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Debate

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Role of multimodality therapy in cIIIA-N2 non–small cell lung cancer: perspective[§]

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[§]This is one of three papers discussing the role of surgery in clinical N2 non-small-cell lung cancer: for the 'pro' viewpoint see volume 46 number 12 pp. 1168–1173, 2016 and for the 'con' viewpoint see volume 46 number 11 pp. 1022–1025, 2016.

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Abstract

A number of promising new approaches for both local and systemic control of locally advanced non–small cell lung cancer have been examined in clinical trials, aimed at improving the patient survival. Development of better systemic therapies by adopting newer agents (such as epidermal growth factor receptor-tyrosine kinase inhibitors and immune checkpoint inhibitors) from advanced non–small cell lung cancer is mandatory. As for radiotherapy, adaptive radiotherapy and proton therapy are under investigation after the RTOG 0617 trial unexpectedly failed to show the efficacy of high-dose radiotherapy for Stage III disease. To date, no Phase III trial has clearly shown the benefit of adding surgery as a part of multimodality therapy for locally advanced non–small cell lung cancer. Such poor progress in the development of effective treatments for Stage III non–small cell lung cancer is considered to be attributable to the existence of heterogeneities in the disease characteristics, including the biological and anatomic characteristics. Constant effort via well-designed and well-conducted clinical trials is needed to decipher the heterogeneity of Stage III non–small cell lung cancer.

Key words: cIIIA-N2, NSCLC, multimodality therapy

Introduction

In 1968, Roswit et al. reported a randomized controlled trial that demonstrated that thoracic radiotherapy was superior to placebo, in terms of the survival, in patients with lung cancer (1). As early as in the 1970s, the Radiation Therapy Oncology Group (RTOG) conducted an important randomized controlled trial comparing thoracic radiotherapy at the total radiation doses of 40, 50 and 60 Gy in 2 Gy daily fractions. On the basis of the result of this trial, thoracic radiotherapy with 60 Gy in 30 fractions became the standard therapy for locally advanced non–small cell lung cancer (NSCLC) (2). In the RTOG8808 trial, chemoradiotherapy was associated with significant improvement of the overall survival as compared with standard thoracic radiotherapy (60 Gy) (3). Furuse et al. established the superiority of concurrent chemoradiotherapy using mitomycin, vindesine and cisplatin (4). A similar result was reported by Curran et al. from RTOG trial number 9410 (5). On the basis of these results, concurrent administration of cisplatin-based chemotherapy with thoracic radiotherapy at 60–66 Gy became the standard for the treatment of Stage III NSCLC.

Several trials have been conducted to examine the potential benefits of the newer generation chemotherapeutic agents. The OLSCG (Okayama Lung Cancer Study Group) 007 trial was a randomized controlled trial conducted by the Okayama group comparing cisplatin plus docetaxel and mitomycin + vindesine + cisplatin (6). The WJTOG (West Japan Thoracic Oncology Group) 0105 trial was another Japanese clinical trial performed to confirm the superiority of the third-generation chemotherapeutic agents over the older combination regimens (mitomycin + vindesine + cisplatin) (7). Even though these two trials yielded negative results from the statistical point of view, chemotherapeutic regimens containing the newer generation

agents (docetaxel and paclitaxel with platinum agents) came to be considered as standard therapy because of their favorable toxicity profile and comparable efficacy. Therefore, definitive thoracic radiotherapy (60–66 Gy) with third-generation cytotoxic chemotherapy regimens (docetaxel, paclitaxel and vinorelbine) is the state-of-the-art standard treatment. However, the 5-year survival rate even with this approach remains at about only 20% (6–8). To explore treatments that would offer better survival in patients with locally advanced NSCLC, clinical trials of a number of promising new approaches directed at local/systemic control are under way.

Challenges in systemic treatment

At present, it appears mandatory to adopt newer agents from advanced NSCLC regimens to develop better systemic therapies for patients with Stage III NSCLC. Pemetrexed in combination with cisplatin or carboplatin is currently the standard as the induction or maintenance regimen for non-squamous NSCLC (9,10). Recently, Senan et al. reported a negative result of the PROCLAIM trial, which failed to demonstrate the superiority of pemetrexed plus cisplatin over the older combination regimen of etoposide plus cisplatin in patients scheduled for concurrent definitive chemoradiotherapy (11).

Molecular-targeted therapy based on oncogenic drivers in individual patients is an established treatment modality and is used in as much as a half of all patients with advanced NSCLC. Although superiority of erlotinib over placebo could not be demonstrated in the setting of adjuvant therapy in patients with completely resected NSCLC (RADIANT trial), there is still much room to investigate the efficacy and safety of targeted agents based on driver oncogenes for obtaining locoregional control (12). Yagishita et al. reported that the presence of epidermal growth factor receptor (EGFR) mutation in the tumor was associated with better locoregional control after definitive chemoradiotherapy in patients with Stage III NSCLC (13). Many clinical trials are under way and being planned to introduce EGFR inhibitors (gefitinib and erlotinib) and anaplastic lymphoma kinase inhibitors (ALK inhibitors such as crizotinib and ceritinib) in the treatment of locally advanced NSCLC. The LOGIK (Lung Oncology Group in Kyushu) and OLCSG are conducting a Phase II trial to evaluate the efficacy and safety of induction gefitinib therapy followed by cisplatin plus docetaxel with concurrent thoracic radiotherapy in patients with locally advanced NSCLC harboring EGFR mutations. (UMIN000005086) The RTOG 1306 is a randomized Phase II study of individualized combined modality therapy to assess whether patients with unresectable locoregionally advanced NSCLC treated with targeted agents based on molecular characteristics would show a longer progression-free survival than those receiving standard therapy alone. (NCT01822496) The SAKULA trial is a Phase II trial to evaluate the efficacy and safety of preoperative therapy with LDK378 (ceritinib) in patients with ALK fusion gene-positive Stage II/III NSCLC. (UMIN000017906).

Unfortunately, earlier efforts to introduce immune therapies for locally advanced NSCLC did not bear fruit. The START trial was an international, randomized, double-blind trial performed to investigate whether the MUC1 antigen-specific cancer immunotherapeutic drug tecemotide might improve the survival in patients with Stage III unresectable NSCLC when given as maintenance therapy after chemoradiation (14). Another immunotherapeutic approach, mainly immune checkpoint inhibition, has received attention as a new approach for the treatment of advanced NSCLC. Nivolumab was demonstrated to exert fascinating efficacy in comparison with docetaxel in both patients with squamous and non-squamous advanced NSCLC (15,16). Deng et al. reported that PD-L1 is upregulated in the tumor microenvironment after radiotherapy, and that blockade of PD-L1 might enhance the T-cell effector function against the tumor (17). The PACIFIC trial is a Phase III, randomized, double-blind, placebo-controlled, multicenter, international study of MEDI4736 as sequential therapy in patients with locally advanced, unresectable NSCLC (Stage III) not showing disease progression following definitive, platinum-based, concurrent chemoradiation therapy. (NCT02125461). These clinical trials described in this section are summarized in Table 1.

Challenges in radiotherapy

In an attempt to obtain better local control, dose escalation of thoracic radiotherapy has been rigorously investigated. The RTOG 0617 was a Phase III factorially designed trial conducted to compare standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab in patients with Stage III NSCLC (18). Astonishingly,

Table 1. Challenge in systemic therapy

Type of systemic therapy	Trial name or number	Patients	Standard arm	Experimental arm	Result	References
Third generation cytotoxic chemotherapy	PROCLAIM	Non-Sq	CDDP + ETP + TRT	CDDP + PEM + TRT	Negative	11
EGFR-TKI	RADIANT	Not selected	Standard adjuvant therapy	Erlotinib as adjuvant therapy	Negative	12
MUC1-specific cancer vaccine (tecemotide)	START	Not selected	Chemoradiotherapy	Chemoradiotherapy plus tecemotide	Negative	14
EGFR-TKI	UMIN000005086	EGFR mutant	Chemoradiotherapy	Gefitinib before chemoradiotherapy	Ongoing	
EGFR-TKI, ALK-TKI	RTOG 1306	EGFR mutant, ALK gene rearranged	Chemoradiotherapy +/− surgery	EGFR-TKI or ALK-TKI before chemoradiotherapy +/− surgery	Ongoing	
ALK-TKI	SAKULA	ALK rearranged	Not applicable	ALK-TKI before surgery	Ongoing	
PD-L1 antibody	PACIFIC	Not selected	Chemoradiotherapy	Chemoradiotherapy plus MEDI4736	Ongoing	

CDDP, cisplatin; ETP, etoposide; TRT, thoracic radiotherapy; PEM, pemetrexed; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ALK, anaplastic lymphoma kinase.

the experimental arm (higher dose thoracic radiotherapy) showed inferior overall survival and a higher rate of locoregional failure, and the trial turned out to yield a negative result. Although many factors are still under inspection, it would be seem that the relatively higher rate of treatment-related death (especially based on pulmonary and cardiac toxicities) in the high-dose radiotherapy arm may have had a substantial effect on the overall results.

The RTOG is now investigating adaptive radiotherapy and proton radiotherapy, which might provide more effective and safe treatment for patients with locally advanced NSCLC. The RTOG1106 is a randomized Phase II trial of individualized adaptive radiotherapy using during treatment positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro-D-glucose integrated with computed tomography (FDG-PET/CT) to determine whether the tumor dose can be escalated to improve the locoregional progression-free rate at 2 years; in this treatment, an individualized adaptive radiation treatment plan is applied on the basis of the findings of a FDG-PET/CT scan acquired after initial radiotherapy at 40–46 Gy in patients with inoperable or unresectable Stage III NSCLC. (NCT01507428) The RTOG 1308 is a randomized Phase III trial being conducted to compare the overall survival in patients with Stage II-IIIB NSCLC after image-guided, motion-managed photon radiotherapy or after image-guided, motion-managed proton radiotherapy, both given concurrently with platinum-based chemotherapy (NCT01993810). These clinical trials described in this section are summarized in Table 2.

Surgery as definitive local therapy

Surgical resection of the primary tumor and regional lymph nodes is the most radical local therapy for lung cancer. However, surgical alone is not recommended for patients with locally advanced NSCLC because of the extremely high rate of distant relapse in these patients. Therefore, multimodality therapies combining surgery with chemotherapy and/or radiotherapy have been investigated in an attempt to obtain better local/systemic control in patients with Stage III NSCLC. The EORTC conducted a Phase III trial comparing radiotherapy and surgery as definitive local therapy for Stage III NSCLC (19). In this trial, patients who were initially diagnosed as having unresectable disease received induction chemotherapy before definitive radiotherapy (standard arm) or surgery (experimental arm); the results revealed no difference in the overall survival between the two arms. A similar comparison (radiotherapy or surgery as definitive local therapy) was made in the randomized North American intergroup trial (INT-0139) (20). In contrast to the case in the EORTC trial, INT-0139 accrued patients with initially resectable and relatively less extensive Stage III NSCLC. Although the difference was not statistically significant, a tendency towards better survival was noted in the surgery arm. Recently, Eberherdt et al. reported the results of the ESPATUE trial (21). In this multicenter Phase III trial, participants were randomized to radiotherapy or surgery as definitive local therapy after induction treatment. At the point of randomization, an expert panel discussed the resectability in each patient and gave permission to randomize. While the trial yielded negative results from the statistical point of view, both arms (surgery and radiotherapy) were considered to be equally effective "options" for patients with locally advanced NSCLC by the authors. In Japan, the WJTOG (WJOG) conducted a Phase III trial comparing induction chemotherapy with chemoradiotherapy (22). Although this trial closed earlier than expected because of the slow patient accrual, favorable safety and efficacy of the induction chemotherapy and chemoradiotherapy were observed in the selected population.

To date, no Phase III trial has confirmed the clinical significance of surgical resection in patients with Stage III NSCLC (Table 3).

Heterogeneity

While discussing the treatment of Stage III NSCLC, we should be aware of the heterogeneity of this disease from both the biological and anatomic perspective. Furthermore, the diagnosis and treatment guidelines are continually changing according to research findings.

The biologic background of patients is important. Elderly patients usually have poor outcomes, especially from the toxicity point of view (23). It has also been suggested that the socioeconomic status of patients affects their selection of the available treatment options; the more educated a patient is, the more likely he/she is to choose multimodality treatment (24). Tumor histology is one of the oldest known prognostic factors in Stage III disease (25). Recently, the influence of driver oncogenes in patients with locally advanced NSCLC has been

Table 2. Challenges in radiotherapy

Type of local therapy	Trial name or number	Standard arm	Experimental arm	Result	Reference
Higher dose radiotherapy	RTOG 0617	Chemoradiotherapy (60 Gy in 30 fractions)	Chemoradiotherapy (74 Gy in 37 fractions)	Negative	18
Adaptive radiotherapy	RTOG1106	Conventional chemoradiotherapy	Adaptive chemoradiotherapy	Ongoing	
Proton radiotherapy	RTOG 1308	Conventional chemoradiotherapy	Proton radiation therapy with chemotherapy	Ongoing	

Table 3. Surgery as definitive local therapy

Trial name or number	Patients	Standard arm	Experimental arm	Result	References
EORTC08941	IIIA-N2	Induction chemotherapy followed by radiotherapy	Induction chemotherapy followed by surgery	Negative	19
INT-0139	IIIA-N2	Chemoradiotherapy	Induction chemoradiotherapy followed by surgery	Negative	20
ESPATUE	IIIA-N2, selected IIIB	Chemoradiotherapy	Induction chemoradiotherapy followed by surgery	Negative	21
WJTOG9903	IIIA-N2	Induction chemotherapy followed by surgery	Induction chemoradiotherapy followed by surgery	Negative	22

studied. For example, the presence of EGFR mutations in the tumor has been reported to be associated with better locoregional control and poor distant control in patients with locally advanced NSCLC (13). A number of trials are in progress to investigate the efficacy of medical treatments, with huge successes in advanced disease settings being obtained with such agents as EGFR-TKIs and immune checkpoint inhibitors in combination with standard chemoradiotherapy.

Stage III NSCLC shows broad anatomic heterogeneity, covering wide extent of local invasion (T factor) and nodal involvement (N factor). We have previously reported the heterogeneous outcomes of Stage IIIA-N2 disease; in our study, patients who tended to be good candidates for intensive local treatment (e.g. surgery after induction chemoradiotherapy) also showed excellent outcomes of chemoradiotherapy alone (25). It was also suggested that the attending doctor's preference affect the choice of the treatment of Stage IIIA-N2 disease; surgeons appeared to have a tendency to select multimodality therapy, including surgery, while medical oncologists did not (26,27).

It may not be unreasonable to expect it to take10 years or longer for the final results of the clinical trials conducted for patients with Stage III NSCLC to be published (5–7,18–20,22). This length of time is sufficient to expect a tumor, node and metastasis staging update and revolution in medical treatments and radiotherapeutic techniques. Time passage may be the biggest factor of the heterogeneity of Stage III NSCLC, a disease with a relatively favorable prognosis.

Future perspective

Numerous important trials have been carried out in the past in Europe and in the USA of multimodality treatments including surgery for patients with Stage III NSCLC. However, even though Japan is one of the more advanced countries in the area of clinical trial management and performance, no Phase III trials of multimodal approaches (such as surgery, radiotherapy and chemotherapy) for the treatment of Stage III NSCLC have been carried out in this country. The time is right to plan and start a well-designed clinical trial to decipher the heterogeneity of Stage III NSCLC.

Conflict of interest statement

None declared.

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