Original Article

Intracavitary chemotherapy with epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) is not superior to TKI monotherapy in controlling malignant pleural effusion recurrence in *EGFR*-mutated lung cancer patients

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Background: Epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC) patients benefit from EGFR-tyrosine kinase inhibitors (TKIs) therapy. There are few studies comparing the efficacy between intrapleural chemotherapy combination with TKIs and TKIs alone in controlling re-accumulation of malignant pleural effusions (MPEs). The purpose of the study was to determine if patients with EGFR-mutated NSCLC and MPEs would benefit from intrapleural chemotherapeutics with an oral EGFR-TKI than EGFR-TKI alone.

Methods: We evaluated *EGFR*-mutated lung cancer patients with MPEs in Zhejiang Cancer Hospital. We evaluated the efficacy. Progression-free survival (PFS) and overall survival (OS) was evaluated by Kaplan-Meier method.

Results: One hundred one NSCLC patients with MPEs at the time of diagnosis were included. We divided the patients into two groups. The overall response rate (ORR) with respect to MPE recurrence between the TKI alone and combination therapy groups was 65.5% (38/58) and 58.1% (25/43) (P=0.449). The disease control rate was 89.7% (52/58) and 86.0% (37/43) (P=0.579), respectively. The PFS in the TKI alone and TKI plus intrapleural drugs was 10.3 and 9.9 months, respectively (P=0.746). The intrapleural PFS was 11.4 and 11.0 months for the TKI alone and combination groups, respectively (P=0.188). The OS was 24.9 and 22.6 months (P=0.543), respectively. Hematologic toxicity and chest pain were more frequent in the combination therapy than TKI alone groups.

Conclusions: Intrapleural chemotherapy with TKI did not improve the efficacy of controlling MPEs in patients with EGFR-mutated NSCLC, but may increase adverse events, which are typical side effects of chemotherapy. We could treat these patients with TKI drugs alone combined with pleural effusion drainage.

Keywords: Epidermal growth factor receptor (EGFR); tyrosine kinase inhibitor (TKI); intrapleural chemotherapy; pleural effusion; lung cancer

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Introduction

Lung cancer is a leading cause of cancer deaths worldwide (1). Malignant pleural effusions (MPEs) is a common and devastating complication in patients with non-small cell lung cancer (NSCLC). Approximately 15% of lung cancer patients present with MPEs at the time of initial diagnosis and one-half of patients subsequently develop MPEs (2,3). NSCLC patients with MPEs usually have advanced disease and a poor prognosis (4). There are currently several management options for MPEs, including chemical pleurodesis [bleomycin (BLM) or cisplatin] with chest tubes or talc pleurodesis, medical thoracoscopy, pleuroperitoneal shunts, and chronic indwelling pleural catheters (5-7). Cisplatin is the most commonly used for the treatment of NSCLC. It is thus the most frequently used drug for intrapleural therapy of pleural effusions caused by NSCLC. BLM was chosen because it is one of the most frequently used agents and is considered to have high efficacy, low toxicity and high availability. None of these management options, however, are satisfactory in controlling pleural effusions and some of these options have additional adverse reactions.

With advances in molecular detection, the epidermal growth factor receptor (EGFR) gene mutation has been shown to be a major driver gene in Asian patients with NSCLC (8). Lung adenocarcinoma patients with MPEs have a higher *EGFR* mutation rate (approximately 70%) (9). Sensitizing *EGFR* mutations are associated with a better response to first-generation EGFR-tyrosine kinase inhibitors (EGFR-TKIs) than standard chemotherapy, such as gefitinib or erlotinib (10). Icotinib is also a first-generation EGFR-TKI which has been shown to have efficacy as therapy for advanced NSCLC with EGFR-activating mutations (11).

Talc pleurodesis to control MPE is not approved in China. Thus, intrapleural chemotherapy is usually administered to patients with MPE, such as cisplatin or BLM. Although these modes of therapy can alleviate symptoms in some patients, the relapse rate is as high as 50% (12). Pleurodesis with chemotherapy has some side effects, such as nausea, vomiting, chest pain, fever, and hematologic toxicity (6). Therefore, we suggest that EGFR-TKIs without intrapleural chemotherapy have a similar curative effect in controlling MPE, while decreasing adverse events in patients with *EGFR*-mutated NSCLC. There are few studies which have compared EGFR-TKIs with or without intrapleural chemotherapy to control MPE in patients with NSCLC. We conducted a retrospective study and collected MPEs to analyze gene status and used part of the data to investigate if TKIs alone are effective in patients with *EGFR*-mutated NSCLC and MPEs and are associated with fewer adverse effects in preventing re-accumulation of MPEs.

Methods

Study populations

We retrospectively collected NSCLC patients harboring *EGFR* mutations with MPEs treated at the Zhejiang Cancer Hospital between January 2014 and May 2017. The study protocol was approved by our Institutional Review Board (2014-03-32).

The eligible criteria were as follows: histologically- or cytologically-confirmed NSCLC; *EGFR* mutations; moderate-to-massive MPEs at the time of initial diagnosis in need of clinical treatment; MPEs shown by pleural effusion cytology of pleural effusions with confirmed malignant cells; received EGFR-TKI (gefitinib, icotinib, or erlotinib) treatment; and Eastern Cooperative Oncology Group Performance Status score (ECOG PS) of 0–3. Data on patient gender, age, smoking status, baseline ECOG PS at the start of treatment with EGFR-TKIs, the type of *EGFR* mutations, the type of EGFR-TKIs administered (icotinib, gefitinib, or erlotinib), the time-to-effusion recurrence and tumor or other lesion recurrence, and overall survival (OS) were recorded.

EGFR mutation analyses

The specimens from each patient for genetic testing in this study were obtained from primary tumors or metastatic sites by diagnostic or surgical procedures. All samples consisted of paraffin-embedded materials. DNA was extracted from tumor tissues (FFPE DNA kit; AmoyDx, Xiamen, China) and the ARMS assay was used to detect *EGFR* mutation status (*EGFR* 18–21). Using real-time PCR (AmoyDx), analyses of genomic DNAs extracted from cell pellets were performed for detection of *EGFR* mutations of MPE samples in some patients.

Treatment and response assessment

EGFR-TKI with gefitinib (250 mg/day), erlotinib (150 mg/day), or icotinib (125 mg/3 times a day) was administered for NSCLC patients until progression or

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intolerable adverse effects. Intrapleural therapy drugs included BLM and cisplatin. After draining the pleural fluid by thoracentesis, 60 mg of cisplatin or BLM monotherapy [1 mg/kg (maximum, 60 mg/body)] was administered intrapleurally according to their attending doctor and the drain was clamped after the installation of chemotherapeutic. After intrapleural administration, the patients were asked to turn over every 15 min to facilitate full access of the delivered drugs to the chest wall.

Tumor response was evaluated by computed tomography (CT) every 4–8 weeks according to the RECIST 1.1 (13). Recent objective responses were determined according to a previous study involving the effect of MPE treatment (14). MPEs were also evaluated by CT every 4–8 weeks. Complete remission (CR) was considered when the accumulated fluid had disappeared and was stable for at least 4 weeks. Partial remission (PR) was considered when >50% of the accumulated fluid had disappeared, symptoms had improved, and the remaining fluid had failed to increase for at least 4 weeks. Remission not obvious (NC) was considered when <50% of the accumulated fluid had disappeared. Disease progression was considered when the accumulated fluid had increased. The total efficiency was calculated by taking the sum of CR + PR. Progression in non-target lesions was defined as progression of pre-existing lesions, progression due to new lesions in the thoracic cavity, new lesions beyond the thoracic cavity, or a new MPE (15). The rapid progression of MPE was defined as hospitalization or death attributable to disease progression by the research according to Chaft *et al.* (16). Rapid progression included preceding symptoms of disease progression and hospitalization for drainage of an MPE. Adverse reactions were evaluated by the Common Toxicity Evaluation Criteria (CTC) according to the National Cancer Institute (NCI).

Follow-up evaluation

Intrapleural progression-free survival (iPFS) was evaluated from the date of the EGFR-TKI treatment to the date of confirming re-accumulation of MPE progression, the death from any cause, or the last follow-up visit. Extrathoracic PFS (ePFS) was evaluated from the date of the EGFR-TKI treatment to the date of confirming lesion progression, the death from any cause, or the last follow-up visit. Progression-free survival (PFS) was defined from the date of EGFR-TKI treatment to the date of confirming disease progression (intrapleural progression or extrathoracic progression), death from any cause, or the last follow-up visit. OS was measured from the date of the EGFR-TKI treatment to death or the last follow-up visit. If the complete survival time of a patient was impossible to obtain or the disease did not progress, patient status was assumed as the last known survival and/or contact date. We calculated iPFS excluding intervening chemotherapy, anti-angiogenic agents, or other TKIs when MPE progressed. Patients underwent MPE drainage or continued EGFR-TKI until further disease progression and a modified therapeutic regimen.

Statistical analyses

The baseline characteristics were compared using Pearson Chi-squared or Fisher's exact tests (when there were fewer than five expected counts in the contingency table). The Kaplan-Meier method and log-rank test were applied to evaluate the PFS and OS. Multivariate analyses were carried out by the Cox proportional-hazard model. The statistical analysis was computed using SPSS (version 19.0; SPSS, Inc., Chicago, IL, USA). Tests were two-sided and a P value <0.05 was considered statistically significant.

Results

Patient characteristics

One hundred and one patients with lung cancer presenting with MPEs at the time of diagnosis were included. All of the patients had lung adenocarcinomas and received EGFR-TKI treatment. Fifty-eight patients underwent drainage of pleural effusions and were treated with a TKI alone. Forty-three patients (42.6%) were treated with TKIs, pleural effusion drainage, and intracavitary chemotherapy. Intrapleural chemotherapy included BLM (24 patients) and cisplatin (19 patients). The median age was 57 years (range, 29–82 years). Fifty-five patients (54.5%) were female. The percentage of exon 19 deletions and exon 21 L858R mutations was 55 (54.5%) and 39 (38.6%), respectively. Eighty-one patients (80.2%) received EGFR-TKIs as first-line treatment. The patient characteristics according to TKI alone and combination therapy groups are summarized in *Table 1*.

Short-time effect

All 101 patients were evaluated for therapeutic efficacy. The

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Table 1 Clinical characteristics in all 101 patients

Features	TKI with intracavitary therapy (n=43), n (%)	TKI alone (n=58), n (%)	P value
Sex			0.867
Male	20 (46.5)	26 (44.8)	
Female	23 (53.5)	32 (55.2)	
Age			0.652
<65 years	30 (69.8)	38 (65.5)	
≥65years	13 (30.2)	20 (34.5)	
Smoking			0.787
Yes	13 (30.2)	19 (32.8)	
No	30 (69.8)	39 (67.2)	
Types of TKI			0.692
Erlotinib	2 (4.7)	1 (1.7)	
Gefitinib	7 (16.3)	10 (17.2)	
Icotinib	34 (79.1)	47 (81.0)	
PS at EGFR-TKIs treatments			0.118
0–1	29 (67.4)	47 (81.0)	
2	14 (32.6)	11 (19.0)	
Types of *EGFR* mutation			0.471
19	25 (58.1)	30 (51.7)	
21L858R	14 (32.6)	25 (43.1)	
Others	4 (9.3)	3 (5.2)	
Lines of EGFR-TKI			0.078
First line	31 (72.1)	50 (86.2)	
Second line or more	12 (27.9)	8 (13.8)	

PS, performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

objective response rate (ORR) was 67.2% and 53.5% in the TKI alone and combination groups (P=0.076), respectively. The disease control rate (DCR) was 86.2% and 81.4% (P=0.648), respectively.

We then evaluated MPE control in 58 patients treated with EGFR-TKIs alone; the ORR and DCR were 65.5% (38/58) and 89.7% (52/58), respectively. For the 43 patients who were administered TKIs with intrapleural therapy, the ORR was 58.1% (25/43) and the DCR was 86.0% (37/43). The ORR and DCR were not significantly different between the two groups. *Table 2* shows the general response of all the patients treated with a TKI alone and intrapleural chemotherapy combined with a TKI.

In addition, there were 55 patients with *EGFR* 19 deletions and 39 patients with *EGFR* 21 L858R mutations. The ORR and DCR for exon 19 deletions and L858R mutations were 65.5% and 61.5% (P=0.697), and 82.1% and 85.5% (P=0.731), respectively.

Long-time effect

Although all of the patients underwent response evaluations after 2 months treatment, 16 patients did not receive radiographic assessments in our hospital, including 9 patients received TKI alone and 7 patients in TKI plus intrapleural drugs. Therefore, we analyzed 85 patients

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Table 2 General response of all patients between TKI alone and intrapleural administration combination with a TKI

Therapy	Intrathoracic ORR	Intrathoracic DCR	Overall ORR	Overall DCR
Intravenous administration + TKI	58.1% (25/43)	86.0% (37/43)	53.5% (23/43)	81.4% (35/43)
TKI alone	65.5% (38/58)	89.7% (52/58)	67.2% (39/58)	86.2% (50/58)
P value	0.449	0.579	0.076	0.648

TKI, tyrosine kinase inhibitor; ORR, overall response rate; DCR, disease control rate.

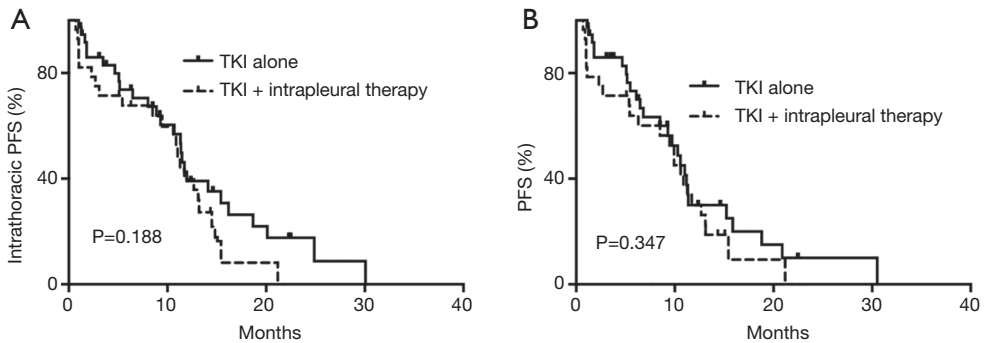

Figure 1 Comparison of intrapleural PFS (iPFS) and PFS in 65 patients who underwent pleural effusion drainage or continued EGFR-TKI when disease progression until disease progression again and a modified therapeutic regimen. (A) The iPFS was 11.4 versus 11.0 months for the TKI and combined groups, respectively (P=0.188); (B) the PFS between the TKI and combined groups was 10.3 versus 9.9 months, respectively (P=0.347). PFS, progression-free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

and the median PFS was 10.3 months The PFS in the TKI alone (49 patients) and TKI plus intrapleural drug (36 patients) groups was 10.3 and 9.9 months, respectively (P=0.746). Multivariate analyses of PFS was performed for 85 patients. The results showed that no factor, including gender (P=0.605), smoking status (P=0.108), performance status (P=0.081), TKI treatment line (P=0.570), and the therapeutic method for controlling MPEs (P=0.744), significantly influenced the PFS.

We separately assessed iPFS and ePFS in the two groups. The iPFS was 11.9 *vs.* 12.7 months for the TKI and combined groups (P=0.654), showing no additive effect of intrapleural treatment in preventing MPE re-accumulation in *EGFR*-mutated patients receiving TKI therapy. The ePFS was not significant between the 2 groups (10.6 *vs.* 11.3 months, P=0.785).

In addition, among these patients, 20 had extrathoracic tumor progression, but MPE remained well-controlled, then the drug treatment regimen was changed. The change in drugs influenced the iPFS. The remaining 65 patients had simultaneous tumor progression and MPE or stable disease. Therefore, we assessed the iPFS and PFS of the 65 patients. The iPFS was 11.4 and 11.0 months for the TKI and combination groups, respectively (P=0.188; *Figure 1A*). The PFS was also not significantly different between the two groups (10.3 *vs.* 9.9 months, P=0.347; *Figure 1B*).

Among the 65 patients, we compared the PFS between patients with *EGFR* 19 deletions (40 patients) and *EGFR* 21 L858R mutations (19 patients). The results showed that the median iPFS was 12.0 and 10.7 months for the 2 gene types in NSCLC patients with MPEs, respectively (P=0.096; *Figure 2A*); however, the ePFS in the exon 19 deletion group had a longer PFS than the L858R mutation group (11.2 *vs.* 6.5 months, P=0.010; *Figure 2B*).

According to last follow-up data (30 August 2017), including outpatient visits or telephone follow-up, 5 patients were lost to follow-up. The OS was 24.9 and 22.6 months in the TKI alone and TKI plus intrapleural drugs, respectively (P=0.543).

Clinical progression of EGFR-TKI failure

We analyzed the patterns of first disease progression in 85 patients. Seventy patients had progressive disease (36 in the TKI alone group and 34 in the combination group) and 15 maintained control of disease. Among the 70 patients

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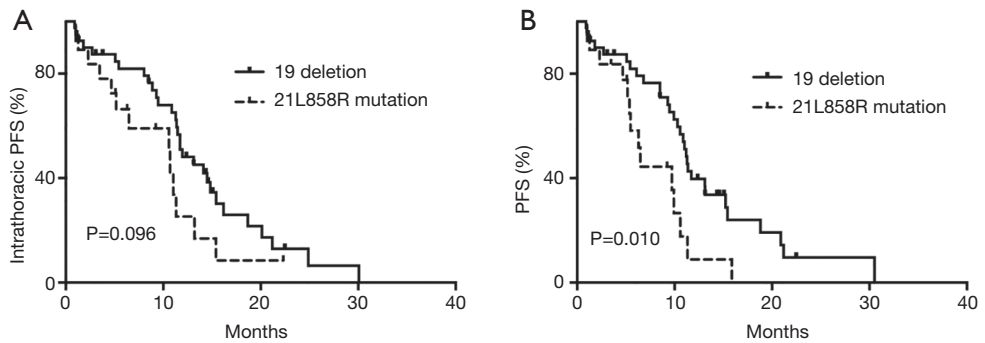

Figure 2 Comparison of intrapleural PFS (iPFS) and PFS in *EGFR* 19 deletion and 21L858R-mutated patients (n=59) who underwent pleural effusion drainage or continued EGFR-TKI when disease progression until disease progression again and a modified therapeutic regimen. (A) Comparison of iPFS between exon 19 and 21L858R mutations patients with MPEs were 12.0 versus 10.7 months, respectively (P=0.096); (B) the PFS between exon 19 and 21L858R mutations was 11.2 versus 6.5 months, respectively (P=0.010). PFS, progression-free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; MPE, malignant pleural effusion.

Table 3 Toxicity for all patients in our study

Variables	BLM + TKI (n=24), n (%)	Cisplatin + TKI (n=19), n (%)	TKI alone (n=58)
Leukopenia			
Grade I–II	2 (8.3)	1 (5.3)	0 (0)
Grade III–IV	0 (0)	1 (5.3)	0 (0)
Neutropenia			
Grade I–II	1 (4.2)	0 (0)	0 (0)
Grade III–IV	0 (0)	0 (0)	0 (0)
Anemia			
Grade I–II	2 (8.3)	1 (5.3)	0 (0)
Grade III–IV	0 (0)	0 (0)	0 (0)
Serum creatinine			
Grade I–II	0 (0)	1 (5.3)	0 (0)
Grade III–IV	0 (0)	0 (0)	0 (0)
Chest pain			
Grade I–II	3 (12.5)	2 (10.5)	0 (0)
Grade III–IV	0 (0)	0 (0)	0 (0)
Fever			
Grade I–II	3 (12.5)	1 (5.3)	0 (0)
Grade III–IV	0 (0)	0 (0)	0 (0)
Nausea/vomiting			
Grade I–II	2 (8.3)	3 (15.8)	3 (5.2)
Grade III–IV	0 (0)	0 (0)	0 (0)

BLM, bleomycin; TKI, tyrosine kinase inhibitor.

in the TKI alone and combination groups the rates of happening intracavitary progression were 27.8% (10/36) and 29.4% (10/34), respectively (P=0.880).

In addition, we compared the rates of rapid progression for MPE in the two groups. Rapid progression included symptomatic disease flares and progression of MPE necessitating hospitalization for drainage. In the TKI alone and combined treatment groups, the progression rate was 44.4% (16/36) and 38.2% (13/34), respectively (P=0.900).

Evaluation of adverse reactions

The toxicities for intrapleural therapy and TKI alone groups are listed in *Table 3*. Hematologic toxicity occurred in the intrapleural chemotherapy treatment. Grade 4 toxicities did not occur in all patients. Chest pain occurred mainly in the chemotherapy arm. Fever and nausea/vomiting occurred most frequently in the chemotherapy group. We analyzed statistically significant difference between TKI alone group and TKI plus intrapleural drugs group. There was a statistically significant difference in leukopenia (P=0.029), chest pain (P=0.011) and fever (P=0.029). There was no statistically significant difference in neutropenia (P=0.424), anemia (P=0.072), serum creatinine (P=0.424) or nausea/vomiting (P=0.275).

Discussion

Our findings indicate that EGFR-TKI therapy without intra-pleural chemotherapy controls MPEs and the efficacy was similar with combination treatment. Our findings are

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the first report to demonstrate that EGFR-TKI treatment alone may be equivalent to the addition of intrapleural chemotherapy in controlling MPE recurrences in *EGFR*-mutated patients.

MPEs are commonly observed in lung cancer patients, especially lung adenocarcinoma and *EGFR*-mutated patients (17). Administration of chemotherapy drugs or biological agents into the thoracic cavity are usually used to control MPEs. Although intra-pleural therapy prevents pleural effusions, all chemotherapeutic agents are associated with side effects, such as fever, nausea, chest pain, or hematologic toxicity. Report has demonstrated that the safety of talc pleurodesis was as thoracoscopic poudrage (18), however, talc is not available commercially in China. With the emergence of targeted drugs, modes of therapy in patients with NSCLC have change. Several prospective randomized trials have demonstrated that first-generation EGFR-TKIs as first-line treatment yield a longer PFS (9–10 months) for patients with *EGFR* mutations than chemotherapy (19-22).

The intrathoracic ORR (65.5% *vs.* 58.1%, P=0.449) and the median iPFS (11.9 *vs.* 12.7 months, P=0.654) did not differ between the EGFR-TKI alone treatment group compared with the combination TKI and intracavitary therapy group. Therefore, we are of the opinion that intrapleural therapy will not improve efficacy in controlling MPE. A study compared the effusion recurrence rate between gefitinib and gefitinib plus pleurodesis, including minocycline or OK432 (23). The report showed that the effusion PFS was not significantly different between the non-pleurodesis (39 patients) and pleurodesis (17 patients) groups (5.0 and 4.8 months, P=0.81). Gefitinib monotherapy provided equal efficacy in effusion control compared with gefitinib plus pleurodesis treatment. Although the results were similar to our findings, the study had only 15 *EGFR* mutation-positive patients. In addition, another study determined if EGFR-TKI therapy for advanced lung adenocarcinoma with MPEs was effective compared with the addition of talc (24). There were 39 patients with activating *EGFR* mutations and the results showed that TKIs alone compared with the addition of talc pleurodesis was adequate for preventing re-accumulation of MPEs (352 *vs.* 298 days, P=0.59). Therefore, these reports all demonstrated that in *EGFR*-mutated NSCLC patients with MPEs, intrathoracic chemotherapy may not confer additional benefit in preventing MPEs.

In addition, with respect to the patterns of MPE progression, our report indicated that 27.8% of patients in the TKI group and 29.4% of patients in the combination group exhibited intracavitary progression first. The rate of rapid progression of MPEs was 44.4% (16/36) and 38.2% (13/34), respectively (P=0.900). Our study is the first to evaluate the patterns of effusion progression between EGFR-TKI and pleurodesis to date. We also demonstrated that intrapleural chemotherapy does not play an important role in controlling re-accumulation of effusions in *EGFR*-mutated lung cancer.

Interestingly, some studies have shown 19 deletions and *EGFR* 21 L858R mutations might have different molecular subtyping and the efficacy of TKIs is also different (22,25). In our study there was no statistical difference between the 19 deletion and 21L858R-mutated patients with respect to iPFS (12.0 *vs.* 10.7, P=0.096); however, the exon 19 deletion group had a longer PFS than the L858R mutation group (11.2 *vs.* 6.5 months, P=0.010). Zheng *et al.* (26) compared between exons 19 and 21 *EGFR* mutations in NSCLC patients with MPEs after TKI therapy. The 19 deletion group had a longer PFS (9.4 *vs.* 7.1 months, P=0.003) and OS (16.8 *vs.* 13.8 months, P=0.003) compared with the L858R mutation group after second-line TKI therapy. PFS was not investigated further in the intracavitary treatment group. Although the number of patients in the 21L858 mutation group was small (19 patients) in our research, we believe this group warrants further exploration.

With respect to adverse reactions, the incidence of hematologic toxicity, fever, and chest pain in the group that received intrapleural chemotherapy was apparently higher than the TKI alone group. Therefore, we considered that TKI with intrapleural treatment had an incidence of additional adverse events similar to chemotherapy.

While our study had clinical significance, it did have limitations. The number of patients may have been insufficient. The number of enrolled *EGFR* L858R-mutated patients was small, thus suggesting that need for a large study. In the future, a prospective randomized design to further compare the difference between TKI alone and TKI with intrapleural treatment and different types of gene mutations is needed. Furthermore, our research mainly focused on *EGFR*-mutated patients with MPEs and demonstrated that the effect of EGFR-TKI monotherapy to control MPE was not difference between intrapleural chemotherapy plus TKI; however, we did not confirm this possibility in EGFR-negative patients. Thus, further research to explore the effect of intrapleural drugs should

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be conducted.

Conclusions

For *EGFR*-mutated lung cancer patients with MPEs, intrapleural chemotherapy does not increase the efficacy of controlling MPEs. In addition, the incidence of adverse events due to chemotherapy may be increased.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Approval was obtained by the Institutional Review Board (IRB) of each investigation site (2014-03-32). As our study was non-interventional and retrospective, formal written consent from patients was not necessary.

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