disease after using SP, even with 40 Gy of concurrent radiation therapy. The toxicity of our SP-RT induction treatment was also excellent, without any grade 4 events, which allowed patients to safely undergo the subsequent surgical resection.

Concerning the survival benefit of concurrent chemoradiotherapy for LA-NSCLC, Segawa and colleagues (OLCSG 0007) [19] compared docetaxel plus cisplatin to mitomycin, and vindesine plus cisplatin with concurrent radiotherapy in their phase III study, and reported better 1- and 3-year progression-free survival rates of 53.4% and 24.9%, respectively, and 1- and 3-year overall survival rates of 82.8% and 38.1%, respectively, in the docetaxel plus cisplatin group. Yamamoto and colleagues [20] (WJOG 0105) also compared mitomycin, vindesine plus cisplatin, irinotecan plus carboplatin and paclitaxel plus carboplatin, and demonstrated that a median progression-free survival rate was 9.5 months and a median overall survival was 22.0 months in their docetaxel plus cisplatin group. Focusing on induction concurrent chemoradiotherapy followed by surgery for LA-NSCLC, some phase I and II studies demonstrated promising results in their surgery arm; Friedel and colleagues [21] showed a better median overall survival of 39 months in the subset analysis of their phase II study, and an improved 5-year overall survival rate of 43.1% in patients who underwent surgical resection after induction chemoradiotherapy with carboplatin and paclitaxel with 45 Gy of concurrent radiotherapy for stage III NSCLC compared with those treated without surgical resection, which were 29.6 months and 0%, respectively. Edelman and colleagues [22] reported a good median overall survival of 55.8 months in their series of stage III NSCLC patients with negative mediastinal nodes after induction concurrent chemoradiotherapy using carboplatin and vinorelbine in their phase I/II study. We also previously showed the impact of induction concurrent chemoradiotherapy with cisplatin and UFT on the survival of stage IIIB NSCLC patients who underwent surgical resection, with 1- and 3-year overall survival rates of 82% and 67%, respectively [23].

In their recent report, Albain and colleagues (INT 0139) [24] reported no significant overall survival difference between patients who received induction concurrent chemoradiotherapy with or without surgery; however, the patients who underwent lobectomy showed significant better survival. Additionally, in their resected pT0N0 patients, an excellent median survival of 39 · 8 months was observed. In the present study, a considerably better prognosis was observed; 1-, 3-, and 5-year disease-free survival rates were 73.8%, 52.0%, and 44.0%, respectively (Fig 1A), and 1-, 3-, and 5-year overall survival rates were 84.3%, 77.4%, and 61.7%, respectively (Fig 1B). Our study also indicated that pathologic good responders (ie, patients with complete pathologic response) showed a 3-year disease-free survival rate of 76.2% and 3-year overall survival of 88.9%. We did not evaluate the relationship between the pre-induction and post-induction treatment TNM stage because we believe that one of the important predictive factors for postoperative survival is the pathologic response. That is the reason why we focused on this issue and did not show the correlation between pre-induction and post-induction staging. These results seem to indicate that SP-RT can provide a sufficient systemic dose to prevent occult distant metastasis. In addition, 5-FU is known to have a radiosensitizing effect [25] and S-1 was orally administered for 14 consecutive days twice during the radiotherapy in the present study.

The limitations of the present study are the retrospective nature of the analysis and the relatively small number of patients. We are currently performing a single institutional phase II study of SP-RT as an induction concurrent chemoradiotherapy, followed by surgical resection, for LA-NSCLC patients.

In conclusion, SP-RT followed by surgery may provide a better prognosis for LA-NSCLC patients. Further clinical investigations are warranted.

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INVITED COMMENTARY

To date, 5-fluorouracil (5-FU) has not been utilized in the treatment of non-small cell lung cancer (NSCLC) because of its bioavailability profile, providing lower levels outside the gastrointestinal system. S-1 is an oral fluoropyrimidine drug that combines tegafur, a prodrug of 5-FU, with gimeracil (CHDP) and potassium oxonate (OXO), to increase serum 5-FU levels and minimize gastrointestinal toxicity, respectively. Usually, approximately 80% to 90% of 5-FU administered intravenously is rapidly catabolized by liver dihydropyrimidine dehydrogenase (DPD), and others have also shown high levels of DPD may exist in lung tumors. With S-1, CHDP inhibits both liver and tumor DPD more than 150 times more effectively than uracil and OXO inhibits 5-FU phosphorylation by gastrointestinal mucosal cells. Capecitabine is another oral 5-FU prodrug, but its metabolism is different from that of than tegafur, relying on a final step requiring the enzyme thymidine phosphorylase, which is expressed variably in NSCLC tumors [1].

Although early reports of S-1 in the treatment of NSCLC are now more than a decade old, the clinical use of S-1 has not gained significant traction worldwide yet. Although S-1, in combination with platinum, exhibits antitumor effects in NSCLC as shown in a recent multicenter phase II study (overall response rate 20%, median time to progression 4 months), these results were comparable but not superior to those of other current platinum doublets [2]. This North American study [3], however, used lower doses of S-1 (25 mg/m^2) than in previous studies from Japan in combination with cisplatin at 75 mg/m^2. Yet, S-1 plus platinum demonstrated 50% fewer grade 4 toxicities as compared with other standard platinum doublets for NSCLC. In the present study by Yamaguchi and colleagues [3], S-1 given at 40 mg/m^2 with cisplatin (60 mg/m^2) resulted in a very favorable toxicity profile. The radiosensitizing effects of 5-FU are well known and the higher S-1 dose in the present study likely contributes to the overall results. However, the cohort size here is small, and additional studies will be needed to further explore the optimum dose levels and most effective drug combinations with S-1 for NSCLC.

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Case report

The first case of lung carcinosarcoma harboring in-frame deletions at exon19 in the *EGFR* gene

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ABSTRACT

Mutations of the *epidermal growth factor receptor* (*EGFR*) gene play a critical role in carcinogenesis of lung cancer, particularly adenocarcinoma. However, to the best of our knowledge, no mutations of the *EGFR* in patients with lung carcinosarcoma have been identified. We herein report the case of a 61-year-old female referred for a detailed examination of a left pulmonary mass shadow. Although bronchoscopy was performed, it failed to lead to a diagnosis, and video-assisted thoracoscopic surgery was therefore carried out to diagnose the tumor. The pathology revealed biphasic features consisting of both adenocarcinoma and chondrosarcoma. Intriguingly, both the adenocarcinoma and chondrosarcoma components were proven to harbor an exon19 deletion in the *EGFR* gene. Although carcinosarcoma is a rare malignancy of the lungs, genetic analyses of oncogenic drivers, such as the *EGFR* gene, should be conducted.

1. Introduction

Carcinosarcoma of the lungs is a subtype of sarcomatoid carcinoma (SC) and a rare malignancy [1]. Although several reports have previously investigated genetic alterations in patients with SC [2–5], no mutations in oncogenic drivers of carcinosarcoma, including *epidermal growth factor receptor* (*EGFR*), have been identified. We herein report the case of a 61-year-old female referred for a detailed examination of a left pulmonary mass shadow. Although advanced left lung cancer with lumbar metastasis was clinically suspected, bronchoscopy failed to lead to a diagnosis, and surgery was therefore performed. The pathological examination revealed that the tumor was composed of a carcinomatous component and a sarcomatous component. Intriguingly, both components harbored the *EGFR* exon19 deletion. As far as we know, this is the first report of a patient with pulmonary carcinosarcoma harboring an exon19 deletion in the *EGFR* gene.

2. Case report

A 61-year-old female nonsmoker was referred to our department for a detailed examination of a persistent cough. A physical examination and laboratory tests, including measurements of the levels of tumor markers, showed no abnormalities. A chest X-ray revealed a mass shadow in the left lower lung field, and computed tomography (CT) showed a mass shadow with a maximum diameter of 3.2 cm (Fig. 1A) and a solitary lesion in the second lumbar vertebra (Fig. 1B, arrow) that was also observed on magnetic resonance imaging (Fig. 1C). Positron emission tomography/CT identified avid intake of [^{18}F]fluorodeoxyglucose in the left hilar lymph node (thin arrow) as well as pulmonary (thick arrow) and bone lesions (arrowhead) (Fig. 1D). Based on these findings, the patient was clinically suspected of having left lung cancer with lumbar metastasis according to the American Joint Committee on Cancer staging criteria (T2aN1M1b, Stage IV) [6]. Although bronchoscopy was performed, it failed to lead to a diagnosis, and video-assisted thoracoscopic surgery was therefore carried out to diagnose the tumor after obtaining the patient's informed consent. A solid mass with a diameter of approximately 3.2 cm was identified in the 9th segment of the left lung, although no pleural dissemination, malignant effusion or pulmonary metastases were observed.

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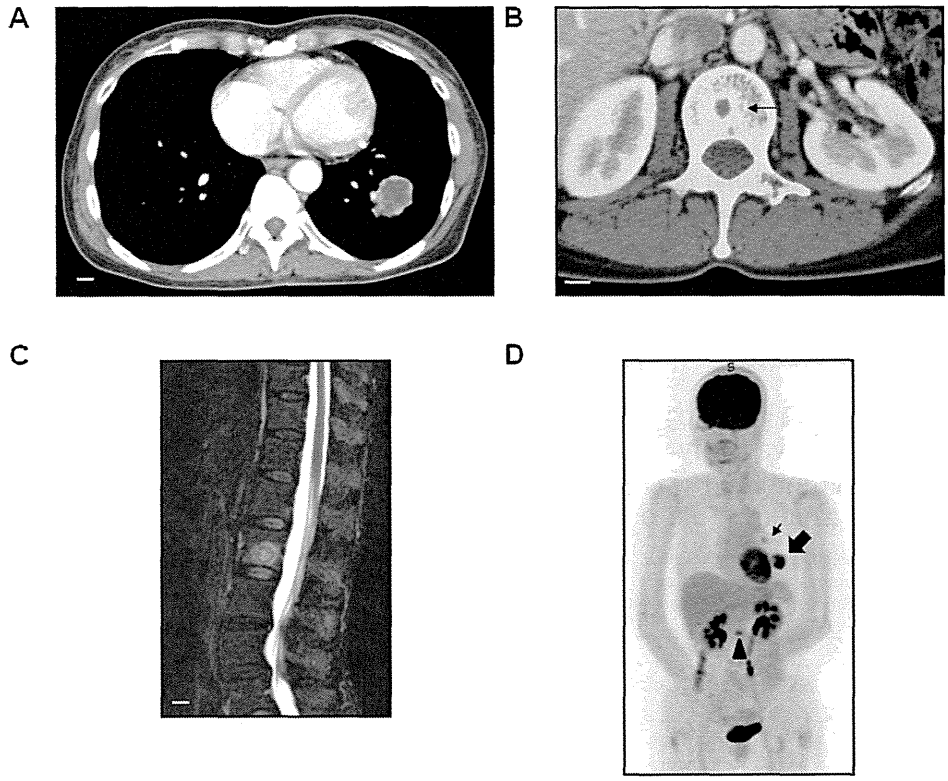

Fig. 1. Computed tomography (CT) showed a mass shadow in the left lower lobe (A) and a solitary lesion in the second lumbar vertebra (B, arrow) that was also observed on magnetic resonance imaging (C). Avid intake of [^{18}F]fluorodeoxyglucose in the left hilar lymph node (thin arrow) as well as pulmonary (thick arrow) and bone lesions (arrowhead) was identified on positron emission tomography/CT (D). Scale bar: 1.0 cm.

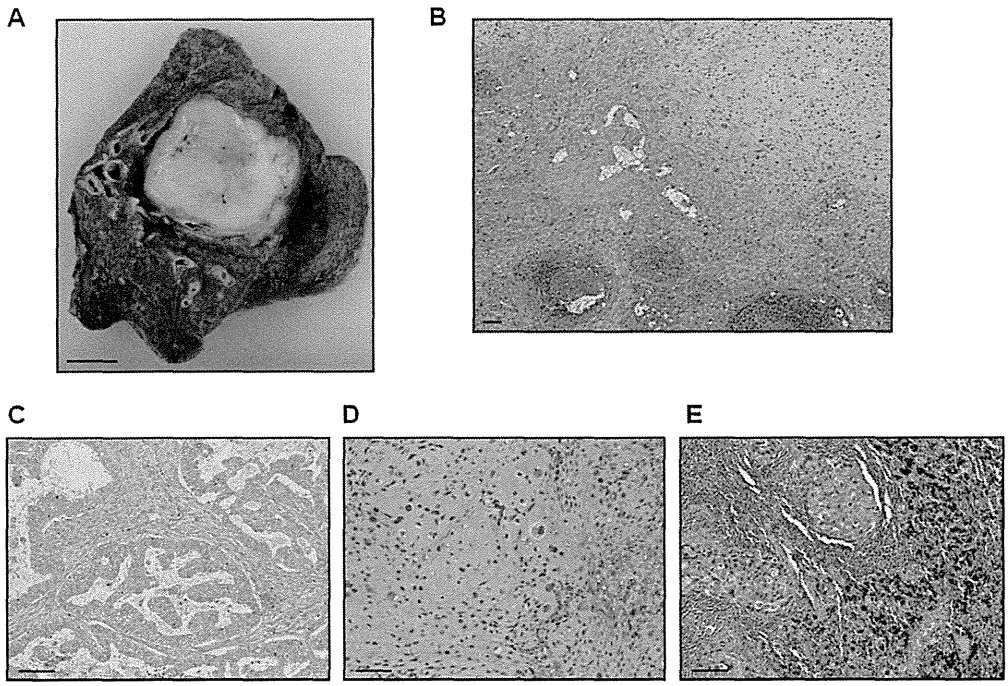

Fig. 2. The cut sections exhibited a gray, whitish component encircled with a yellow, whitish component (A). Microscopic findings of the tumor indicated biphasic features consisting of both adenocarcinoma (B and C) and chondrosarcoma (B and D). The #12l lymph node was metastasized by the adenocarcinoma component (D). Scale bar: 1.0 cm (A) and 100 μm (B–E).

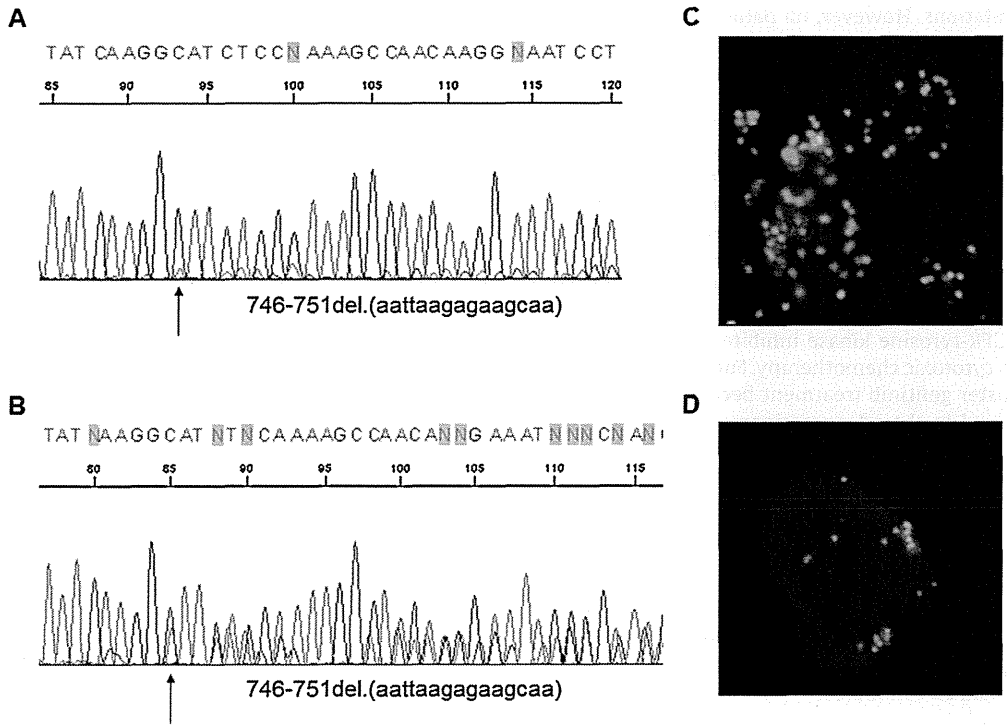

Fig. 3. Direct sequencing method showed that both the adenocarcinoma (A) and chondrosarcoma components (B) harbored an exon19 deletion in the *epidermal growth factor receptor* (*EGFR*) gene. Representative images of a fluorescence in situ hybridization assay showing the amplification of the *EGFR* gene in both the adenocarcinoma (C) and chondrosarcoma components (D). Orange color: *EGFR* DNA; green color: chromosome 7 control (*CEP7*) DNA.

Since the tumor was located in the proximal region of the 9th segment, it was impossible to perform partial resection, and left lower lobectomy with nodal resection was therefore completed. The cut sections exhibited a gray, whitish component encircled with a yellow, whitish component, with a maximum diameter of 3.7 cm (Fig. 2A). The pathological examination revealed that the tumor was composed of a carcinomatous component and a sarcomatous component (Fig. 2B). The carcinomatous component exhibited adenocarcinoma, papillary and acinar subtypes with focal neuroendocrine differentiation (Fig. 2C), whereas the sarcomatous component was composed of chondrosarcoma (Fig. 2D). In addition, metastasis of the adenocarcinoma component to the #12l lymph node was observed (Fig. 2E). Based on these findings, the patient was pathologically diagnosed with stage T2aN1M1b (Stage IV) lung carcinosarcoma.

Genetic analyses were performed to detect mutations in the *EGFR* gene and rearrangement of the *anaplastic lymphoma kinase* (*ALK*) gene. Microdissection was conducted to separate the two components, followed by reverse transcription-polymerase chain reaction (RT-PCR) and direct sequencing methods. Intriguingly, both the adenocarcinoma and chondrosarcoma components were proven to harbor an exon19 deletion in the *EGFR* gene (Fig. 3A: adenocarcinoma and Fig. 3B: chondrosarcoma). Furthermore, the same *EGFR* mutation was identified in the metastasized lymph node (data not shown). A fluorescence in situ hybridization assay identified the amplification of the *EGFR* gene in both components, predominantly in the adenocarcinoma component (Fig. 3C: adenocarcinoma and Fig. 3D: chondrosarcoma), which was perfectly in line with the finding that the signals of the mutant allele were more predominant than those of the wild-type in both components (Fig. 3A and B), although more so in the adenocarcinoma component than in the chondrosarcoma component. No rearrangement of the *ALK* gene was identified in either component. The patient was discharged with no complications nine days after the operation and is undergoing radiotherapy of the lumbar lesion. The patient approved this case report and the accompanying images for publication.

3. Discussion

Sarcomatoid carcinomas (SCs) are rare malignancies of the lungs, accounting for 1% or less of all lung tumors, and are known to behave in a more aggressive fashion than other histological subtypes of non-small cell lung cancer (NSCLC) [7,8]. The histologic subtypes of SC are divided into five groups, i.e., pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma and pulmonary blastoma [1]. Regarding carcinosarcomas, Koss et al. conducted a clinicopathologic analysis of a large series of 66 patients with these lesions [9]. Carcinosarcomas were identified predominantly in male smokers compared to females, and the median patient age was 65 years. The 5-year survival rate was 21.3%, which is similar to that reported by Martin et al. [8]. Additionally, the frequency of epithelial components was as follows: squamous cell carcinoma (46%), adenocarcinoma (31%) and adenosquamous carcinoma (19%). The sarcomatous components included rhabdomyosarcoma, chondrosarcoma, osteosarcoma and combinations of these elements. In the present female patient, chondrosarcoma was observed concomitantly with adenocarcinoma.

Mutations of oncogenic drivers, such as *EGFR* [10], *ALK* [11] and so on, have been identified, and molecular-targeted therapy has been proven to be effective for treating NSCLC patients with mutations in these genes [12]. As for SCs, several reports have previously investigated the *EGFR* mutation status [2–5]. Studies by Italiano and Pelosi reported that no mutations of the *EGFR* gene were observed in 22 and 23 cases of lung SC, respectively [2,3]. In contrast, there exist two reports identifying *EGFR* mutations in patients with lung SC [4,5]. Jiang et al. showed that nine of 32 patients with lung SC

harbored *EGFR* mutations. However, no patients with carcinosarcoma were included in that study. Furthermore, Leone et al. analyzed mutations of the *EGFR* gene in 23 cases of lung SC, and identified two patients who harbored *EGFR* mutations; both patients had exon19 in-frame deletions [5]. Importantly, the two patients with *EGFR* mutations cases both exhibited pleomorphic and giant cell carcinoma features (the author's reply). Accordingly, to the best of our knowledge, no mutations in the *EGFR* gene have been identified in patients with carcinosarcoma, and the current patient therefore represents the first case of lung carcinosarcoma with an *EGFR* mutation. Although SCs of the lungs are generally thought to be chemorefractory [13], the present patient would benefit more from EGFR-tyrosine kinase inhibitors, such as gefitinib and erlotinib, than cytotoxic chemotherapy. Furthermore, it may be feasible to administer gefitinib treatment because the metastatic lymph node involved in the adenocarcinoma component exhibited the *EGFR* mutation, indicating that the lumbar lesion was also assumed to be an adenocarcinoma harboring the *EGFR* mutation.

4. Conclusion

In summary, we herein reported the very rare case of a 61-year-old female patient with carcinosarcoma harboring an exon19 deletion in the *EGFR* gene. Although carcinosarcoma is a rare malignancy of the lungs, genetic analyses of oncogenic drivers, such as the *EGFR* gene, should be conducted.

Conflict of interest statement

None declared.

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We thank Mrs. Yoko Takeda for performing the RT-PCR and direct sequencing methods, Mrs. Yuko Mitsuoka for conducting the immunohistochemistry and Dr. Brian T. Quinn for providing critical comments on the manuscript. Furthermore, we express special thanks to Drs. Alvaro Leone and Paolo Graziano for providing their data showing that the two patients with *EGFR* mutations in Reference 5 both exhibited pleomorphic and giant cell carcinoma features.

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Case report

An extremely rare case of small-cell lung cancer harboring variant 2 of the *EML4-ALK* fusion gene

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ABSTRACT

Anaplastic lymphoma kinase (*ALK*) fuses *echinoderm microtubule-associated protein-like 4* (*EML4*) to acquire a transforming activity in lung adenocarcinomas. However, the presence of an *EML4-ALK* fusion gene in other lung cancer histologies is an extremely rare phenomenon. A 43-year-old female was referred to our department due to dyspnea on effort and left back pain. Computed tomography (CT) showed a large mass in the upper lobe of the left lung and a massive left pleural effusion, while a CT-guided needle biopsy confirmed a diagnosis of small-cell lung cancer (SCLC). Surprisingly, the tumor was genetically considered to harbor the *EML4-ALK* fusion gene (variant 2). Although the patient underwent two regimens of cytotoxic chemotherapy for SCLC, she died approximately seven months after the administration of first-line chemotherapy. Our analysis of 30 consecutive patients with SCLC for *EML4-ALK* revealed that two patients, including the current patient and a patient we previously reported, harbored the *EML4-ALK* fusion gene.

1. Introduction

Oncogenic driver mutations, such as *epidermal growth factor receptor* (*EGFR*), *anaplastic lymphoma kinase* (*ALK*) and so on, have been shown to play essential roles in tumorigenesis, survival and proliferation in lung cancer, especially adenocarcinoma [1,2]. Driver mutations have attracted attention as potential targets of kinase inhibitors [2,3]. In addition to the molecular pathogenesis of lung adenocarcinomas, genetic insights into the pathogenesis of squamous cell carcinoma and small-cell lung cancer (SCLC) have recently been reported [4,5]. However, to the best of our knowledge, there is only one case of *echinoderm microtubule-associated protein-like 4* (*EML4*)-*ALK*-positive SCLC combined with adenocarcinoma, which we previously reported [6]. We herein report a genetically rare case of SCLC harboring an *EML4-ALK* fusion gene and describe the patient's clinical course.

2. Case report

A 43-year-old female ex-smoker of five pack-years was referred to our hospital due to dyspnea on effort and left back pain. A chest X-ray showed a large mass shadow in the left upper lung field and decreased transparency in the left lower lung field. Computed tomography (CT) revealed a large, irregular mass with a maximum diameter of 10 cm in the left upper lobe invading the 4th rib (Fig. 1A) and a massive left pleural effusion. Laboratory examinations revealed elevations in the levels of neuron specific enolase (NSE; 37.7 ng/ml) and pro-gastrin-releasing peptide (ProGRP; 1740 ng/ml), whereas no abnormalities were observed in other tumor markers. A CT-guided tumor biopsy was then performed, and the tumor was pathologically diagnosed as small-cell lung cancer (SCLC) with immunoreactivity to synaptophysin and CD56 (Fig. 2A and B), while no immunoreactivity against thyroid transcription factor-1 (TTF-1) was observed (Fig. 2C). The clinical stage was ultimately determined to be IV (cT3N0M1a: extensive disease). Multiplex reverse transcription-polymerase chain reaction (RT-PCR) and direct sequencing methods revealed the tumor to harbor variant 2 of the *EML4ALK* fusion gene (Fig. 2D), whereas no mutations of *epidermal growth factor receptor* (*EGFR*) or *TP53* were observed (data not shown). As the performance status of the patient

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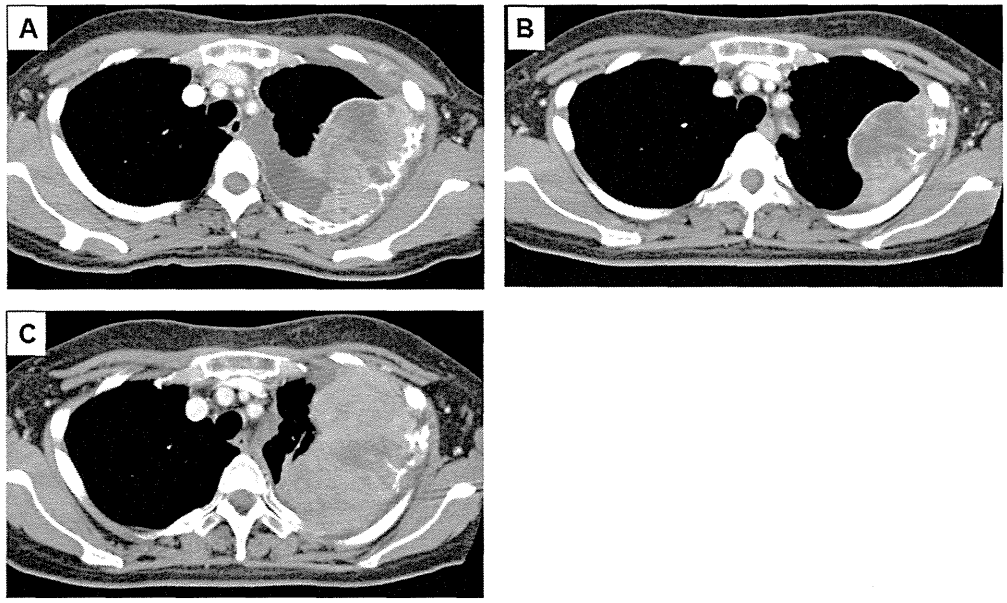

Fig. 1. Computed tomography showed a large mass invading the left 4th rib. (A) CT showed the mass approximately 2.5 (B) and four months (C) after the administration of first-line chemotherapy.

was 3, carboplatin (CBDCA) in combination with etoposide (VP-16) was administered as a first-line regimen with daily thoracocentesis of the pleural effusion. Since the PS improved from 3 to 0 following the administration of one cycle of CBDCA + VP-16, the patient underwent three cycles of cisplatin (CDDP) + VP-16. Although a partial response (PR) was achieved (Fig. 1B) and the levels of NSE and ProGRP decreased (9.9 and 409 ng/ml, respectively) after four cycles of chemotherapy, progressive disease was observed 1.5 months

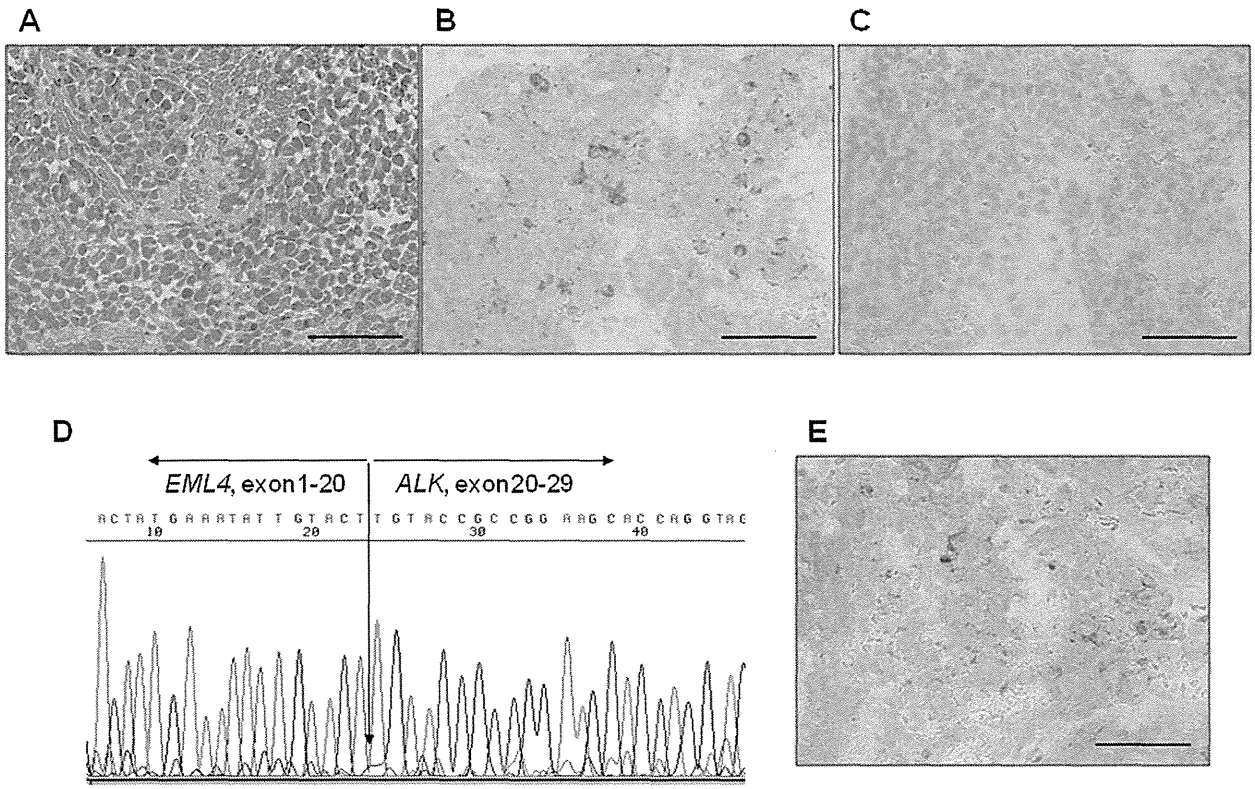

Fig. 2. (A) Microscopic findings of the tumor indicated small, round cells with abundant chromatin. (B) Immunohistochemistry using a specific antibody against synaptophysin (27G12, Novocastra) showed the tumor to be positively stained. (C) Immunohistochemistry using an antibody with specificity for thyroid transcription factor-1 (TTF-1; 8G7G3/1, Dako) showed that the tumor did not have immunoreactivity for TTF-1. (D) The direct sequencing method identified variant 2 of the *echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase* (*ALK*) fusion gene. (E) Immunostaining using an antibody that specifically detects ALK (5A4, Nichirei) revealed immunopositivity of the tumor for ALK. Scale bar (A–C, E): 50 μm.

after the confirmation of a PR (Fig. 1C). Thereafter, a CT-guided biopsy was performed again, and the SCLC histology was reconfirmed. Furthermore, the presence of the *EML4-ALK* fusion gene was confirmed on immunohistochemistry (IHC) using an antibody that specifically detects ALK (Fig. 2E). Although amrubicin was then administered, the disease continued to progress. Approximately six months after the administration of the first-line chemotherapy, the patient was transferred to another hospital for hospice care and died 18 days after the transfer. Based on her clinical course, the progression-free survival (PFS) and overall survival (OS) from the administration of the first-line therapy were approximately four and seven months, respectively.

3. Discussion

Gene mutations in tyrosine kinases play essential roles in the pathogenesis of lung adenocarcinoma and have attracted much attention as potential therapeutic targets in the treatment of adenocarcinoma. The *ALK* gene has been shown to fuse the *EML4* gene, and as a consequence, to possess a transforming activity [1]. Importantly, tumors with the *EML4-ALK* fusion gene, the second most well-known tyrosine kinase in lung adenocarcinoma, can be successfully treated with ALK inhibitors [7]. Mutations of the *EGFR* gene in SCLC have already been identified (5/122: 4%) [8], and integrative genomic analyses have revealed mutations of tumor suppressor genes (TP53 and RB1), histone modifiers (MLL1) and so on in SCLC. However, to the best of our knowledge, there has been only one case of an SCLC patient harboring the *EML4-ALK* fusion gene [6]. In our previous case, fusion of the *ALK* gene to the *EML4* gene was intriguingly detected only in the SCLC component of the resected combined adenocarcinoma with SCLC. Although this previous patient harbored variant 1 of the *EML4-ALK* fusion gene, variant 2 of the fusion gene was identified in the current case. Based on these findings, there are considered to be multiple *EML4-ALK* variants in SCLC patients as well as adenocarcinoma patients. We analyzed 30 consecutive SCLC patients whose RNAs were available for RT-PCR and direct sequencing methods between April 2010 and March 2012. Two of the patients, the present patient and the patient we previously reported [6], were found to harbor the fusion gene. Although a positive reaction of IHC for the ALK protein expression without *ALK* fusion was reported to be found in a patient with SCLC [9], this does not apply to the current case because the fusion was detected using RT-PCR and direct sequencing methods. Furthermore, the possibility of the transformation of adenocarcinoma into SCLC, which is associated with the acquisition of resistance to EGFR-tyrosine kinase inhibitors (TKIs), should be taken into consideration [10]. However, this mechanism does not apply to the present patient, since no EGFR-TKIs were administered because of the absence of the *EGFR* mutations.

One of the limitations of the current case report is that the tumor was diagnosed to be SCLC by a biopsy sample. Although biopsy samples do not always reflect the exact histology of the whole tumor, and the absence of lymphadenopathy and *p53* mutations, which occur in more than 90% of all SCLCs [11], is relatively rare, the SCLC histology was confirmed by several findings in the present case. First, a CT-guided biopsy before and after the first-line chemotherapy diagnosed the tumor to be morphologically SCLC. Second, immunoreactivity of the tumor for synaptophysin and CD56 was observed. Third, the levels of tumor markers associated with SCLC, i.e., NSE and ProGRP, were elevated, while no elevation was observed in the levels of carcinoembryonic antigen and cytokeratin 19 fragment. Finally, combination chemotherapy with platinum plus VP-16, one of the standard regimens for patients with SCLC, led to a partial response. With regard to TTF-1 expression, TTF-1 was reported to be expressed in all adenocarcinomas harboring the *ALK* rearrangement [12], and TTF-1 expression was also observed in about 80% of SCLCs [13]; however, the current patient showed no expression of TTF-1, as shown in Fig. 2C, which was different from the results we previously reported in Ref. [6], and no definite correlation between TTF-1 expression and the *EML4-ALK* rearrangement in SCLC has been demonstrated so far. Although these findings show an apparently rare presentation of SCLC in the current patient, future studies would help to elucidate the characteristics of patients with SCLC harboring the *EML4-ALK* rearrangement.

Although SCLC manifests with aggressive features, such as rapid progression, these tumors are generally sensitive to chemotherapy. For first-line therapy, the response rate, median PFS and OS range from 67.5 to 84.4%, 4.7–6.9 months and 9.4–12.8 months, respectively [14,15]. Although the current patient achieved a PR after undergoing four cycles of platinum-based chemotherapy, the PFS and OS were much worse than those of historical controls. As a reason for the poor clinical course of the present patient, there is a possibility that the fusion gene affects sensitivity to chemotherapy. There have been two reports on chemosensitivity in patients with the *EML4-ALK* fusion gene [16,17]. Lee et al. reported that *ALK*-positive non-SCLC patients would benefit significantly from pemetrexed chemotherapy, whereas Takeda et al. demonstrated that the efficacy of first-line platinum-based chemotherapy does not depend on the presence or absence of the *EML4-ALK* fusion gene. Therefore, although the significance of *ALK*-positivity for chemosensitivity has yet to be clarified, *EML4-ALK* fusion may be involved in the sensitivity of platinum-based chemotherapy.

4. Conclusion

We herein reported a very rare case of SCLC in which the patient harbored variant 2 of the *EML4-ALK* fusion gene. Although the frequency and significance of the fusion gene in SCLC patients has not been determined, this phenomenon suggests that SCLC patients harboring the *EML4-ALK* fusion gene can be successfully treated with ALK inhibitors.

Conflict of interest statement

Drs. Takenoyama, Shiraishi, Hirai, Yamaguchi, Seto and Ichionose have conflicts of interest with Pfizer, AstraZeneca and Chugai to disclose as shown in the attached file. The other authors have no conflicts of interest to declare.

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ORIGINAL ARTICLE

Gemcitabine and vinorelbine as second-line or beyond treatment in patients with malignant pleural mesothelioma pretreated with platinum plus pemetrexed chemotherapy

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Abstract
Background Malignant pleural mesothelioma (MPM) is an aggressive neoplasm that responds poorly to chemotherapy. Although treatment with pemetrexed in combination with cisplatin serves as first-line chemotherapy for MPM, the optimal second-line and beyond therapy has not yet been fully examined.
Methods Between March 2008 and October 2011, 17 consecutive Japanese patients pretreated with at least one regimen of platinum plus pemetrexed chemotherapy received gemcitabine and vinorelbine. Responses, survival time, and toxicity were retrospectively evaluated.
Results Response [partial response (PR) + complete response (CR)] and disease control [stable disease (SD) + PR + CR] rates were 18 and 82 %, respectively. The median progression-free survival (PFS) after combination chemotherapy was 6.0 months, whereas the median overall survival (OS) was 11.2 months. Grade 3 or 4 neutropenia and anemia were observed in 41 and 29 % of patients, respectively, and one patient experienced febrile neutropenia. Grade 3 or 4 nonhematologic toxicities included constipation (6 %) and phlebitis (6 %).
Conclusion Combination chemotherapy using gemcitabine with vinorelbine was shown to have moderate activity in Japanese MPM patients pretreated with platinum plus pemetrexed chemotherapy. A further multicenter phase II trial is warranted to confirm the efficacy and safety of this combination treatment.

Keywords Malignant pleural mesothelioma · Gemcitabine · Vinorelbine · Second-line treatment and beyond

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Introduction

Malignant pleural mesothelioma (MPM) is a relatively rare tumor arising from mesothelial cells, and prognosis is very poor. Asbestos exposure has been shown to be a main cause of MPM [1], and in Japan, it accounts for approximately 75 % of MPM cases [2]. As another predisposing factor, mutations of BRCA-1-associated protein-1 and neurofibromatosis type 2 can also cause MPM [2, 3]. The natural course of MPM is poor, and median survival ranges from 4 to 12 months without intervention [4]. Although surgical excision can be considered part of multimodal therapy, its impact on patient survival and quality of life is controversial [5, 6]. Therefore, chemotherapy is considered to be the main therapeutic modality.

A phase III study by Vogelzang and colleagues showed the superior activity of treatment with pemetrexed (PEM) plus cisplatin [cis-diamminedichloroplatinum(II) (CDDP)] to CDDP alone for patients with MPM [7]. The median survival time and response rates in the PEM/CDDP arm were 12.1 months and 41.3 % compared with 9.3 months and 16.7 % in the CDDP arm ($P = 0.020$ and $P < 0.0001$, respectively), confirming this combination chemotherapy to be a standard first-line chemotherapy in patients with MPM. However, there have so far been very few reports of a second-line or beyond treatment for patients with MPM

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pretreated with platinum plus PEM chemotherapy as first-line chemotherapy.

The efficacy and safety of vinorelbine (VNR) have been assessed in both second- and first-line settings [8, 9]. In a single-center phase II study, Stebbing et al. reported that VNR monotherapy for relapsed MPM patients produced partial responses (PR) in 16 % of patients and stable disease (SD) in 68 %, with an overall survival (OS) of 9.6 months [9]. In addition, gemcitabine (GEM) proved to be active as both a first- and second-line treatment when used in combination with other drugs, such as CDDP or oxaliplatin [10, 11]. Based on these findings, combination chemotherapy using GEM with VNR, the significance of which was assessed in lung cancer patients [12], was suggested to have potential antitumor activity for patients with MPM as a second-line and beyond therapy. Additionally, the general condition of patients is often good at the time of disease progression following first-line chemotherapy. Therefore, even relapsed patients are considered able to receive this combination therapy. We retrospectively investigated the use of the combination of GEM with VNR for Japanese MPM patients pretreated with platinum plus PEM.

Patients and methods

Patients

We conducted a retrospective search of the medical records at National Kyushu Cancer Center for patients treated from March 2008 through October 2011. Among the 27 patients with MPM during this period, there were 17 consecutive patients with nonresectable or with recurrent disease after surgical resection who had been pretreated with at least one platinum agent plus PEM chemotherapy as a first-line regimen and who received GEM and VNR as a second or beyond treatment. All patients had sufficient data to evaluate their characteristics and clinical outcomes for the analysis. Their age, sex, asbestos exposure, Eastern Cooperative Oncology Group performance status (ECOG-PS), histology, stage, first-line chemotherapy, and responses to the combination chemotherapy were assessed. The clinical or pathological stage of the disease was based on the International Mesothelioma Interest Group (IMIG) staging system [13]. Histological subtypes were determined using the World Health Organization (WHO) classification for cell types. Patients were evaluated for response every two cycles according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria [14]. The National Cancer Institute Common Toxicity Criteria, version 4.0, was applied to evaluate adverse events. Written informed consent was obtained from all patients, and the institutional review board of our institution approved this study.

Treatment schedule and dose adjustment

All patients were treated with GEM 1000 mg/m^2 plus VNR 25 mg/m^2 on days 1 and 8 every 3 weeks, and the treatment was repeated until disease progression or unacceptable toxicity occurred. VNR doses were first reduced by 20 % in patients who experienced grade 4 hematological toxicities or grade 3 or greater nonhematological toxicities or whose scheduled treatment was skipped on day 8 in the previous cycle. Second, GEM doses were reduced by 20 % when these conditions were met again. If further dose reduction was required, the chemotherapy regimen was stopped.

Statistical analysis and survival data

Survival time was calculated from the beginning of GEM plus VNR treatment to disease progression or death from any cause. The survival curve was produced using the Kaplan–Meier method. Univariate and multivariate analyses were performed by the logrank test and a stepwise method.

Results

Patient characteristics

From March 2008 to October 2011, 17 consecutive Japanese patients with MPM who had been pretreated with at least a regimen containing one platinum agent plus PEM as a first-line chemotherapy received GEM and VNR on days 1 and 8. Fourteen of the 17 patients received the combination chemotherapy as a second-line treatment, and three patients received it as a third-line or beyond treatment. Patient characteristics are summarized in Table 1. Median age was 58 (range 41–75) years, and 88 % of patients were men. Although exposure to asbestos was known in 65 % of cases, 6 % of cases showed no findings of asbestos exposure, and it was unclear in 29 %. The majority of patients (71 %) had an ECOG-PS of 1. Histological subtypes were as follows: epithelioid (82 %), biphasic (6 %), and sarcomatoid (12 %). Three patients (18 %) had stage I disease, none (0 %) had stage II, four (24 %) had stage III, and ten (58 %) had stage IV disease. Sixteen of the 17 patients (94 %) had received CDDP plus PEM, and one had received carboplatin (CBDCA) plus PEM as the first-line regimen; ten patients (58 %) achieved PR or SD, and six (35 %) had progressive disease (PD).

Table 1 Patient demographics and baseline characteristics

Characteristics	Number (%)
Median age (range)	58 (41–75)
Sex	
Male	15 (88)
Female	2 (12)
Asbestos exposure	
Yes	11 (65)
No	1 (6)
Unknown	5 (29)
Performance status	
0	5 (29)
1	12 (71)
Histology	
Epithelioid	14 (82)
Biphasic	1 (6)
Sarcomatoid	2 (12)
IMIG stage	
I	3 (18)
II	0 (0)
III	4 (24)
IV	10 (58)
First-line chemotherapy	
Cisplatin + pemetrexed	16 (94)
Carboplatin + pemetrexed	1 (6)
Response to first-line chemotherapy[a]	
CR	0 (0)
SD + PR	9 (53)
PD	6 (35)

IMIG International Mesothelioma Interest Group, *CR* complete response, *SD* stable disease, *PR* partial response, *PD* progressive disease

[a] Responses of two patients were not evaluable

Table 2 Hematological and nonhematological toxicities

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	2	4	4	1
Leucopenia	0	5	0	4
Neutropenia	0	0	3	4
Thrombocytopenia	0	2	0	0
Nonhematological				
Nausea	1	0	0	0
Appetite loss	7	0	0	0
General fatigue	8	0	0	0
Constipation	0	0	1	0
Phlebitis	3	2	1	0
Febrile neutropenia	0	0	1	0
AST elevation	2	0	0	0
ALT elevation	1	0	0	0
Creatinine elevation	3	0	0	0

AST aspartate aminotransferase, *ALT* alanine aminotransferase

In total, 106 cycles were delivered to the 17 patients, and 38 cycles (35 % of all cycles: 38 VNR and 24 GEM) were reduced. The median number of cycles of the combination chemotherapy using GEM and VNR was five, with a range from one to 19 cycles, and all but one patient received two or more cycles.

Toxicity

Table 2 demonstrates treatment-related toxicities. Grade 3 or 4 anemia, leucopenia, and neutropenia, respectively, were observed in 29, 24, and 41 % of cases. Although grade 3 or 4 nonhematological toxicities included constipation (6 %) and phlebitis (6 %), these were manageable. One patient experienced febrile neutropenia. There were no treatment-related deaths. Three patients required dose reduction of both GEM and VNR, whereas three and 11 patients required dose reduction of VNR only and no dose reduction, respectively.

Response and survival

All 17 patients were evaluable for response assessment. Three [18 %; 95 % confidential interval (CI) 3.8–43.4 %] achieved PR, 11 (64 %; 95 % CI 38.3–85.8 %) had SD, and PD was observed in three (18 %; 95 % CI 3.8–43.4 %). No complete response (CR) was seen. Response [partial response (PR) + complete response (CR)] and disease control [stable disease (SD) + PR + CR] rates were 18 and 82 %, respectively. The median progression-free survival (PFS) after combination chemotherapy was 6.0 months, and the 1-year PFS rate was 17.6 % (95 % CI 0.0–35.6 %; Fig. 1, solid line). Median OS and the 1-year OS rate after administration of the combination chemotherapy were 11.2 months and 43.9 % (95 % CI 19.6–68.2 %), respectively (Fig. 1, dashed line). As shown in Table 3, the median PFS according to sex (male versus female), IMIG stage (I–III versus IV), and responses (SD + PR versus PD) for platinum plus PEM were 3.0 versus 14.5 months, 8.8 versus 2.4 months, and 6.8 versus 1.6 months, respectively ($P = 0.015$, 0.032 and 0.012, logrank test). No significant impact on PFS was observed for other variables, and none of the variables had any significant impact on OS. On multivariate analysis, relationships between clinical variables and survivals could not be evaluated using a stepwise method for multivariate analysis, because this study did not have a sufficient number of patients.

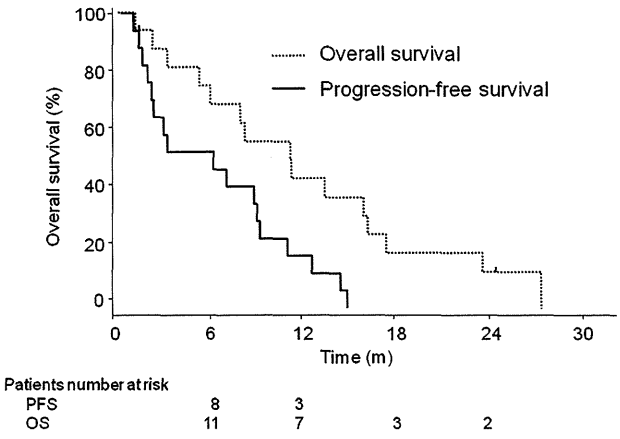

Fig. 1 Progression-free (PFS) (*solid line*) and overall (OS) (*dashed line*) survival after administration of gemcitabine and vinorelbine

Table 3 Progression-free (PFS) and overall (OS) survival according to patient characteristics

Characteristics	Number (%)	PFS (months)		OS (months)	
		Median	*P* value	Median	*P* value
Sex					
Male	15 (88)	3.0		11.1	
Female	2 (12)	14.5	0.0147	25.5	0.0766
Performance status					
0	5 (29)	3.0		11.2	
1	12 (71)	6.4	0.2632	11.1	0.5552
Age					
<65	12 (71)	6.4		9.7	
>65	5 (29)	2.7	0.7521	13.7	0.8299
Curative surgery					
Yes	4 (24)	10.5		16.7	
No	13 (76)	2.7	0.2942	11.1	0.30690
Histology					
Epithelioid	14 (82)	4.5		11.1	
Nonepithelioid	3 (18)	8.6	0.9047	15.9	0.9043
IMIG stage					
I–III	7 (42)	8.8		16.2	
IV	10 (58)	2.4	0.0315	7.9	0.1162
Response to first-line chemotherapy[a]					
SD + PR	9 (53)	6.8		11.2	
PD	6 (35)	1.6	0.0120	5.9	0.2032

IMIG International Mesothelioma Interest Group, *SD* stable disease, *PR* partial response, *PD* progressive disease

[a] Responses of two patients were not evaluable

Discussion

In this study, the efficacy and safety of combination chemotherapy with GEM plus VNR as a second-line and beyond treatment were retrospectively evaluated. Response and disease control rates were 18 and 82 %, respectively, with a median PFS and OS of 6.0 and 11.2 months, respectively. Although this was a retrospective study analyzing a small Japanese population of 17 patients at a single institute, these findings are comparable with or superior to those obtained using other retrospective and prospective second-line cytotoxic agents in pretreated MPM patients (Table 4). With regard to adverse events, grade 3 or 4 anemia, leucopenia, and neutropenia were observed in 29, 24 and 41 % of patients, respectively, and two patients (12 %) experienced grade 3 or 4 nonhematological toxicities, such as constipation and phlebitis. These events were all manageable, and it was also interesting to note that no treatment-related death was observed. These results suggested that combination chemotherapy using GEM with VNR might be a potential therapeutic regimen for MPM patients pretreated with platinum plus PEM chemotherapy. With regard to response evaluations, modified RECIST criteria were applied, as in other studies. However, Tsutani et al. [15] reported on the prognostic significance of metabolic response using positron emission tomography (PET)/computed tomography (CT) after neoadjuvant chemotherapy for resectable MPM, demonstrating that radiological responses did not have prognostic significance in these patients. In our study, metabolic response using PET/CT was not assessed, and a future analysis using PET/CT should therefore be performed to clarify the significance of metabolic response after combination chemotherapy with GEM and VNR.

The standard first-line regimen for MPM is CDDP plus PEM, and this regimen gives a median OS of approximately 1 year after administration of the drugs [7]. As shown in Table 4, various types of chemotherapy have been prospectively explored for treating MPM patients as second-line and beyond treatment; however, no standard regimen has been established [16]. Furthermore, very few regimes as second-line chemotherapy after platinum plus PEM chemotherapy as the first-line treatment have so far been assessed. The significance of VNR in the second-line setting has been evaluated by some groups [9, 16]. Stebbing et al. [9] showed the high disease control rate using VNR monotherapy in 84 % of patients with relapsed MPM in a single-center phase II study, with an OS of 9.6 months. With regard to GEM, combination chemotherapy with oxaliplatin was assessed in MPM pretreated with PEM by Xanthopoulos et al. [11], and the median survival time from oxaliplatin/GEM administration and the disease control rate was reported to be 24.3 weeks and 44.8 %, suggesting its efficacy. Additionally, we previously assessed combination chemotherapy using GEM with VNR plus CDDP for MPM patients as first-line therapy and found it highly effective with manageable toxicities [17]. Given these findings and the evidence that combination chemotherapy of CDDP with PEM is a standard first-line therapy,

Table 4 Second-line chemotherapy for patients with malignant pleural mesothelioma

Author	Phase	Chemotherapy	Number	Response rate (%)	Median PFS (months)	Median OS (months)
Xanthopoulos et al.	Retrospective	Oxaliplatin ± GEM	29	7	2.7	5.6
Zucali et al.	II	GEM + VNR	30	10	2.8	10.9
Nowak et al.	II	Sunitinib	53	12	3.5	6.1
Jackman et al.	II	Erlotinib + bevacizumab	24	0	2.2	5.8
Ramalingam et al.	II	Belinostat	13	0	1.0	5.0
Our result	Retrospective	GEM + VNR	17	18	6.0	11.2

GEM gemcitabine, *VNR* vinorelbine, *PFS* progression-free survival, *OS* overall survival

we investigated the efficacy and safety of combination chemotherapy using GEM with VNR for patients with MPM as a second-line and beyond therapy, finding moderate antitumor activity and acceptable toxicities. Zucali and colleagues reported the activity and safety of GEM with VNR for MPM patients pretreated with PEM, and the response rate and PFS were 10 % and 2.8 months, respectively [18]. Our study differs in regard to the fact that all patients were pretreated with platinum plus PEM, whereas four (13 %) were pretreated with PEM monotherapy in the previous report. Furthermore, response rate and PFS were 18 % and 6.0 months, respectively, which were comparable with those reported previously. Based on these findings, our results are considered to support the findings of the phase II trial by Zucali et al., and we considered the combination chemotherapy using GEM with VNR to be one of the effective regimens for relapsed MPM patients after the failure of platinum with PEM.

Molecular-targeted therapy has also been evaluated to treat MPMs. Kindler and colleagues reported in their phase III trial that bevacizumab (BEV), a vascular endothelial growth factor inhibitor, in combination with CDDP plus GEM produced no additional benefit for MPM patients compared with CDDP plus GEM [19]. Median OS time and overall response rate were not significantly different between the two arms of their study (15.6 and 14.7 months, 24.5 and 21.8 %, respectively, $P = 0.91$ and $P = 0.74$). In second-line settings, inhibitors, including sunitinib [20], erlotinib [21], and belinostat [22], specifically targeting some molecules have also been examined, as shown in Table 4. However, these reagents are considered to be less effective than cytotoxic reagents. Therefore, focus should be placed on cytotoxic chemotherapy, such as combination treatment using GEM with VNR, in second-line treatments and beyond for MPM patients.

The optimal regimen to be used as second-line and beyond treatment for patients with MPM remains to be determined. Although this was a retrospective study with only 17 patients, results were comparable with or superior to those obtained using other chemotherapy regimens [18]. A prospective study including multiple centers is needed to clarify the efficacy and safety of this combination therapy.

In conclusion, combination chemotherapy using GEM with VNR showed moderate activity with manageable toxicities in relapsed Japanese patients with MPM after failure of platinum with PEM chemotherapy. A multicenter phase II trial is needed to clarify the efficacy and safety of this combination treatment.

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Conflict of interest Drs. Hirai, Shiraishi, Yamaguchi, Seto and Ichinose have financial relationships with Eli Lilly Japan and Kyowa Hakko Kirin Co., Ltd., and other authors have no conflict of interest to declare.

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Do Mutations of the Enhancer of Zeste Homolog 2 Gene Exist in Small-Cell Lung Cancer?

To the Editor:

I read the article by Hubaux et al.[1] entitled "EZH2 promotes E2F-driven SCLC tumorigenesis through modulation of apoptosis and cell-cycle regulation" with much interest. In their study, the authors indicated that the stable down-regulation of the enhancer of zeste homolog 2 (*EZH2*) gene by short hairpin RNA modulates apoptosis and the cell cycle, which results in a reduction of the viability of small-cell lung cancer (SCLC) cell lines, and concluded that EZH2 can be a potential therapeutic target for SCLC. Indeed, EZH2 is known to be targeted by Polycomb repressor complex 2 inhibitors, that is, S-adenosyl-homocysteine hydrolase inhibitor 3-deazaneplanocin A.[2]

Several reports suggested that EZH2 is overexpressed at the protein level in various types of solid tumors, including lung cancer, and its overexpression correlates with a poor prognosis in patients with resected lung cancer.[3] Additionally, somatic mutations within two residues in the catalytic SET domain of the *EZH2* gene (Y641 and A677) were identified to have increased H3K27 trimethylation and to alter the substrate specificity of the mutated *EZH2* in diffuse large B-cell lymphoma and follicular lymphoma. Importantly, lymphomas harboring these mutations in the *EZH2* gene can be successfully targeted by a potent, highly selective, S-adenosylmethionine-competitive, small-molecular inhibitor of EZH2 methyltransferase activity, that is, GSK126, in in vitro and in vivo models.[4]

Although recent integrative genomic analyses identified recurrent mutations of SCLC, such as the cAMP-response element binding protein (CREB) binding protein (*CREBBP*), E1A binding protein p300 (*EP300*), and mixed-lineage leukemia (*MLL*) genes that encode histone modifiers, as well as the inactivation of tumor protein p53 (*TP53*) and retinoblastoma 1 (*RB1*), mutations of the *EZH2* gene have not yet been identified. In addition to the report by Peifer et al.,[5] our analysis of 35 patients diagnosed with SCLC failed to identify mutations of the *EZH2* gene in the SET domain.

In conclusion, we feel that further studies should be focused on the identification of mutations of the *EZH2* gene, and if any are found, it should be clarified which of the overexpressed or mutated *EZH2* genes most intensely promote SCLC tumorigenesis. Furthermore, it should be elucidated which of these alterations can be successfully targeted for patients with SCLC.

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In Response:

We thank Dr. Toyokawa and colleagues for their interest and for their thoughtful comments regarding our article demonstrating the importance of EZH2 in small-cell lung cancer (SCLC) tumorigenesis.[1] Their letter to the Editor reiterates that EZH2 overexpression occurs in several cancer types and that it correlates with poor prognosis in lung cancer patients. Importantly, they also discuss the role of mutations in the catalytic SET domain as a mechanism of EZH2 activation in lymphomas, for which potent inhibitors have been shown to have therapeutic efficacy in vivo. They reaffirm EZH2 as an attractive therapeutic target given the prominence of its activation in SCLC. However, EZH2 mutations were not detected in a recent SCLC study (N = 29), nor in Toyokawa's own cohort of SCLCs (N=35), raising the question of how EZH2 becomes aberrantly activated in SCLC.[2]

We further investigated public data to detect EZH2 SET domain mutations in SCLC. None were identified in the NCI-H209 SCLC cell line sequence, in 42 SCLC exome sequences,[3] or in 121 SCLCs with EZH2 mutation status in the COSMIC database. It is apparent that unlike other cancer types, mutations are not a common mechanism of EZH2 activation in SCLC. Furthermore, analysis of data from two recent studies on SCLC tumors and cell lines from

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the Sanger Institute's Cancer Genome Project revealed that EZH2 was not a target of DNA amplification, which is consistent with our recent findings,[4] ruling out copy number alteration as a mechanism of EZH2 activation.[2,3] MicroRNA down-regulation is another possible mechanism of EZH2 up-regulation. EZH2 is a known target of miR-101, which is downregulated in cancer, although we have shown that miR-101 DNA copy loss is not prominent in SCLC.[5] We assessed copy status of other EZH2-targeting miRNA using Sanger's data on 53 SCLC lines. miR-124, miR-138, miR-26a, and miR-98 exhibited frequent single copy loss (38%–81% of samples), however, none of these miRNA were located within significant chromosomal regions of loss in recent tumor profiling studies, and expression should be assessed to accurately determine miRNA status.[2,3]

Recently, we investigated the E2F/Rb pathway upstream of EZH2 and discovered that disruption of this pathway is a prominent mechanism of EZH2 activation in SCLC.[4] We identified copy loss of *RB1* or gains of *E2F1*, *E2F2*, or *E2F3* in 96% of the SCLCs we investigated. EZH2 is an established transcriptional target of this pathway, and concordantly, we found that pathway disruption was strongly correlated with EZH2 expression. Furthermore, we showed that E2F manipulation caused changes in EZH2 protein expression, demonstrating the consequence of E2F/Rb pathway disruption on EZH2 in SCLC. These results suggest that genomic disruption of upstream regulators is a prominent mechanism of EZH2 activation in SCLC.[4]

Regardless of the EZH2 activation mechanism, based on the facts that (1) EZH2 overexpression is nearly universal in SCLC, (2) EZH2 expression is scarcely detectable in nonmalignant tissues throughout the body,[4] and (3) EZH2 inhibitors are currently available, we agree with Toyokawa et al. and strongly believe that EZH2 is an extremely promising therapeutic target for this very aggressive cancer.

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Surgical Outcomes after Initial Surgery for Clinical Single-station N2 Non-small-cell Lung Cancer

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Objective: Single-station N2 (Stage IIIA) non-small-cell lung cancer has been reported to have a relatively favorable prognosis after surgery. However, most previous studies examined surgical outcomes in N2 disease by pathologic nodal status but not by clinical nodal status. The objective of this study was to clarify the surgical outcomes in clinical single-station N2 non-small-cell lung cancer patients.

Methods: A total of 125 consecutive patients with clinical single-station N2 non-small-cell lung cancer were treated in our institution between 1992 and 2008. Among them, 97 (78%) patients underwent thoracotomy, and were included in this retrospective study. We defined clinical single-station N2 node as a node measuring 1–2 cm in a single mediastinal station observed on contrast-enhanced computed tomography. The median follow-up period was 5.9 years (range, 1.8–12.6).

Results: Eighty-eight (91%) patients underwent lung resection. Of them, 17 (19%) had true (pathologic) single-station N2 disease. Twenty-eight (32%) had pathologic multistation N2 and 43 (49%) had pN0–1 disease with favorable prognoses. The overall survival of the clinical single-station N2/pathologic N2 patients after initial surgery was unsatisfactory with a 5-year overall survival of 23.6%, but their prognoses were heterogeneous. True single-station pathologic N2 status (hazard ratio = 0.35, $P = 0.008$) and negative subcarinal node status (hazard ratio = 0.34, $P = 0.022$) were independent favorable prognostic factors after initial resection for clinical single-station N2/ pathologic N2 patients. The patients with both factors revealed a relatively favorable 5-year overall survival of 43.8%.

Conclusion: Clinical single-station N2 status does not always correspond with pathologic true N2 status. From a prognostic point of view, initial surgery for clinical single-station N2 patients is indicated if their true single-station N2 status and negative subcarinal involvement are preoperatively confirmed.

Key words: non-small-cell lung cancer – Stage IIIA – N2 – single-station – initial surgery – chemoradiotherapy

INTRODUCTION

Non-small-cell lung cancer (NSCLC) of clinical N2 (cN2) Stage IIIA disease is considered to be an occult systemic disease with a significantly poor prognosis (1). The survival of cN2 patients with pathologically confirmed N2 (pN2) after surgery alone has been reported to be dismal (~10–15% of 5-year overall survival [OS]) in previous series (2,3), and initial surgery is generally not indicated for cN2 patients, even

if the tumor is technically resectable (1). Many researchers have conducted clinical trials of induction chemotherapy or chemoradiotherapy (CRT) followed by surgery since the 1990s (4–8), but the role of surgery in the multimodality approach is still controversial. Selected N2 patients having downstaged N status or resectable lesion by lobectomy might have surgical indication after CRT (8). However, definitive CRT is currently the recommended treatment of choice for cN2 disease, irrespective of resectability (1). On the other hand, several researchers have demonstrated that minimal N2 disease, such as single-station N2 disease (N2 disease limited to a single mediastinal station), is a favorable prognostic indicator of resected pN2 disease (9–15). Therefore, the question arises as to whether patients with clinical single-station N2 (csN2) NSCLC benefit from initial complete resection. Most previous studies examined surgical outcomes of N2 disease by 'pathologic' nodal status but not by 'clinical' nodal status. The objectives of this study were to retrospectively clarify the outcome of csN2 NSCLC patients after initial surgery.

PATIENTS AND METHODS

Study Population

This study was approved by the Institutional Review Board in June 2010, and written informed consent was waived. Patients' baseline characteristics, treatment modalities and treatment outcomes were obtained retrospectively from the medical records. We reviewed the clinical and pathologic records of NSCLC patients at our hospital between 1993 and 2008. Among them, there were 595 cN2 Stage IIIA patients. Our diagnostic criterion of cN2 has been the presence of enlarged ($\geq$1 cm) mediastinal node on contrast-enhanced computed tomography (CT). A CONSORT diagram of these patients is shown in Fig. 1. A total of 125 (21%, 125/595) patients had csN2 disease, which was defined as NSCLC with non-bulky (1–2 cm) N2 node in a single mediastinal station on the Naruke's lymph node map on contrast-enhanced CT, and were enrolled in this study. The remaining 470 patients had multistation or bulky N2 disease, or poor performance status which precluded active treatment. Before treatment, all the patients underwent thorough staging examinations with chest roentgenography, chest and abdominal contrast-enhanced CT, brain CT or magnetic resonance imaging and bone scintigraphy or positron emission tomography (PET). All diagnoses of csN2 were made based on contrast-enhanced chest CT scans. Although PET was performed in selected patients from 2002, csN2 status was determined by CT findings for all the patients in this series.

Treatment Decision Making

The management of the csN2 patients was decided by the institutional cancer board, which consisted of thoracic

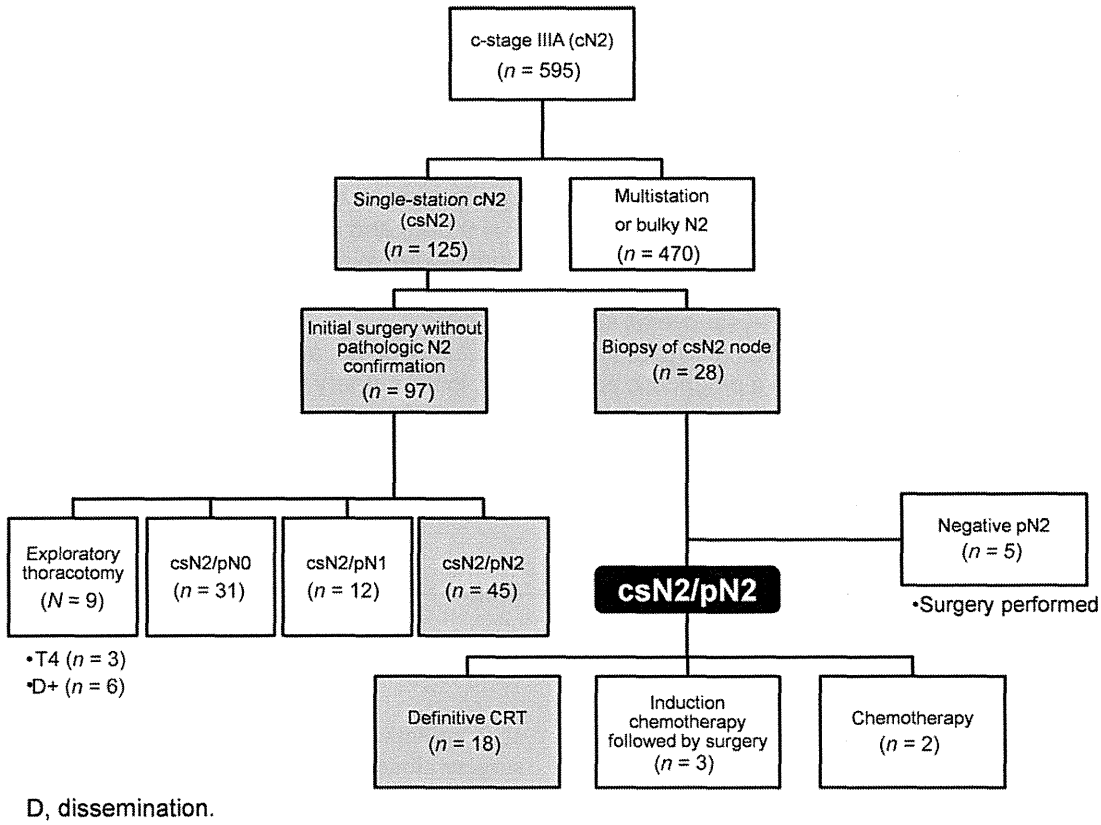

Figure 1. CONSORT diagram for c-stage IIIA (N2) non-small-cell lung cancer patients. D, dissemination; CRT, chemoradiotherapy.