ANTICANCER RESEARCH *40*: 1117-1121 (2020)
doi:10.21873/anticanres.14051

Prognosis of *EGFR*-mutant Lung Adenocarcinoma Patients With Malignant Pleural Effusion Receiving First-line EGFR-TKI Therapy Without Pleurodesis: A Single-institute Retrospective Study

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Abstract. *Background/Aim: The survival benefit of first-line epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) therapy without pleurodesis in EGFR-mutant lung adenocarcinoma patients with malignant pleural effusions (MPE) remains unclear. Patients and Methods: We retrospectively evaluated overall survival (OS) among EGFR wild-type lung adenocarcinoma patients with MPE who received chemotherapy with pleurodesis (CT+PLD) and without pleurodesis (CT-PLD), and EGFR-mutant lung adenocarcinoma patients with MPE who received EGFR-TKI therapy with pleurodesis (TKI+PLD) and without pleurodesis (TKI-PLD). Results: There was no difference in OS between the CT+PLD and the CT-PLD groups (10.8 months vs. 7.4 months). As compared to the TKI+PLD group, OS tended to be longer in the TKI-PLD group (21.8 months vs. 31.1 months). Patients in the TKI-PLD group had no hypoalbuminemia or deterioration of performance status during management of MPE and could receive second- and further-line therapy. Conclusion: EGFR-mutant patients with MPE who received first-line EGFR-TKI therapy without pleurodesis may show a better prognosis than those with pleurodesis.*

Malignant pleural effusions (MPE) occur frequently in advanced or recurrent non-small cell lung cancer (NSCLC) patients. The standard management for MPE in symptomatic patients is single or repeated thoracentesis and/or chest tube drainage. It has been strongly recommended that chest tube drainage should be followed by pleurodesis, and that the chest tube should be removed when the fluid drainage is under 150 ml a day after pleurodesis (1-3). In addition, cytotoxic chemotherapy should be administered after the management of MPE is completed, because cytotoxic drugs accumulate in the pleural effusion, resulting in increased toxicity (4). Therefore, some patients show deterioration of the performance status (PS) or delay in the initiation of chemotherapy until management of MPE is completed.

However, few trials have demonstrated that good MPE control was achieved in epidermal growth factor receptor (*EGFR*)-mutant NSCLC patients receiving EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy without pleurodesis (5-7). The survival benefit offered by first-line EGFR-TKI therapy without pleurodesis in *EGFR*-mutant NSCLC patients with MPE remains unclear. Herein, we retrospectively compared the time of progression-free survival without re-accumulation of MPE (MPE-FS) and overall survival (OS) in *EGFR*-mutant lung adenocarcinoma patients with MPE receiving first-line EGFR-TKI therapy without and with pleurodesis.

Patients and Methods

This retrospective single-institute study was approved by the Institutional Review Board of the Kumamoto Regional Medical Center (approval date, June 24, 2019; approval number, 19-006) and was conducted in 74 previously untreated lung adenocarcinoma patients with MPE (histologically confirmed pleural malignancy) with an Eastern Cooperative Oncology Group PS score of 0 to 2 who received first-line anticancer therapy after the management of MPE was completed during the 10-year period from April 1, 2008 to March 31, 2018. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Symptomatic patients received single or repeated thoracentesis and/or chest tube drainage. If the MPE could not be controlled within two weeks by the above methods, pleurodesis was performed using sterile talc (8) or hypotonic cisplatin (9) as sclerosant at the

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Key Words: Adenocarcinoma, EGFR-TKI, pleurodesis, malignant pleural effusions, hypoalbuminemia.

Table I. *Patient characteristics, management of MPE, anti-cancer therapy and prognosis.*

	EGFR wild-type patients		EGFR-mutant patients	
	CT+PLD n=28	CT-PLD n=16	TKI+PLD n=18	TKI-PLD n=12
Age, years	70 (50-89)	63 (34-83)	72 (42-94)	71(47-85)
Women	5 (18)	5 (31)	15 (83)	6(50)
ECOG PS 2	5 (18)	3 (19)	7 (39)	0*
Never smokers	6 (21)	7 (44)	15 (83)	8 (68)
Stage IV	27 (96)	14 (88)	14 (78)	10 (83)
Postoperative recurrence	1 (4)	2 (11)	4 (22)	2 (17)
Management of MPE				
Thoracentesis alone	0	8 (50)*	0	7 (58)*
Chest tube drainage	28 (100)	8 (50)*	18 (100)	5 (42)*
Drainage periods, day	8 (3-21)	-	7 (3-25)	-
Adverse events	8 (29)	-	5 (28)	-
MPE control rate, %	21 (75)	6 (38)*	14 (78)	11 (92)
Serum levels of albumin before and after MPE managements				
Before, g/dl	3.6±0.5	3.6±0.5	3.6±0.4	3.7±0.4
After, g/dl	3.0±0.5	3.5±0.6*	3.1±0.5	3.7±0.5*
Period from diagnosis until initiation of first-line therapy, day	26 (12-59)	17 (5-27)	19 (5-40)	11 (1-20)
First-line therapy				
EGFR-TKI	0	0	18 (100)	12 (100)
Platinum-doublet	23 (82)	15 (94)	0	0
Monotherapy	5 (18)	1 (6)	0	0
Bevacizumab	10 (36)	4 (25)	0	0
Toxicity of first-line therapy, NCI-CTCAE; grade ≥3				
Neutropenia	8 (28)	4 (25)	0	0
Thrombocytopenia	3 (11)	2 (12)	0	0
Pneumonitis	0	1 (6)	2 (11)	0
AST/ALT in serum	2 (7)	0	1 (6)	1 (8)
Skin rush	0	1 (6)	0	1 (8)
Anorexia	2 (7)	1 (6)	0	0
Fatigue	2 (7)	1 (6)	0	0
MPE-FS, month	10.1	2.5*	19.2	21.7
Second-line therapy	20 (71)	8 (50)	8 (45)	11 (92)*
Third- or further-line therapy	9 (32)	6 (38)	5 (28)	8 (67)*
Patient death from any cause	25 (89)	12 (75)	16 (89)	6 (50)
OS, month	10.8	7.4	21.8	31.1

Data are expressed as percentages (%) or median values (range). ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR: epidermal growth factor receptor; MPE: malignant pleural effusion; MPE-FS: Progression free survival without re-accumulation of MPE; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria adverse events; OS: overall survival; PLD: pleurodesis; TKI: tyrosine kinase inhibitor. *$p<0.05$ *vs.* patients with pleurodesis using the Mann-Whitney *U*-test, χ^2 test or Fisher's exact probability test.

judgment of the doctor. Among the 46 patients needed pleurodesis, 28 *EGFR* wild-type cases received chemotherapy (CT+PLD group) and 18 *EGFR*-mutant cases received EGFR-TKI (TKI+PLD group). Among the 28 patients in whom good control of MPE was achieved without pleurodesis, 16 *EGFR* wild-type cases received chemotherapy (CT-PLD group) and 12 *EGFR*-mutant cases received EGFR-TKI (TKI-PLD group).

The MPE control rate was defined as the percentage of patients in whom no re-accumulation of MPE could be identified on posteroanterior chest radiographs obtained at four weeks after the start of first-line anticancer therapy. Patients in whom the chest radiographs showed pleural fluid opacity occupying more than 25% of the hemithorax were defined as showing re-accumulation of MPE. MPE-FS was defined as the period from the initiation of first-line therapy until the re-accumulation of MPE, detection of disease progression and/or death of the patient from any cause. OS was defined as the period from the initiation of first-line therapy until death of the patient from any cause. Hematological or non-hematological toxicities were evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Statistical analysis was performed using the Stat View J 5.0 statistical program (SAS, Institute Inc., Berkeley, CA, USA). Differences in clinical data were evaluated using the Mann-Whitney *U*-test, χ^2 test or Fisher's exact probability test. Univariate analyses were performed to identify the risk factors for re-accumulation of MPE and mortality. Significant variables (p-values<0.10) identified by the log rank tests were included in the Cox proportional hazards

Table II. *Multivariate analysis*.

	Univariate analysis (log rank test) *p*-Value	Multivariate analysis (Cox's proportional hazard model)		
		HR	95%CI	*p*-Value
Performing pleurodesis	0.227	1.439	0.720-2.878	0.303
Age (≥69 year *vs*. <69 year)	0.358			
Gender (women *vs*. men)	0.736			
Performance status (2 *vs*. 0-1)	0.030	1.980	1.034-3.790	0.039
Smoking habit (yes *vs*. no)	0.339			
Clinical stage (stage IV *vs*. postoperative recurrence)	0.011	1.685	0.666-4.263	0.271
EGFR mutations (no *vs*. yes)	0.018	2.288	1.261-4.151	0.007
Period from diagnosis to the start of first-line therapy	0.382			
Hypoalbuminemia before first-line therapy	0.096	2.183	1.166-4.082	0.014

CI: Confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; MPE: malignant pleural effusion; TKI: tyrosine kinase inhibitor.

model. The hazard ratio (HR) and corresponding 95% confidence intervals (CIs) were calculated. The MPE-FS and OS were estimated using the Kaplan-Meier method. A two-tailed *p*-value of less than 0.05 was considered as being indicative of a statistically significant difference.

Results

The patient and disease characteristics, management of MPE and anti-cancer therapy are summarized in Table I. Among the patients who did not undergo pleurodesis, good MPE control was achieved by thoracentesis alone in 50% of the CT-PLD group and 58% of the TKI-PLD group. Among the patients who needed pleurodesis, sterile talc was used in 32% of the CT+PLD group and 11% of the TKI+PLD group. There was no difference in the median drainage period or percentage of adverse events associated with pleurodesis between the CT+PLD and TKI+PLD groups. In most patients, the adverse events were chest pain or fever. The mean serum albumin levels decreased during the management of MPE in the CT+PLD (3.6 g/dl→3.0 g/dl) and the TKI+PLD groups (3.6 g/dl→3.1 g/dl).

The median period from the diagnosis until the initiation of first-line therapy was shorter in the TKI-PLD group than in the other three groups. The *EGFR* wild-type patients received first-line chemotherapy with platinum-doublet regimens (n=38) or monotherapy with third-generation cytotoxic agents (n=6); 14 of these patients also received additional bevacizumab therapy. All the *EGFR*-mutant patients received EGFR-TKI with gefitinib (n=22), erlotinib (n=6) or afatinib (n=2). According to National Cancer Institute-Common Terminology Criteria adverse events version 4.0, there were no differences in the incidence of grade ≥3 toxicities of first-line anticancer therapy between the CT+PLD and CT-PLD groups or between the TKI+PLD and TKI-PLD groups. The MPE-FS was shorter in the CT-PLD group than in the CT+PLD group (2.5 months *vs*. 10.1 months, p=0.044), whereas there was no difference in the MPE-FS between the TKI-PLD and TKI+PLD groups (21.7 months *vs*. 19.2 months, p=0.839) (Figure 1a).

The percentage of patients that could receive second- or further-line therapy was higher in the TKI-PLD group than in the other three groups and patients in the TKI-PLD group could continue anticancer therapies including bevacizumab or immune checkpoint inhibitors. During the median follow-up period of 14.4-months from the initiation of first-line therapy, 59 patients died from any cause. There was no difference in OS between the CT+PLD and CT-PLD groups (10.8 months *vs*. 7.4 months, p=0.978): however, the OS tended to be longer in the TKI-PLD group than in the TKI+PLD group (31.1 months *vs*. 21.8 months, p=0.106) (Figure 1b).

The Cox proportional hazards model analysis showed that PS score of 2 before first-line therapy (HR=1.98, 95%CI=1.03-3.79, p=0.039), *EGFR* wild-type (HR=2.28, 95%CI=1.26-4.15, p=0.007), and hypoalbuminemia before first-line therapy (HR=2.18, 95%CI=1.16-4.08, p=0.014) were associated with an increased risk of mortality (Table II).

Discussion

Our study showed that patients in the TKI-PLD group achieved equivalent MPE-FS to patients in the TKI+PLD group and tended to show a longer survival as compared to the TKI+PLD group. Pleurodesis was performed in patients in whom the MPE could not be controlled by thoracentesis and/or chest tube drainage within a period of two weeks. Patients in the TKI+PLD group possibly had more aggressive malignancy than those in the TKI-PLD group. We speculate that patients with more aggressive disease need a longer period of chest tube drainage followed by pleurodesis,

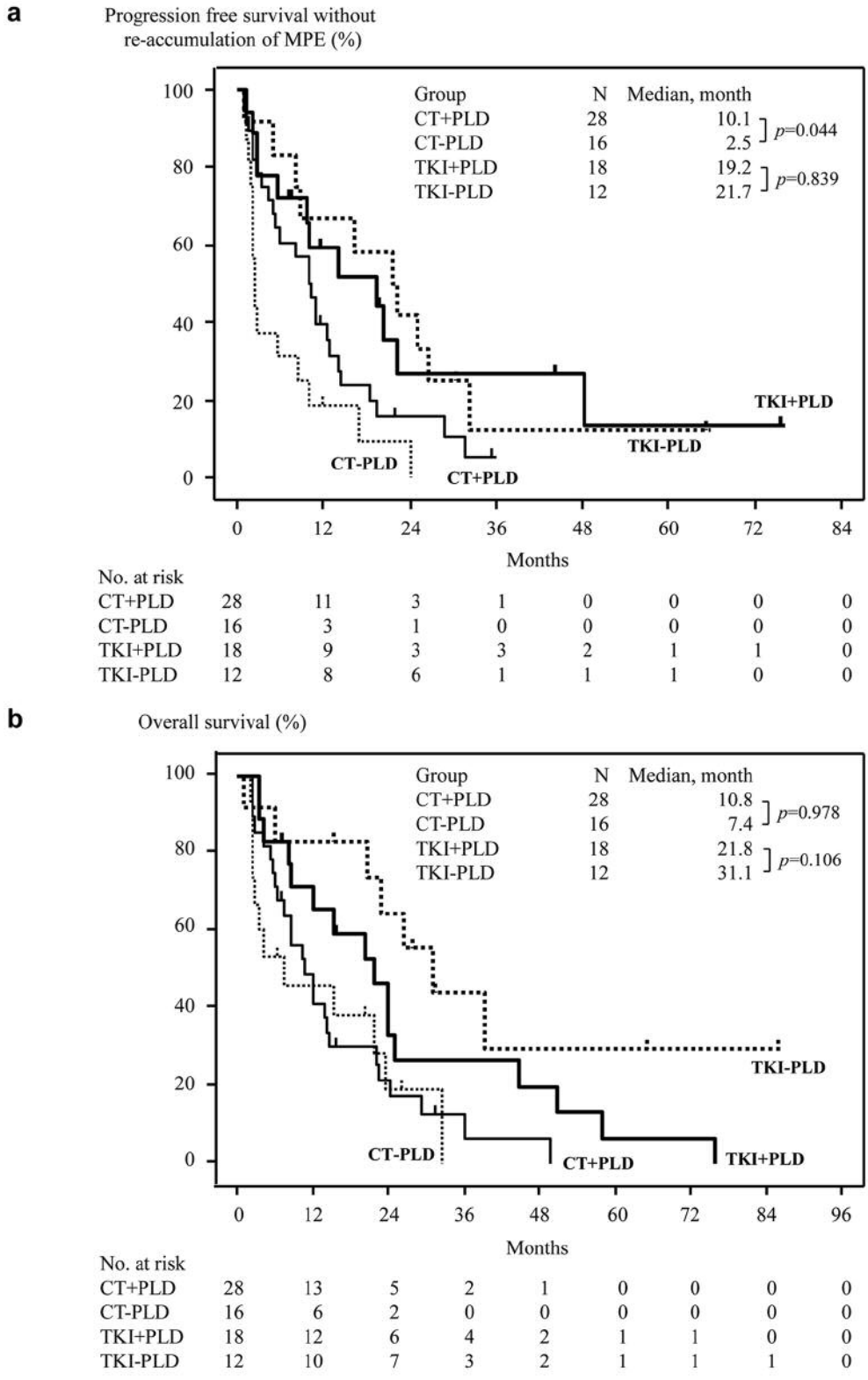

Figure 1. *Progression-free survival without re-accumulation of MPE (a) and overall survival (b) in EGFR wild-type lung adenocarcinoma patients who received chemotherapy with pleurodesis (CT+PLD) and those without pleurodesis (CT-PLD), and EGFR-mutant lung adenocarcinoma patients who received EGFR-TKI with pleurodesis (TKI+PLD) and those without pleurodesis (TKI-PLD). EGFR: Epidermal growth factor receptor; MPE: malignant pleural effusions; TKI: tyrosine kinase inhibitor.*

resulting in hypoalbuminemia before first-line therapy. Survival has been reported to be shorter in advanced NSCLC patients with hypoalbuminemia than in those without (10). In contrast, patients in the TKI-PLD group had less aggressive malignancy and no hypoalbuminemia, which could be among the reasons for the better prognosis in this patient group.

Of the *EGFR* wild-type patients, however, we found that the MPE-FS in the CT-PLD group was shorter than that in the CT+PLD group and there was no difference in the OS between the two groups. This result suggests that the good prognosis in the TKI-PLD group cannot be explained solely by the suggestion that they had less aggressive malignancy. Multivariate analysis in our study identified that poor PS and hypoalbuminemia before the start of first-line therapy were associated with an increased risk of mortality, regardless of whether pleurodesis had been performed or not. Another possible reason for the good prognosis in the TKI-PLD group was that these patients could continue to receive different types of anticancer therapies (including bevacizumab or immune checkpoint inhibitors) as second- or further-line therapies after the failure of EGFR-TKI therapy, without any significant decline in the quality of life.

The sample size in our study was relatively small, because this study was a retrospective study performed at a single institute. Our study, however, demonstrated that it is important to prevent the development of hypoalbuminemia or deterioration of PS during the management of MPE, and that first-line EGFR-TKI therapy without pleurodesis allowed good MPE control and good prognosis in *EGFR*-mutant lung adenocarcinoma patients. Although all the *EGFR*-mutant patients in this study started to receive EGFR-TKI therapy after the management of MPE was completed, they could receive EGFR-TKI therapy early regardless of whether pleurodesis was needed, because EGFR-TKI therapy is as effective as pleurodesis for the management of MPE.

In conclusion, *EGFR*-mutant lung adenocarcinoma patients with MPE receiving first-line EGFR-TKI therapy without pleurodesis showed a better prognosis than the same subset of patients with pleurodesis.

Conflicts of Interest

The Authors declare no conflicts of interest and no funding of this work.

Authors' Contributions

Kosuke Kashiwabara: Conceptualization, data curation, methodology, investigation, formal analysis, visualization, writing - original draft, writing - review & editing; Shinji Fujii: Investigation, visualization, writing - original draft, writing - review & editing; Shinsuke Tsumura: Investigation, writing - original draft, writing - review & editing; Kazuhiro Sakamoto: Investigation, writing - original draft, writing - review & editing.

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Received December 19, 2019
Revised December 31, 2019
Accepted January 2, 2020