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Rationale and protocol design for the TORG1835/NEXT-SHIP study: a phase II study of carboplatin, etoposide and nintedanib for unresectable limited/extensive disease small cell lung cancer with idiopathic pulmonary fibrosis

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Abstract

Background: Interstitial pneumonia (IP) is one of the most common and poor prognostic comorbidities in patients with small cell lung cancer (SCLC). The pharmacotherapy for SCLC occasionally induces fatal acute exacerbation of comorbid IP, especially in patients with idiopathic pulmonary fibrosis (IPF). Safe and effective pharmacotherapy is of greater importance in patients with SCLC and IPF, because SCLC presents a poor prognosis without systemic treatment. Nintedanib is expected to restrain acute exacerbation and present angiogenesis-inhibiting effects.

Methods: The TORG1835/NEXT-SHIP study is the world's first multi-center, single-arm, phase II trial for unresectable limited or extensive disease SCLC with IPF. The patients receive carboplatin (area under the curve 5, day 1), etoposide (<75 years old: 100 mg/m^2; ⩾75 years old: 80 mg/m^2; days 1–3), and nintedanib (150 mg twice a day) every 3 weeks for four cycles. After completion or discontinuation of carboplatin plus etoposide, the patients continue nintedanib until the discontinuation criteria are met. The primary endpoint is the incidence of acute exacerbation of IPF at 28 days after last administration of cytotoxic anti-cancer agents. We set an expected value of 5% and a threshold value of 20%. Taking statistical points (a/b errors: 0.05/0.75) and ineligible patients into account, the sample size was set at 33. The key secondary endpoints are time to first acute exacerbation of IPF, overall response rate, progression-free survival, overall survival, and toxicities.

Discussion: Because there is no clinical trial for unresectable SCLC with IPF, our study would provide a major impact on clinical practice.

Trial registration: Japan Registry of Clinical Trials, jRCTs031190119, registered date: October 18, 2019 – Retrospectively registered, https://jrct.niph.go.jp/en-latest-detail/jRCTs031190119

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Background

Small cell lung cancer (SCLC) accounts for approximately 15% of lung cancer cases, of which 30–40% are classified as limited disease (LD; limited to the ipsilateral hemithorax and regional lymph nodes) and 60–70% are classified as

extensive disease (ED).[1] SCLC is distinguished from non-small cell lung cancer (NSCLC) by its rapid growth characteristics and the early development of widespread metastases, thus surgical resection is indicated for only ⩽5% of the patients with SCLC. Without systemic treatment, median survivals for patients with LD-SCLC and ED-SCLC are approximately 3 months and 1.5–2 months, respectively.[2,3] On the other hand, SCLC is highly responsive to chemotherapy and radiotherapy, and chemotherapy dramatically prolongs survival.

Some 5–10% of patients with SCLC are diagnosed with concomitant interstitial pneumonia (IP), which has a poor prognosis.[4] As mentioned above, chemotherapy and radiotherapy play a critical role in unresectable SCLC. However, in SCLC patients with comorbid IP, stereotactic radiotherapy frequently induces serious radiation pneumonitis or acute exacerbation of pre-existing IP.[5] In addition, the pharmacotherapy for SCLC occasionally induces acute exacerbation of pre-existing IP (5–20%) with a high mortality rate of 30–50%, thus, it is considered to be a major problem.[6] There is a particularly high risk of acute exacerbation in patients with idiopathic pulmonary fibrosis (IPF). Irinotecan or amrubicin (which are the key SCLC drugs) had a high risk of developing acute exacerbation of pre-existing IP and are contraindicated in patients with IP, thus resulting in more limited treatment options than those available for SCLC patients without IP.

To date, there has been only one prospective pilot study, which targeted 17 patients with unresectable SCLC with idiopathic IP.[7] In that study, the results of carboplatin plus etoposide administration showed an incidence of acute exacerbation of IP at the primary endpoint of 5.9%, with an overall response rate (ORR) of 88.2%, a median progression-free survival (PFS) of 5.3 months, and a median overall survival (OS) of 10.6 months. Based on these results, a combination of carboplatin plus etoposide is considered the standard treatment. However, when limited to patients with SCLC with IPF, past retrospective studies have shown that even the combination of platinum plus etoposide induced acute exacerbation, with an incidence of 24–27%.[6,8] Due to the lack of prospective studies on SCLC with IPF, there is an urgent need to establish an effective medical treatment.

Nintedanib is a small-molecule tyrosine kinase inhibitor that inhibits vascular endothelial growth factor, platelet-derived growth factor, and fibroblast growth factor. Nintedanib acts as an anti-angiogenic agent that blocks the formation of new blood vessels within tumors. The results of the LUME-Lung 1 study showed a significant lengthening of PFS due to the addition of nintedanib, and it was subsequently approved as a secondary treatment drug for NSCLC in Europe.[9] In many countries apart from Europe, nintedanib was approved only for IPF as an anti-fibrotic agent. Importantly, nintedanib is expected to restrain acute exacerbation of IPF.[10] Based on these reports, a randomized study of carboplatin plus nab-paclitaxel with or without nintedanib for patients with advanced NSCLC with IPF (J-SONIC trial) is currently in progress.[11]

Although molecular targeted therapies have not been established for SCLC, the tolerability and safety of nintedanib monotherapy has already been validated with limited activity in a phase II trial on previously treated patients with SCLC.[12] Given that nintedanib is expected not only to have angiogenesis-inhibiting effects, but also to restrain acute exacerbation of IPF, a combination therapy involving the use of nintedanib with carboplatin plus etoposide would be the most promising candidate as a standard future treatment for unresectable SCLC with IPF.

The objective of this study is to assess the safety and efficacy of carboplatin, etoposide, and nintedanib combination therapy for unresectable LD or ED-SCLC with IPF.

Methods/design

Study design and treatment

This study was designed as a multi-center, single-arm, phase II trial conducted by the Thoracic Oncology Research Group (TORG) in accordance with the Declaration of Helsinki and the Clinical Trials Act in Japan (Figure 1). The protocol was approved by the Niigata University Certified Review Board of Clinical Research (approval date: 23 August 2019, approval number: SP19004). This clinical trial is registered in the Japan Registry of Clinical Trials (registered date: 18 October 2019, registry number: jRCTs031190119).

The patients receive carboplatin (area under the curve 5 mg/mL, intravenously, day 1), etoposide (<75 years old: 100 mg/m^2; ⩾75 years old:

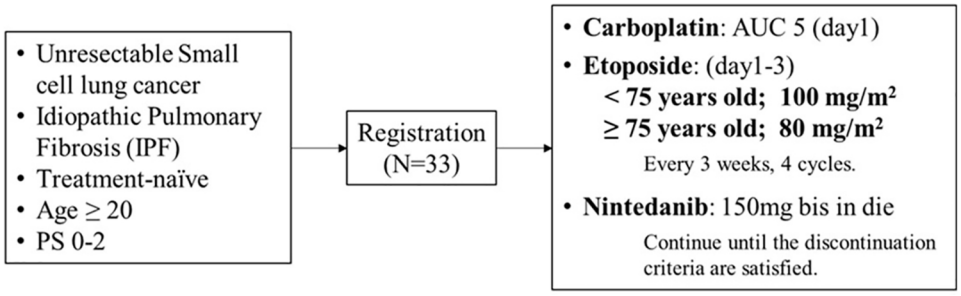

Figure 1. Study design.

80 mg/m^2; intravenously, days 1–3), and nintedanib (150 mg twice a day, orally). The patients receive combination chemotherapy every 3 weeks for four cycles until disease progression or unacceptable toxicity occurs. After completion or discontinuation of carboplatin plus etoposide, the patients continue nintedanib until the discontinuation criteria are met.

Eligibility criteria

The key patient inclusion and exclusion criteria are detailed in Table 1.

Patient registration

After the eligibility criteria have been confirmed and the patients have provided informed consent, eligible patients will be registered and the planned treatment initiated by the investigators. Accrual began in October 2019, and should continue for 3 years.

Evaluation of response

Computed tomography (CT) scans of the chest and abdomen, a CT or magnetic resonance imaging scan of the brain, a bone scan or positron emission tomography scan, and an electrocardiogram are required before initiation of study treatment. Patients will undergo a tumor assessment at baseline, every 6 weeks during the first 24 weeks, and every 9 weeks thereafter. The tumor response will be evaluated in accordance with the Response Evaluation Criteria in Solid Tumors, version 1.1. Adverse events will be recorded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0.

Evaluation of acute exacerbation of IPF

A high-resolution CT scan of the chest is mandatory before the initiation of the study treatment. Laboratory testing including Krebs von den Lungen-6 and blood gas analysis are also mandatory within 14 days prior to enrollment. Patients will also undergo an assessment of respiratory symptoms at baseline, on the day of chemotherapy administration, and at every visit after completion or discontinuation of chemotherapy. When development of pneumonitis or acute exacerbation of IP is suspected by the investigator, a chest CT, laboratory testing (e.g. brain natriuretic protein, Krebs von den Lungen-6, β-D glucan, cytomegalovirus antigen), blood gas analysis, and echocardiogram are recommended for assessing whether acute exacerbation of IPF has developed. A central review committee will adjudicate all 'investigator-reported' acute exacerbation events to determine whether the events meet the criteria defined in the protocol.

Statistical design

The primary endpoint is the incidence of acute exacerbation of IPF at 28 days after last administration of cytotoxic anti-cancer agents (carboplatin and etoposide). The key secondary endpoints are time to first acute exacerbation of IPF, ORR, PFS, OS, and toxicities.

The prospective study administering carboplatin plus etoposide in patients with unresectable SCLC with idiopathic IP showed a 5.9% incidence of acute exacerbation at the primary endpoint. Also, nintedanib is expected to inhibit acute exacerbation. Thus, we set an expected value of 5%. Meanwhile, there is a particularly high risk of chemotherapy-induced acute exacerbation in patients with IPF. Past retrospective studies on patients with SCLC and IPF showed that platinum plus etoposide induced acute exacerbation, with an incidence of 24%;[6] therefore, we set a threshold value of 20%. Based on exact binomial test, the planned sample size was determined to

Table 1. Key eligibility criteria.

Inclusion criteria	
1	Histologically or cytologically proved small cell lung cancer
2	Unresectable limited disease or extensive disease
3	No previous chemotherapy for small cell lung cancer
4	(1) Definite honeycomb lung destruction with basal and peripheral predominance; or (2) Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
5	%FVC $\geqslant$ 50%, %DLCO $\geqslant$ 30%
6	Age $\geqslant$20 years
7	ECOG Performance status 0–2
8	With measurable or unmeasurable lesions according to RECIST version 1.1
9	Vital organ functions are preserved
10	Received sufficient explanations about the name and severity of the illness
11	Written informed consent
Exclusion criteria	
1	Ground glass opacity pattern more extensive than reticular opacity pattern
2	Other interstitial lung disease of known etiology (including infection, pneumoconiosis, drug-induced pneumonitis, sarcoidosis, and collagen vascular disease)
3	History of acute exacerbation of IPF
4	Synchronous or metachronous active double malignancies
5	Symptomatic brain metastasis or spinal cord metastases
6	Treatment history with pirfenidone, immunosuppressants, and N-acetylcysteine within 56 days before registration
7	Treatment history with nintedanib, cytotoxic chemotherapy, and immune checkpoint inhibitors
8	Systemic treatment with steroids at a daily dose $>$10 mg of prednisolone equivalent
9	High hemorrhage risk
10	Serious complications
11	Local or systemic active infection requiring treatment
12	Pregnant or breastfeeding
13	Disapprove of contraception during the protocol treatment period
14	History of serious drug allergies
15	Other conditions not suitable for the study

IPF, idiopathic pulmonary fibrosis.

reject a null value of 20%, at a one-sided significance level of 0.05, under an expected value of 5%, with a power of 0.75. Taking ineligible patients into account, the sample size was set at 33 patients.

Discussion

Safe and effective chemotherapy is of greater importance in patients with unresectable SCLC and IPF because unresectable SCLC presents a much poorer prognosis than advanced NSCLC without chemotherapy. This is the world's first phase II trial on unresectable SCLC with IPF, and its findings are expected to have a major impact on clinical practice.

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Author contributions

SI, TO, TK, HK, TM, TY and HO were involved in study conception and design. SI, TO, TK, HK, TI, TM, TY and HO will be involved in the analysis and interpretation of the data; SI, TO, TK and HK were involved in drafting the manuscript; and SI, TO, TK, HK, TI, TM, TY and HO were involved in revising the manuscript. All authors have read and approved the final manuscript.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

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Conflict of interest

SI received honoraria from Boehringer Ingelheim. TO received honoraria and research funding from Boehringer Ingelheim. TK received honoraria from Boehringer Ingelheim, Takeda Pharmaceutical, Pfizer, and Bristol-Myers Squibb; and research funding from Pfizer and Bristol-Myers Squibb. HK received honoraria from Boehringer Ingelheim and Bristol-Myers Squibb; and research funding from Boehringer Ingelheim. TI received honoraria from Boehringer Ingelheim. TY received honoraria from Boehringer Ingelheim, Takeda Pharmaceutical, and Pfizer; and research funding from Boehringer Ingelheim and Takeda Pharmaceutical. HO received research funding from Bristol-Myers Squibb and Takeda Pharmaceutical. TM declared no potential conflicts of interest with any companies or organizations whose products or services might be discussed in this article.

Consent for publication

Consent for publication must be obtained from all patients.

Ethics approval and consent to participate

The Niigata University Certified Review Board of Clinical Research approved this protocol on 23 August 2019 (approval number: SP19004). This clinical trial is registered in the Japan Registry of Clinical Trials (registered date: 18 October 2019, registry number: jRCTs031190119). Written informed consent must be obtained from all patients.

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