〈Review〉

Perioperative therapy for non-small cell lung cancer - Current status and future perspective -

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ABSTRACT Lung cancer is the leading cause of cancer-related death. Surgery has been playing a pivotal role in the treatments with curative intent for non-small cell lung cancer (NSCLC). However, the outcome after surgery alone remains unsatisfactory. During the last two decades, several attempts have been made to improve the postoperative outcome. Meta-analysis demonstrated that adjuvant cisplatin-based chemotherapy achieved 4-5% of benefit in the 5-year survival as compared to surgery alone. Preoperative induction chemotherapy also yielded a 5% improvement of the 5-year survival rate, showing a similar efficacy with adjuvant chemotherapy. Induction chemoradiotherapy enhanced local control, whereas it was not associated with any survival benefit. Recently, the development of new drugs, such as tyrosine kinase inhibitors and immune checkpoint inhibitors, represents a major treatment advance for patients with lung cancer. Several attempts have been made to apply these drugs to perioperative treatments.

In this review, we sought to summarize the developments of perioperative therapy in the treatments of NSCLC, and discuss the future perspectives.

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INTRODUCTION

Lung cancer remains the leading cause of cancer-related death worldwide. In Japan, more than 73000 people died of lung cancer in 2016. Non-small cell lung cancer (NSCLC) accounts for about 85% of all cases of lung cancer. A survey conducted by the Japanese Lung Cancer Registry showed that the postoperative survival rates of patients with NSCLC had improved over the last few decades, with the current 5-year survival rate of 82.0% in clinical stage IA patients and 63.4% in clinical stage IB patients[1)]. These improvements are thought to be due to improvements in the treatments and perioperative management techniques, and stage

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migration with radiological advances. However, the postoperative outcomes in patients with locally advanced NSCLC still remains unsatisfactory, with a current 5-year survival rate of 43.3% in clinical stage IIIA patients[1]. Recurrence in distant organs is reported as the most common pattern of recurrence after complete resection in patients with locally advanced NSCLC[2-4]. During the last two decades, several attempts have been made to improve the postoperative outcomes in patients with NSCLC. In this review, we present an overview of the current status and future perspectives of the post and preoperative treatments for NSCLC.

Adjuvant Chemotherapy for Completely Resected Locally Advanced NSCLC

In 1995, the Non-small Cell Lung Cancer Collaborative Group reported the efficacy of adjuvant chemotherapy after complete resection in patients with NSCLC[5]. This meta-analysis, which included 14 trials and 4357 patients, demonstrated that cisplatin-based adjuvant chemotherapy yielded a 5% survival benefit at 5 years, although the difference was not significant, with a hazard ratio (HR) of 0.87 (P = 0.08).

In 2004, the International Adjuvant Lung Cancer Trial (IALT) showed, for the first time, a significant improvement in the postoperative survival associated with cisplatin-based adjuvant chemotherapy as compared to surgery alone[6]. In this study, patients with pathological stage I to III NSCLC were randomly assigned to the cisplatin-based adjuvant chemotherapy or surgery alone group. The treatment offered a 4% benefit in the 5-year survival rate (44.5% in the chemotherapy group vs. 40.4% in the control, surgery-alone group) and the HR was 0.86 (95% CI, 0.76 to 0.98, $p < 0.03$).

After this milestone trial, results of important studies were published in succession (Table 1). The JBR.10 trial compared the benefit of adjuvant vinorelbine plus cisplatin therapy as compared to surgery alone in patients with stage IB or stage II NSCLC[7]. The overall survival was significantly better in the group that received adjuvant chemotherapy, with a 15% advantage in the 5-year survival rate (69% vs. 54%, p = 0.03). The Adjuvant Nabelbine International Trialist Association (ANITA) study compared the benefit of adjuvant vinorelbine plus cisplatin therapy over observation alone in patients with completely resected stage IB-IIIA NSCLC[8]. The median survival time was 65.7 months in the adjuvant chemotherapy group and 43.7 months in the observation alone group, with

Table 1. Results of phase III trials of adjuvant chemotherapy

Study	Stage	No. of patients	Adjuvant intervention	Outcome		p
ALPI[9](2003)	I – IIIA	1209	MVP observation	Median Survival	55.2mo 48mo	0.589
Big Lung Trial[10](2004)	I – III	381	CDDP-based observation	Median Survival	33.9mo 32.6mo	0.9
IALT[6](2004)	I – III	1867	CDDP-based observation	5-year OS	44.5% 40.4%	< 0.03
Kato, *et al.*[17](2004)	I (Ad)	999	UFT observation	5-year OS	88% 85%	0.047
JBR.10[7](2005)	IB – II	482	CDDP+VNR observation	5-year OS	69% 54%	0.03
ANITA[8](2006)	IB – IIIA	840	CDDP+VNR observation	Median Survival	65.7mo 43.7mo	0.017
CALGB9633[21] (2008)	IB	344	CBDCA+PAC observation	Median Survival	98mo 78mo	0.125

Abbreviations: Ad, adenocarcinoma; MVP, mitomycin + vindesin + cisplatin; CDDP, cisplatin; UFT, uracil-tegafur; VNR, vinorelbine; CBCDA, carboplatin; PAC, paclitaxel; OS, overall survival

a HR of 0.80 (95% CI, 0.66 to 0.96, p = 0.017); adjuvant chemotherapy offered a survival benefit of 8.6% at 5 years. On the other hand, the Adjuvant Lung Cancer Project Italy (ALPI) study[9] and the Big Lung Trial[10] failed to demonstrate any benefit of adjuvant chemotherapy after surgical resection in patients with NSCLC.

Following these conflicting results, two meta-analyses were conducted. The Lung Adjuvant Cisplatin Evaluation (LACE) analysis, which analyzed the results of the IALT, JBR.10, ANITA, ALPI, and Big Lung Trial, revealed a 5.4% benefit in the 5-year survival rate of adjuvant cisplatin-based chemotherapy, with a HR of 0.89 (95% CI, 0.82 to 0.96, p = 0.005)[11]. The NSCLC Meta-analyses Collaborative Group conducted a meta-analysis of the results of 34 trials including 8447 patients to compare the survival outcomes of surgery plus chemotherapy with those of surgery alone[12]. The results showed a 4% benefit in the 5-year survival of surgery plus chemotherapy as compared to surgery alone, with a HR of 0.86 (95% CI, 0.81 to 0.92, p < 0.0001). The results of these meta-analyses established the efficacy of adjuvant chemotherapy following complete resection in patients with NSCLC, with a 5-year survival benefit of 4-5%, which was similar to the result of the Non-small Cell Lung Cancer Collaborative Group published in 1995.

Some studies have also reported the long-term effects of adjuvant chemotherapy. In the IALT study, cisplatin-based adjuvant chemotherapy yielded a survival benefit over a median follow-up of 7.5 years, but the difference in the outcomes was not statistically significant (HR 0.91: 95% CI, 0.81 to 1.02, p = 0.10)[13]. On the other hand, in JBR.10, a significant survival benefit of adjuvant vinorelbine plus cisplatin continued to be observed after a median follow-up of 9.3 years (HR 0.78: 95% CI, 0.61 to 0.99, p = 0.04)[14].

As for the chemotherapy regimen, the LACE study demonstrated that cisplatin plus vinorelbine was marginally more effective than other drug regimens. A search for the optimal regimen is still ongoing. The E1505 trial was conducted to investigate the effect of addition of bevacizumab to cisplatin-based chemotherapy[15]. A total of 1501 patients with completely resected stage IB (tumor larger than 4 cm) -stage IIIA NSCLC were assigned to the cisplatin-based chemotherapy group or the cisplatin-based chemotherapy plus bevacizumab group. The choice of chemotherapeutic agents administered in combination with cisplatin was left to the investigators' choice (vinorelbine, docetaxel, gemcitabine, or pemetrexed). The results showed that addition of bevacizumab had no effect of improving the overall survival (HR 0.99: 95% CI, 0.82 to 1.19, p = 0.90). The JIPANG study is an ongoing study being conducted to evaluate the efficacy of pemetrexed plus cisplatin, as compared to that of vinorelbine plus cisplatin, in patients with completely resected stage II-IIIA non-squamous NSCLC[16]. A total of 800 patients were enrolled and are now being followed-up.

In conclusion, although adjuvant chemotherapy for completely resected locally advanced NSCLC appears to be beneficial, the survival benefit is not sufficient and the long-term efficacy remains controversial. Furthermore, the ideal chemotherapy regimen is also still under investigation.

Adjuvant Chemotherapy for Early-Stage NSCLC

In contrast to the case for locally advanced NSCLC, the efficacy of adjuvant chemotherapy for completely resected T1N0M0 NSCLC still remains under debate.

In 2004, postoperative adjuvant chemotherapy with uracil-tegafur was reported to offer significant survival benefit for patients with pathological stage I lung adenocarcinoma[17]. In this study, 999 patients with stage I (T1N0M0 or T2N0M0) adenocarcinoma were randomly assigned to oral uracil-tegafur

therapy given twice daily for two years, or observation alone. The 5-year survival rate was significantly better in the uracil-tegafur group (HR 0.71: 95% CI, 0.52 to 0.98, p = 0.04), with the 3% benefit in the 5-year survival rate (88% in the uracil-tegafur group vs. 85% in the observation alone arm). However, a subgroup analysis revealed that the survival benefit was seen only in patients with T2 disease (tumors larger than 3 cm in diameter) (HR 0.48: 95% CI, 0.29 to 0.81, p = 0.005), with no difference seen in those with T1 disease (HR 0.97: 95% CI, 0.64 to 1.46, p = 0.87). A meta-analysis of 6 studies including 2003 patients revealed that adjuvant uracil-tegafur therapy was associated with a significantly improved 5-year overall survival rate as compared to surgery alone (HR 0.74: 95% CI, 0.61 to 0.88, p = 0.001)[18]. The 5-year survival rate in the uracil-tegafur group was 4.6% higher than that in the observation group (81.8% vs. 77.2%). Notably, a subset analysis in this meta-analysis demonstrated the survival benefit of uracil-tegafur therapy even in patients with T1 disease (HR 0.73: 95% CI, 0.56 to 0.93). As for the influence of the histologic type, the outcome of uracil-tegafur therapy was also favorable in patients with squamous cell carcinoma (HR 0.82: 95% CI, 0.57 to 1.19). Another meta-analysis of the same 6 studies showed that uracil-tegafur therapy significantly improved the postoperative survival in patients with T1 tumors larger than 2 cm in diameter (HR 0.62: 95% CI, 0.42 to 0.90, p = 0.011), but not in patients with T1 tumors smaller than 2 cm in diameter (HR 0.84: 95% CI, 0.58 to 1.23, p = 0.37)[19]. Based on these lines of evidence, postoperative adjuvant uracil-tegafur therapy is recommended in Japan for patients with T1 tumors larger than 2 cm in diameter. Recently, the Japan Clinical Oncology Group (JCOG) conducted a trial comparing uracil-tegafur with S-1, an oral agent consisting of tegafur and gimeracil, for patients with stage I NSCLC. Enrollment has been completed, and the results are awaited.

As for platinum-based chemotherapy, Cancer and Leukemia Group B (CALGB) Protocol 9633 was a study conducted to investigate the efficacy of paclitaxel plus carboplatin as postoperative adjuvant chemotherapy for patients with NSCLC[20]. A total of 344 patients with T2N0M0 Stage IB NSCLC were randomized to adjuvant paclitaxel plus carboplatin therapy, or observation alone. The preliminary result, obtained after a median follow-up of 34 months, showed that the 4-year overall survival in the paclitaxel plus carboplatin group was significantly better than that in the observation alone group (71% vs. 59%)[20]. However, the survival difference was no longer statistically significant after a long-term median follow-up period of 74 months (HR 0.83: 95% CI, 0.64 to 1.08, p = 0.12)[21]; on the other hand, an exploratory analysis in this study demonstrated that the outcome in the chemotherapy group was more favorable in patients with tumors ≧ 4 cm in diameter (HR 0.69: 95% CI, 0.48 to 0.99, p = 0.043).

JBR.10 and ANITA were also trials including patients with stage IB disease. In JBR.10, adjuvant vinorelbine plus cisplatin showed a significant survival benefit in patients with stage II NSCLC, whereas no benefit was noted in patients with stage IB disease (HR 1.03: 95% CI, 0.70 to 1.52, p = 0.87)[14]. Even in stage IB patients with tumors ≧ 4 cm in diameter, no significant benefit was observed in the chemotherapy group (HR 0.66: 95% CI, 0.39 to 1.14, p = 0.133). In the ANITA study also, which included patients with stage IB-IIIA disease, a subset analysis revealed the absence of any survival benefit of chemotherapy in patients with stage IB disease (HR 1.10: 95% CI, 0.76 to 1.57)[8]. Considering these results, it could be concluded that the efficacy of postoperative adjuvant chemotherapy with a platinum-based regimen for patients with stage IB disease remains unconfirmed yet. Several studies have suggested that some

clinicopathological factors, including the tumor size[21], tumor histology[22], presence/absence of lymphovascular invasion[23, 24], and presence/absence of pleural invasion[25], could be useful for selecting suitable candidates for postoperative adjuvant chemotherapy among patients with resected early NSCLC. However, further study is warranted to confirm these results.

Customized Chemotherapy with Biomarkers

Although the efficacy of adjuvant chemotherapy for NSCLC has been confirmed, the survival benefit remains far from satisfactory. In 2006, the IALT Bio study suggested that the excision repair cross-complementation group 1 (ERCC1) could be a predictive biomarker to select suitable candidates for cisplatin-based chemotherapy[26]. ERCC1 is thought to be one of the nucleotide excision repair factors, which remove cisplatin-induced DNA adducts, inducing resistance to cisplatin-based chemotherapy. In this study, paraffin-embedded tumor samples of 761 patients enrolled in the IALT were subjected to immunostaining for ERCC1 protein. While the overall survival was significantly better in the chemotherapy group than in the surgery alone group among the patients with ERCC1-negative tumors, (HR 0.65: 95% CI, 0.50 to 0.86, p = 0.002), no such difference in the survival between the two groups was observed among the patients with ERCC1-positive tumors (HR 1.14: 95% CI, 0.84 to 1.55, p = 0.40). This study concluded that patients with ERCC1-negative tumors were probably better candidates for cisplatin-based adjuvant chemotherapy than those with ERCC1-positive tumors.

Since then, several studies have attempted to confirm this result. However, the results are conflicting[27–31]. As possible reasons for this inconsistency, Friboulet *et al*. pointed out that the ERCC1 gene generates four isoforms, and that the available antibodies used for the detection of ERCC1 expression cannot precisely identify the functional ERCC1 isoform[32]. A meta-analysis suggested that high ERCC1 expression might be adversely related to the efficacy of platinum-based chemotherapy[33], but definitive evidence is lacking. The International Tailored Chemotherapy Adjuvant (ITACA) trial was a randomized controlled study performed to validate the efficacy of biomarker-based customized adjuvant chemotherapy[34]. In the experimental arm of this study, chemotherapy regimens were determined according to the ERCC1 and thymidylate synthase (TS) messenger RNA expression levels. Patient enrolment was completed in 2014, and the final results of the trial are awaited.

Other biomarkers which have been expected to be useful predictors of the responses to certain chemotherapies are RRM1 for gemcitabine[35, 36] and class III β-tubulin for the taxanes[37, 38]. However, the results are again conflicting. At present, customized chemotherapy according to predictive biomarkers is not yet possible in clinical practice.

Postoperative Radiotherapy

In 1998, the PORT Meta-analysis Trialists Group demonstrated that postoperative radiotherapy after complete resection was associated with an adverse effect on the survival in patients with NSCLC (HR 1.21: 95% CI, 1.08 to 1.34), based on the analyses of 2128 individual patient data from 9 randomized studies[39]. According to this analysis, for patients with N0-1 disease, postoperative radiotherapy was associated with a worsened survival, as compared to surgery alone. On the other hand, the survival was equivalent between the two groups in patients with N2 disease. At the time when this analysis was reported, the results were criticized, because it included studies that employed outdated radiation techniques or inadequate radiation regimens. As for pN2 disease, Douillard *et al*. reported the improved survival in the patients who received PORT compared with that in the patients who did not in

the retrospective study of ANITA trial[40].

In 2016, the meta-analysis was updated and was conducted based on 14 randomized controlled trials that used the latest radiological techniques, including 2343 patients[41]. The results again showed a significant adverse effect of postoperative radiotherapy on the overall survival (HR 1.18: 95% CI, 1.07 to 1.31, p = 0.001). Locoregional recurrence-free survival was also significantly inferior in the adjuvant radiotherapy group (HR 1.12: 95% CI, 1.01 to 1.24, p = 0.03). No difference was noted depending on the nodal status.

These results suggested that postoperative radiotherapy after complete resection had a detrimental effect on the survival in patients with NSCLC. However, for N2 disease, the ongoing Lung ART trial, which is a randomized study targeted at patients with N2 disease, is expected to clarify the effect of adjuvant radiotherapy.

Induction Chemotherapy

During the 1990s, epoch-making results of three phase III trials were reported, which suggested the effectiveness of induction chemotherapy for NSCLC. In 1992, Pass *et al*. reported a more favorable median survival associated with preoperative chemotherapy with etoposide/cisplatin as compared to that with surgery alone in 27 patients with stage IIIA NSCLC (p = 0.095)[42]. Rosell *et al*. compared preoperative chemotherapy using mitomycin/ifosfamide/cisplatin with surgery alone in 60 patients with stage IIIA NSCLC. Each of the treatment arms included postoperative radiation. The median survival was 26 months in the induction arm and 8 months in the non-induction arm (p < 0.001)[43]. The study of Roth *et al*., in which preoperative cyclophosphamide/etoposide/cisplatin therapy was compared with surgery alone in 60 patients with stage IIIA NSCLC, the median survival was 64 months in the induction arm vs. 8 months in the surgery alone arm (p < 0.008)[44]. These results indicate the efficacy of induction chemotherapy for locally advanced NSCLC, however, some concerns were pointed out, including the small sample size and the poorer than expected outcome in the surgery alone group.

Thereafter, several randomized trials have been conducted. In 2014, the NSCLC Meta-analysis Collaborative Group conducted a systematic review and meta-analysis of individual participant data of 15 randomized trials including 2385 patients[45]. The results revealed a significant survival benefit of preoperative chemotherapy as compared to surgery alone (HR 0.87: 95% CI, 0.78 to 0.96, p = 0.007). There was a 5% improvement of the 5-year survival rate, with a 13% reduction in the relative risk of death. Notably, this benefit of 5% was seen from stage IB through stage III. The chemotherapy regimen, whether cisplatin-based or carboplatin-based, has no influence on the results.

Based on these results, induction chemotherapy has come to be recognized as one of the treatment strategies for locally advanced NSCLC.

Induction Chemotherapy vs. Adjuvant Chemotherapy

The Neoadjuvant versus Adjuvant Taxol/Carbo Hope (NATCH) trial was the first randomized controlled trial to directly compare the benefits of induction chemotherapy with those of adjuvant chemotherapy[46]. A total of 624 patients with stage IA (tumor at least 2 cm in diameter), IB, II, or IIIA (T3N1) NSCLC were randomly assigned to the surgery alone group, the adjuvant therapy group, or the induction chemotherapy group. The chemotherapy regimen used in the adjuvant and induction therapy groups were 3 cycles of paclitaxel and carboplatin. The results showed that there were no significant differences in the 5-year overall survival rates among the three groups, with the rates being 46.6%, 45.5%, and 44.0% in the induction, adjuvant, and surgery alone arms, respectively.

These unexpected results were likely attributable to the fact that more than 70% of the enrolled patients had stage IA disease. In terms of the tolerability, the chemotherapy was better tolerated in the induction therapy arm. A larger number of patients allocated to the induction arm underwent planned chemotherapy as compared to those in the adjuvant arm (97% vs. 66.2%, $p < 0.0001$).

A systematic review of 32 randomized trials demonstrated that the relative hazards of the adjuvant chemotherapy as compared to induction therapy was 0.99 (95% CI, 0.81 to 1.21, $p = 0.91$)[47]. This review had the limitation that the study was made with the indirect comparison including the relatively small studies. However, the results were convincing, considering that the hazard ratios of adjuvant chemotherapy and induction chemotherapy were similar (0.86-0.89) in previous individual meta-analyses comparing these treatments with surgery alone[12, 45].

Induction Chemoradiotherapy

Responding to the positive results of induction chemotherapy, the effect of induction chemoradiotherapy to enhance the local control has been investigated. In 1995, Albain *et al*. studied the feasibility of concurrent chemoradiotherapy for locally advanced NSCLC[48]. In this phase II study, 126 patients with stage IIIA and IIIB NSCLC were treated with two cycles of cisplatin/etoposide and concurrent radiotherapy at the dose of 45 Gy, followed by surgery. The response rate to induction therapy was 59%, and 107 of the 126 patients became suitable candidates for surgical treatment. The 3-year survival rates were 27% in the patients with stage IIIA disease and 24% in those with stage IIIB disease.

However, none of the subsequent randomized controlled trials have been able to confirm the additional survival benefit over induction chemotherapy to date. Thomas *et al*. conducted a study to compare preoperative concurrent chemoradiotherapy (45 Gy) with preoperative chemotherapy alone in patients with stage III NSCLC[49]. The results showed more favorable mediastinal downstaging and pathological response in the chemoradiotherapy group, but the median progression-free survivals were equivalent (HR 0.99: 95% CI, 0.81 to 1.19, $p = 0.87$). Similarly, Pless *et al*. conducted a randomized controlled trial to compare preoperative chemoradiotherapy (cisplatin plus docetaxel and total radiation dose 44 Gy) and preoperative chemotherapy alone[50]. The results again showed more favorable response rates in the chemoradiotherapy group, whereas the median event-free survivals were similar (HR 1.1: 95% CI, 0.8 to 1.4, $p = 0.67$). In 2016, a meta-analysis of 4 randomized controlled studies revealed that tumor downstaging ($p = 0.01$) and local control ($p = 0.002$) were better in the chemoradiotherapy, but that there was no benefit in the 5-year overall survival (HR 0.89: 95% CI, 0.68 to 1.19, $p = 0.44$) or progression-free survival (HR 0.72: 95% CI, 0.60 to 0.88, $p = 0.26$)[51]. Considering these results, it could be concluded that enhanced local control by intensive preoperative concurrent chemoradiotherapy is not associated with any survival benefit in patients with locally advanced NSCLC.

On the other hand, for patients with superior sulcus tumor (T3-4N0-1), preoperative chemoradiotherapy followed by surgery is considered to be the standard treatment. This strategy is based on the results of two phase II studies. The Southwest Oncology Group Trial 9416 (SWOG9416/Intergroup Trial 0160) demonstrated that after 2 cycles of cisplatin/etoposide and radiation therapy (45 Gy), 76% of patients could undergo complete resection, and the 5-year survival rate was 44%[52]. In the Japan Clinical Oncology Group trial 9806, after MVP and radiation therapy (45 Gy), the complete resection rate was 68%, and the 5-year survival rate was 56%[53]. Due to the rarity of this disease,

randomized controlled trials seem impossible, however, considering the similarity of these results and the superiority of the results as compared to the historical data, induction chemoradiotherapy is now strongly recommended for patients with superior sulcus NSCLC.

Should cN2-NSCLC be resected?

Although the significance of perioperative therapies for locally advanced NSCLC are described in the above sections, most cases with infiltrative N2-NSCLC are treated by definitive chemoradiotherapy without surgical resection. The INT0139 study was designed to clarify the significance of radical surgery after concurrent chemoradiotherapy for patients with Stage IIIA (pN2) NSCLC[54]. In this study, 396 patients were randomly assigned to definitive chemoradiotherapy, which included 2 cycles of cisplatin/etoposide and concurrent radiotherapy at the total dose of 60 Gy, or to 2 cycles of chemotherapy plus radiation at the total dose of 45 Gy followed by surgical resection. The results showed that the median overall survivals in the two groups were 23.6 months and 22.2 months, respectively, with no significant difference between the two treatment arms (HR 0.87: 95% CI, 0.70 to 1.10, p = 0.24). On the other hand, the progression-free survival was significantly better in the definitive chemoradiotherapy group (12.8 months vs. 10.5 months, HR 0.77: 95% CI, 0.62 to 0.96, p = 0.017). These results suggest that the surgical resection after chemoradiotherapy has little impact on the prognosis in patients with N2 disease.

On the other hand, the PACIFIC study was a randomized controlled study conducted to compare durvalumab, a monoclonal antibody to programmed death ligand 1 (PD-L1), with placebo as consolidation therapy after platinum-based chemoradiotherapy for unresectable stage III NSCLC[55]. Of the 713 patients who underwent randomization, 348 patients (52.9%) had stage IIIA. The median progression-free survival was 16.8 months in the durvalumab arm vs. 5.6 months in the placebo arm (HR 0.52: 95% CI, 0.42 to 0.65, p < 0.001). The 24-month overall survival rate was also significantly superior in the durvalumab arm as compared to that in the placebo arm (66.3% vs. 55.6%, HR 0.68: 95% CI, 0.47 to 0.997, p = 0.0025)[56]. This survival benefit was observed across all the prespecified subgroups.

Considering the results of these studies, the standard treatment, to date, for locally advanced NSCLC, including infiltrative N2 disease, is thought to be induction platinum-based chemoradiotherapy followed by consolidation therapy with durvalumab; surgical resection after induction chemoradiotherapy may be attempted in selected candidates.

FUTURE PERSPECTIVES

1) EGFR-TKIs

Epidermal growth factor receptor (EGFR) -tyrosine kinase inhibitors (TKIs) have been the standard first-line treatment for advanced NSCLC patients harboring EGFR mutations. It is not surprising that EGFR-TKIs have been expected to prolong the survival of patients with resected NSCLC. Several randomized trials have been conducted to date to clarify the efficacy of postoperative EGFR-TKI therapy as adjuvant therapy.

BR19 was a phase III study comparing gefitinib with placebo as postoperative adjuvant therapy after complete resection in patients with NSCLC[57]. A total of 503 patients with stage IB, II, or IIIA NSCLC were randomly assigned to the two arms. The results revealed no significant difference in the overall survival (HR 1.24: 95% CI, 0.94 to 1.64, p = 0.14) or progression-free survival (HR 1.22: 95% CI, 0.93 to 1.61, p = 0.15) between the two arms. The RADIANT study compared erlotinib with placebo as postoperative adjuvant therapy for patients with stage IB- IIIA NSCLC[58]. The disease-

free survival, the primary endpoint of this study, was comparable between the two groups (50.5 months for erlotinib vs. 48.2 months for placebo, HR 0.90: 95% CI, 0.74 to 1.10, p = 0.324). However, among the patients with EGFR-mutant NSCLC, the median disease-free survival was more favorable in the erlotinib group (46.4 months vs. 28.5 months).

The CTONG1104 study[59] and EVAN study[60] compared EGFR-TKI therapy with chemotherapy as postoperative adjuvant therapy. In the CTONG1104 study, gefitinib was compared with cisplatin plus vinorelbine for patients with stage II-IIIA EGFR-mutant NSCLC. The disease-free survival was significantly better in the gefitinib group (28.7 months vs. 18.0 months, HR 0.60: 95% CI, 0.42 to 0.87, p = 0.0054). The EVAN study was a randomized phase II study comparing erlotinib with cisplatin plus vinorelbine for patients with stage IIIA EGFR-mutant NSCLC. The trial revealed that the 2-year disease-free survival rate was significantly better in the erlotinib group (81.4% vs. 44.6%, p = 0.0054).

On the other hand, CTONG1103 study was a randomized phase II study comparing erlotinib with gemcitabine plus cisplatin as preoperative therapy for N2 EGFR-mutant NSCLC[61]. The primary endpoint was the response rate. The results showed that the response rate was superior in the erlotinib arm (54.1% vs. 34.3%, p = 0.092), but the difference was not significant, meaning the primary endpoint was not met. However, the progression-free survival was significantly better in the erlotinib arm (HR 0.39: 95% CI, 0.23 to 0.67, p < 0.001).

The results of these studies indicate that perioperative EGFR-TKIs prolong the disease-free survival in patients with EGFR-mutant NSCLC. However, the benefit on the overall survival still remains unknown. At present, the ADAURA trial is ongoing to evaluate the efficacy of osimertinib, a third-generation EGFR inhibitor, as postoperative adjuvant therapy in patients with EGFR-mutant NSCLC[62]. Osimertinib has already been established to be superior to the first-generation EGFR-TKIs, gefitinib and erlotinib[63]; therefore, the results of the ADAURA trial are eagerly awaited.

2) Immune Checkpoint Inhibitors

The recent development of immune checkpoint inhibitors (ICI), which block the immune inhibitory pathway of PD-1/PD-L1, represents a major treatment advance for patients with lung cancer. Since these drugs have become key drugs for the treatment of advanced NSCLC, several attempts have also been made to apply ICIs to perioperative treatments.

Forde *et al*. reported the results of the first phase II trial conducted to evaluate the efficacy of preoperative nivolumab therapy for patients with resectable NSCLC[64]. Twenty-one patients with stage I-IIIA resectable NSCLC were administered 2 courses of preoperative nivolumab therapy every 2 weeks. Of the 21 patients, 2 patients (10%) showed partial response, 18 (86%) showed stable disease, and 1 (5%) showed progressive disease. Of the 21 patients, 20 underwent complete resection, and a major pathological response was obtained in 9 patients (45%). Bott *et al*. reported the safety of surgery after preoperative nivolumab therapy[65]. In this study, of 20 patients who underwent resection after 2 cycles of nivolumab, there was no operative mortality, while perioperative morbidity occurred in 10 patients (50%).

These results suggest that preoperative ICI therapy may be safe and promising. At present, several trials are ongoing. Although the primary endpoint of some of these trials is the pathological response, survival data in comparison with those for the current standard strategies are eagerly awaited.

CONCLUSION

To date, much effort has been expended to establish effective perioperative treatments for

Table 2. Ongoing trials of induction therapy with immune checkpoint inhibitors

NCT number	Phase	Stage	Neoadjuvant intervention	Primary endpoint	Target accrual
02259621	II	IB-IIIA	Nivolumab with or without ipilimumab	MPR	30
02273375	III	IB-IIIA	Durvalumab vs placebo (BR31)	DFS	1360
02486718	III	IB-IIIA	Atezolizumab vs BSC after platinum doublet (IMpower010)	DFS	1280
02504372	III	IB-IIIA	Pembrolizumab vs placebo after platinum doublet (PEARLS)	DFS	1080
02572843	II	IIIA(N2)	Cisplatin/docetaxel with durvalumab	Event-free survival	68
02595944	III	IB-IIIA	Nivolumab vs BSC after platinum doublet (ALCHEMIST)	DFS	903
02818920	II	IB-IIIA	Pembrolizumab (neoadjuvant and adjuvant) (TPO1501)	Surgical feasibility	32
02927301	II	IB-IIIA	Atezolizumab (LCMC3)	MPR	180
02998528	III	IB-IIIA	Nivolumab with ipilimumab vs nivolumab with platinum doublet vs platinum doublet (CheckMate816)	MPR	624
03237377	II	IIIA	Durvalumab with radiation	Safety	32
03425643	III	II-IIIB (T3-4N2)	Pembrolizumab with platinum doublet vs platinum doublet (KeyNote671)	Event-free survival	786
03456063	III	II-IIIB	Atezolizumab with platinum doublet vs platinum doublet (IMpower030)	MPR	374
03800134	III	II-III	Durvalumab with platinum doublet vs platinum doublet (AEGEAN)	MPR	300

Abbreviations: BSC, best supportive care; MPR, major pathologic response; DFS, disease-free survival

Table 3. Ongoing trials of adjuvant therapy with immune checkpoint inhibitors

NCT number	Phase	Stage	Adjuvant intervention	Primary endpoint	Target accrual
02273375	III	IB-IIIA	Durvalumab vs placebo (BR31)	DFS	1360
02486718	III	IB-IIIA	Atezolizumab vs BSC after platinum doublet (IMpower010)	DFS	1280
02504372	III	IB-IIIA	Pembrolizumab vs placebo after platinum doublet (PEARLS)	DFS	1080
02595944	III	IB-IIIA	Nivolumab vs BSC after platinum doublet (ALCHEMIST)	DFS	903

Abbreviations: BSC, best supportive care; DFS, disease-free survival

locally advanced NSCLC, and several treatments have come to be recognized as standard strategies.

For patients with completely resected stage II-III NSCLC, cisplatin plus vinorelbine is the standard adjuvant treatment based on several clinical trials. The prognosis has steadily improved, although no cure has yet been accomplished. Establishment of customized chemotherapy according to predictive biomarkers have been expected, whereas much effort would be necessary before applying in clinical practice.

For cN2 disease, several strategies including adjuvant chemotherapy, induction chemotherapy, and induction chemoradiotherapy have been studied. However, with the development of ICI, the standard treatment for cN2 disease is being replaced by non-surgical strategies.

On the other hand, another breakthrough is expected using new drugs as perioperative treatments. Postoperative EGFR-TKIs could provide favorable disease-free survival for patients with EGFR-mutant NSCLC. Similarly, many studies are ongoing to test the efficacy of ICIs as perioperative treatment for NSCLC (Table 2 and 3). We hope that with the evolution of treatment strategies, a cure is found in the near future for patients with resectable NSCLC.

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