chemotherapy are equally effective (*14*). However, the early establishment of postoperative chemotherapy led to early discontinuation of many preoperative clinical trials thereby limiting evidence. Moreover, due to the evolution of chemoradiation therapy, preoperative chemotherapy is used less frequently in clinical practice. Also, two study results suggested that the effect of preoperative chemotherapy is poorly efficacious for the N0 and N1 stage. Those two results were the subgroup analysis of stage IB to IIA (TNM 7th edition, IB to IIB in 8th edition), in other words, stage N0 and N1 in the phase III study using CDDP + gemcitabine (GEM); the ChEST study (HR for OS 1.02, 95% CI: 0.58-1.19) (*15*) and the results of the phase III study which excluded N2 and used CBDCA + PTX (HR for disease-free survival (DFS) 0.92, 95% CI: 0.81-1.04) (*16*) .

On the other hand, in N2 or higher stage patients, the subgroup analysis of stage IIB to IIIA (TNM 7th edition, IIB to IIIB in 8th edition) in the ChEST trial (*15*) showed improved overall survival compared with surgery alone (HR for OS 0.42, 95% CI: 0.25-0.71). However, as we mentioned before, according to the development of chemoradiation therapy such as intensity-modulated radiation therapy, as well as the effectiveness of consolidation therapy following chemoradiation therapy in patients with unresectable stage III lung cancer treated with durvalumab (the PACIFIC study) (*17*), the usefulness of preoperative chemotherapy in patients with N2 or higher stage should be reviewed in future.

Perioperative treatment with molecular targeted agents

The best-tested molecular targeted agent for perioperative use is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (EGFR-TKI). Since EGFR-TKI was first developed as a molecular targeting agent for advanced NSCLC, the efficacy of perioperative treatment with EGFR-TKI has been studied as well as cytotoxic anticancer agents (Table 2). The CTSUBR19

study, which compared gefitinib with placebo as a postoperative treatment, failed to show an improvement in OS (HR for OS 1.24, 95% CI: 0.94-1.64), and the trial was stopped early (*18*). Similarly, the RADIANT study, in which patients were treated with erlotinib, failed to show prolongation of DFS (*19*). However, because the discovery of EGFR-sensitive mutations (*20*) occurred after design and conduct of these studies, they were not performed using appropriate patients. Specifically, the CTSUBR19 study included only 15 patients with EGFR-sensitive mutations, and the RADIANT study included only 16.5% (161 patients) of the total, so it cannot be interpreted literally. For reference, a subgroup analysis of positive patients with EGFR-sensitive mutations in the RADIANT study showed prolonged DFS (HR for DFS 0.61, 95% CI: 0.38-0.98).

Subsequently, several trials compared EGFR-TKI with cytotoxic anticancer agents as a postoperative treatment in patients with EGFR-sensitive mutations. The CTONG1104 trial comparing gefitinib with chemotherapy also showed an increase in DFS (HR for DFS 0.60, 95% CI: 0.42-0.87) (*21*) but no improvement in OS (*22*). A similar trend was seen in the EVAN trial, a phase II trial comparing erlotinib with chemotherapy (*23*). In June 2020, the phase III double-blinded randomized trial of osimertinib, the ADAURA trial, showed a more significant effect on DFS (HR for DFS 0.20, 95% CI: 0.14 to 0.30) compared with placebo (*24*). This trial was unblinded early because the results were more positive than anticipated, with expectations of a similar effect for OS. However, at present, EGFR-TKI only prolongs DFS in perioperative chemotherapy, with no evidence that it prolongs OS. Current knowledge suggests that it is necessary to consider the pros and cons of extending only the DFS in regard of medical-economic issues.

As of September 2020, the only ongoing perioperative treatment trials, involve the use of other molecular targeted agents. We look forward to these future reports. The ALCHEMIST trial (NCT02201992) and the ALINA trial (*25*) for patients with ALK mutations, and a phase II trial to confirm the safety of a perioperative treatment, including patients with ROS1, NTRK, and BRAF mutations, are ongoing (NCT04302025).

Perioperative treatment with an immune checkpoint inhibitor

Perioperative therapies using immune checkpoint inhibitors (ICI) are likely to better develop in the future, but unfortunately, they are only investigational at present. ICI have been used in many different ways in advanced NSCLC, including single-agent therapy, combined use with another ICI, and combined chemotherapy use. Therefore, even in perioperative therapies, ICI have been extensively studied in many strategies as in the advanced NSCLC setting. Only representative trials are listed in Table 3. The rationale for perioperative treatment with ICI is characterized by preoperative treatment, which is essentially tumor-rich, to obtain lymphocyte aggressiveness for cancer.

The first reported article was a retrospective analysis of the TOP1201 study by Yang and colleagues. In this paper, they retrospectively analyzed a phase II trial of the anti-CTLA-4 antibody, ipilimumab, plus chemotherapy before or after surgery, and reported that the addition of immunotherapy did not significantly alter safety (*26*). Forde and colleagues reported preoperative immunotherapy with nivolumab, an anti-PD-1 antibody, in a pilot study. There were no significant safety issues, and 45% achieved a major pathological response (MPR) (*27*). In the same year, previous results from the NEOSTAR study (*28*), a preoperative phase II study of nivolumab plus ipilimumab, and results from the MK3475-223 study (*29*), a phase I study of pembrolizumab, were reported, both of which had similar safety and MPR values of 20-30%. Other Phase II and Ib studies of various drugs (atezolizumab and durvalumab, an anti-PD-L1 antibody, and sintilimab, a recently emerging anti-PD-1 antibody) in combination with chemotherapy have been reported, all of which have shown similar results (*30-32*).

The final contribution to survival by immunotherapy in perioperative treatment awaits the results of ongoing phase III trials, which may affect long-term prognosis considering the efficacy of immunotherapy in advanced NSCLC. On the other hand, anticancer therapy after relapse for NSCLC has progressed steadily, so it is expected that it will need a very long period to evaluate preoperative treatment by use of OS. Therefore, event-free survival (EFS) and DFS are primary endpoints in many developing clinical trials. However, a certain degree of caution should be exercised in interpreting the results because it may prolong DFS only as described in the EGFR-TKI chapter. Besides, unlike molecular targeted agents, because ICI and chemotherapy are relatively non-selective drugs, many people are likely to benefit from them. However, ICIs are costly so medical and economic issues need to be considered more carefully.

Conclusion

We described the current evidence and prospects for perioperative therapy in treating NSCLC. First, standard postoperative chemotherapy with cytotoxic anticancer agents should be given for stage IIB to III if possible, and preoperative treatment is recommended for patients with N2 or higher disease. However, advances in chemoradiotherapy can be predicted to change the significance of preoperative therapy. Although perioperative therapy with molecular targeted agents, including osimertinib, appears efficacious for DFS, effective for OS remains unknown. Perioperative treatment with ICI requires further investigation of

Table 3. Clinical trials of perioperative therapy using ICI

Authors (*Ref.*)	Abbreviation of trials	Phase	Trial number	Status*	Stage	Result‡	Regimen
Bott *et al*. (*34*)	NA_00092076	I	NCT02259621	Recruiting	I to IIIA§	MPR 45%	Nivo
Forde *et al*. (*27*)	NA_00092076	II	NCT02259621	Recruiting	I to IIIA§	MPR 45%	Nivo
Cascone *et al*. (*28*)	NEOSTAR	II	NCT03158129	Recruiting	I to IIIA§	MPR 24%	Nivo or Nivo + Ipi
Yang *et al*. (*26*)	TOP1201	II	NCT01820754	Completed	IB to IIIA§	Equivalent in safety	Ipi + CDDP or CBDCA + PTX
Zinner *et al*. (*35*)	(NA)	II	NCT03366766	Active, not recruiting	IB to IIIA§	MPR 46%	Nivo + CDDP + PEM or Nivo + CDDP + GEM
Chaft (*36*)	ANVIL	III	NCT02595944	Active, not recruiting	IB to IIIA§	DFS, OS	Nivo
Forde *et al*. (*37*)	Checkmate 816	III	NCT02998528	Active, not recruiting	IB to IIIA§	MPR	Nivo
Bristol-Myers Squibb (*38*)	(NA)	III	NCT04025879	Recruiting	IIA to IIIB	EFS	Nivo + platinum-based doublet chemotherapy
Ben Nun *et al*. (*29*)	MK3475-223	I	NCT02938624	Recruiting	I to II§	MPR 33%	Pembro
Paz-Ares *et al*. (*39*)	PEARLS	III	NCT02504372	Active, not recruiting	IB to IIIA§	DFS	Pembro
Fernando *et al*. (*40*)	KEYNOTE-671	III	NCT03425643	Recruiting	IIB to IIIA	EFS, OS	Pembro + CDDP + PEM or Pembro + CDDP + GEM
Sands *et al*. (*41*)	ALCHEMIST	III	NCT02194738	Recruiting	IB to IIIA§	DFS	Pembro ± platinum-based doublet chemotherapy
Kwiatkowski *et al*. (*30*)	LCMC3	II	NCT02927301	Active, not recruiting	IB to IIIB§	MPR 18%	Atezo
Hoffmann-La Roche (*42*)	IMpower010	III	NCT02486718	Active, not recruiting	IB to IIIA§	DFS	Atezo
Hoffmann-La Roche (*43*)	IMpower030	III	NCT03456063	Recruiting	IIA to IIIB	MPR, EFS	Atezo+ platinum-based doublet chemotherapy
Rothschild *et al*. (*31*)	SAKK 16/14	II	NCT02572843	Active, not recruiting	IIIA§	1-yr EFS 73.3%	Durva
Heymach (*44*)	AEGEAN	III	NCT03800134	Recruiting	IIA to IIIB	MPR, EFS	Durva+ platinum-based doublet chemotherapy
Peters (*45*)	MERMAID-1	III	NCT04385368	Recruiting	II to III	DFS	Durva+ platinum-based doublet chemotherapy
Gao *et al*. (*32*)	(NA)	IB	ChiCTR-OIC-17013726	Not yet recruiting	IA to IIIB	MPR 40.5%	Sintilimab

Atezo, atezolizumab; CBDCA, carboplatin; CDDP, cisplatin; DFS, disease-free survival; Durva, durvalumab; EFS, event free survival; GEM, gemcitabine; ICI, immune checkpoint inhibitor; Ipi, ipilimumab; MPR, major pathological response; NA, not applicable; Nivo, nivolumab; OS, overall survival; PEM, pemetrexed; Pembro, pembrolizumab; PTX, paclitaxel. *As of November, 2020. §Classification according to TNM 7th edition, the others according to 8th edition. ‡Important results were described for those reported, and primary end points were described for those not reported.

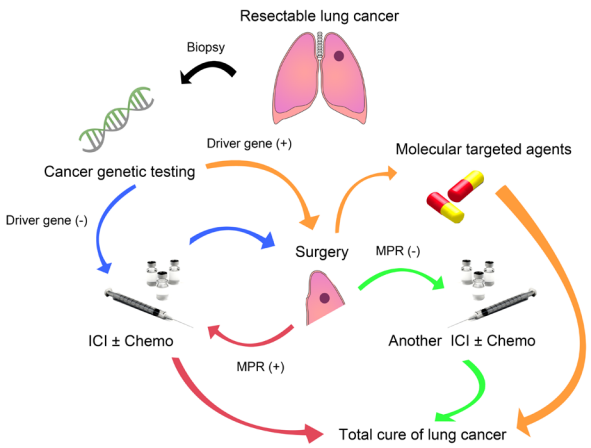

Figure 1. Possible future treatment of resectable lung cancer. This figure is a schematic view of our consideration for future resectable lung cancer treatment. Genetic testing of the biopsy specimen determines the presence of a driver gene. If not, ICI ± Chemotherapy is used as preoperative therapy. Subsequent surgery confirms the pathologic response, followed by postoperative chemotherapy with the same regimen as preopartive if there is a response, or a change in the regimen if there is no response. No preoperative treatment is given if the driver gene is present, and molecular targeting is introduced into the postoperative treatment. These strategies will be used to achieve a total cure for lung cancer. ICI, immune checkpoint inhibitor; Chemo, chemotherapy; MPR, major pathological response.

the evidence, but is likely to be effective and may be a promising method. Based on these findings, we show a schematic diagram of future operable lung cancer treatment in Figure 1. Preoperative biopsy should be performed to confirm the presence or absence of mutations in the driver gene, and if present, treatment with molecular targeted agents should be performed after surgery. If not, ICI ± chemotherapy should be performed before surgery, and if a pathological response is not confirmed, a switch should be made to another postoperative treatment. Such a strategy may reduce postoperative recurrence and increase the chances of cure. Although there are various difficulties, perioperative treatment continues to evolve toward a cure for NSCLC.

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