Original Article

Impact of docetaxel plus ramucirumab on metastatic site in previously treated patients with non-small cell lung cancer: a multicenter retrospective study

Kinnosuke Matsumoto[1]^, Akihiro Tamiya[1], Yoshinobu Matsuda[1], Yoshihiko Taniguchi[1], Shinji Atagi[2], Hayato Kawachi[3], Motohiro Tamiya[3], Satoshi Tanizaki[4], Junji Uchida[4], Kiyonobu Ueno[4], Takafumi Yanase[5], Hidekazu Suzuki[5], Tomonori Hirashima[5]

[1]Department of Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan; [2]Clinical Research Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka, Japan; [3]Department of Respiratory Medicine, Osaka International Cancer Institute, Osaka, Japan; [4]Department of Respiratory Medicine, Osaka General Medical Center, Osaka, Japan; [5]Department of Respiratory Medicine, Osaka Prefectural Medical Center for Respiratory and Allergic Disease, Osaka, Japan

Contributions: (I) Conception and design: K Matsumoto, A Tamiya; (II) Administrative support: A. Tamiya; (III) Provision of study materials or patients: K Matsumoto, H Kawachi, S Tanizaki, T Yanase; (IV) Collection and assembly of data: K Matsumoto; (V) Data analysis and interpretation: K Matsumoto, A Tamiya, Y Matsuda; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kinnosuke Matsumoto, MD. Department of Internal Medicine, National Hospital Organization Kinki-Chuo Chest Medical Center, 1180 Nagasone-cho, Kita-Ku, Sakai City, Osaka, 591-8555, Japan. Email: m.kinnosuke@gmail.com.

Background: Docetaxel (DOC) plus ramucirumab (RAM) has been recommended as an optimal therapy for previously treated patients with non-small cell lung cancer (NSCLC). In a clinical setting, there are few reports about DOC plus RAM, therefore its effect on factors such as Eastern Cooperative Oncology Group (ECOG) performance status (PS) and metastatic sites is still unknown.

Methods: We recruited NSCLC patients who received DOC plus RAM in four medical facilities in Japan from June 2016 to March 2020. We retrospectively investigated the overall response rate (ORR), disease control rate (DCR), and progression-free survival (PFS) of DOC plus RAM and conducted univariate and multivariate analyses using PFS as a dependent factor. Patients were followed up until June 30, 2020.

Results: A total of 237 patients were consecutively enrolled. For all patients, the ORR, DCR, and median PFS were 25.2%, 63.9%, and 4.5 months, respectively. The ORR and DCR for malignant pleural effusion (MPE), lung metastasis, and liver metastasis were 7.7% and 53.8%, 30.3% and 77.5%, and 48.6% and 71.4%, respectively. In the multivariate analysis, MPE, lung metastasis, and liver metastasis were not prognostic factors for poor PFS. However, ECOG-PS 2 or more [hazard ratio (HR): 1.66, 95% confidence interval (CI): 1.14–2.40, P=0.008] and brain metastasis (HR: 1.71, 95% CI: 1.23–2.37, P=0.001) were significant and independent factors associated with shorter PFS.

Conclusions: DOC plus RAM could be an optimal therapy for previous treated NSCLC patients with lung and liver metastasis, and furthermore, should be used carefully for patients with poor ECOG-PS or brain metastasis.

Keywords: Docetaxel and ramucirumab; non-small cell lung cancer (NSCLC); metastatic site; poor performance status

Submitted Dec 13, 2020. Accepted for publication Feb 23, 2021.
doi: 10.21037/tlcr-20-1263
View this article at: http://dx.doi.org/10.21037/tlcr-20-1263

^ ORCID: 0000-0002-4930-6997.

Introduction

Non-small cell lung cancer (NSCLC) is a common cause of cancer mortality worldwide (1). A majority of patients with NSCLC have a metastatic disease at diagnosis, for which no curative therapy exists. Although treatments for driver mutations have yielded impressive improvements in many regions, most patients relapse despite using breakthrough tyrosine kinase inhibitors such as osimertinib (2). Actually, a majority of the patients do not have sensitive driver mutations associated with approved targeted drugs, and platinum-based chemotherapies plus immune checkpoint inhibitors (ICIs) are the standard first-line treatment for NSCLC patients with good performance status in recent years (3-5). Although some patients have long-term survival after using platinum-based chemotherapy combined with ICIs, most patients experience disease progression after administration.

Some clinically approved second-line therapies for NSCLC patients include docetaxel (DOC), pemetrexed, and vinorelbine (6-8). Particularly, DOC plus ramucirumab (RAM) significantly increased the progression-free survival (PFS), overall survival (OS), and complete overall response rate (ORR) when directly compared to DOC monotherapy in the REVEL trial (9). Therefore, DOC plus RAM has been recommended as an optimal therapy for previously treated patients in many countries.

Although a few reports have been published concerning the retrospective analysis of DOC plus RAM as a therapeutic regimen, such as evaluating the effect of age and previous ICIs usage, analyses of the effect of clinical factors, such as Eastern Cooperative Oncology Group (ECOG) performance status (PS) on survival are still limited (10-13).

Currently, two anti-vascular endothelial growth factor (VEGF) antibodies have been clinically used for NSCLC patients: bevacizumab (BEV) and RAM. BEV is a humanized monoclonal antibody (mAb) that targets all isoforms of VEGF-A, which prevents the activation of the membrane receptors such as vascular endothelial growth factor receptor (VEGFR) 1 and VEGFR2. RAM is a fully human antagonistic mAb which targets VEGFR2. By binding to VEGFR1 and VEGFR2, VEGF-A induces inflammatory responses and disrupts cell-to-cell connections to increase vascular permeability (14). BEV has been effective in patients with malignant pleural effusion (MPE) by blocking the binding of VEGF-A to its receptors (15-17). Liver metastases also benefit from BEV because of the overexpression of VEGF-A in liver lesions (4,18-21). However, the clinical efficacy of RAM for these metastatic sites is still unknown.

Therefore, we performed a multicenter retrospective observational cohort study for previously treated patients with NSCLC who were administered DOC plus RAM to identify the clinical factors which affect its efficacy and to elucidate the relationship between metastatic sites and efficacy.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-1263).

Methods

Study population

This study was a multicenter, observational, retrospective study. Participants consisted of previously treated NSCLC patients who received DOC plus RAM between June 2016 and March 2020 in four medical facilities in Japan, including the Osaka International Cancer Institute, the Osaka Habikino Medical Center, the Osaka General Medical Center, and the National Hospital Organization Kinki-Chuo Chest Medical Center. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the World Health Organization's Guidelines for Good Clinical Practice, and the protocol was reviewed and approved by the Institutional Review Board at the Osaka International Cancer Institute (IRB No.20098), the Osaka Habikino Medical Center (IRB No.1046), the Osaka General Medical Center (IRB No.2020-060), and the National Hospital Organization Kinki-Chuo Chest Medical Center (IRB No. 2020-034). The patient's informed consent was waived for the retrospective nature of study, and we used an opt-out method so that patients and families could refuse to participate in the study.

Data collection

We collected data on age, sex, smoking status, ECOG-PS, histology, EGFR mutation, and metastatic site (MPE, lung, liver, or brain) from electronic medical records and pharmacy databases. Data on age, ECOG-PS, and metastatic site were evaluated just before the start of DOC plus RAM. Clinical responses were defined according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (22).

The ORR included all patients with complete response

Table 1 Clinical characteristics of 237 patients

Characteristics	N (%)
Median age [range], years	66 [33–82]
Age group, years	
<75	207 (87.3)
≥75	30 (12.7)
Sex	
Male	150 (63.3)
Female	87 (36.7)
Histology	
Adenocarcinoma	180 (75.9)
Squamous cell carcinoma	38 (16.0)
Other	19 (8.1)
Smoking status	
No	58 (24.5)
Yes	179 (75.5)
ECOG-PS	
0	28 (11.8)
1	161 (67.9)
2	40 (16.9)
3	6 (2.5)
4	2 (0.9)
EGFR mutation	
Positive	66 (29.5)
Negative	158 (70.5)
Median number of prior treatments (range)	2.0 (1.0–11.0)
Malignant pleural effusion	71 (30.1)
Lung metastasis	100 (42.2)
Liver metastasis	38 (16.0)
Brain metastasis	60 (25.4)

ECOG-PS, Eastern Cooperative Oncology Group-performance status; EGFR, epidermal growth factor receptor.

(CR) and partial response (PR). The disease control rate (DCR) included the patients with stable disease (SD) or PR. We defined the anti-tumor effect of MPE as follows: PR was defined as the status with an obvious decrease of MPE without thoracentesis and SD was defined as the status without an unequivocal increase of MPE at the evaluation after more than 6 weeks from initiation of DOC plus RAM compared to baseline. The PFS was determined from the date of commencing DOC plus RAM therapy to the date of disease progression or death from any cause. The OS was determined from the date of commencement of the relevant therapy to the date of death. Patients were followed until June 30, 2020.

Statistical analysis

The survival outcomes were analyzed using the Kaplan-Meier method. The differences between patient groups according to each factor were compared using the log-rank test. P values <0.05 were regarded as statistically significant. Cox regression analysis was used to calculate the hazard ratio (HR) of each factor with 95% confidence interval (CI). To identify prognostic factors (such as age, sex, smoking status, ECOG-PS, and metastatic site), univariate and multivariate analyses were conducted. χ^2 test was used for categorical variables. Statistical analyses were performed using SPSS version 26.0 (IBM, Armonk, NY).

Results

Patient characteristics

A total of 237 previously treated patients with NSCLC were included in this study. Patient characteristics are summarized in *Table 1*. The median age was 66.0 years (range, 33–82 years), and a few elderly (≥75 years) patients (12.7%) were included. A majority of the patients were men (63.3%), had adenocarcinoma (75.9%), had a history of smoking (75.5%), and had an ECOG-PS of 0–1 (79.7%). Sixty-six patients (29.5%) had sensitive EGFR mutations. Approximately 60% of patients received DOC plus RAM on the early line such as 2nd or 3rd line. In addition, 40% of patients received immunotherapy as the front-line treatment (Table S1). RAM was not used with any regimens except for DOC. Of the investigated metastatic sites, lung metastasis (100 cases) was the most detected site, followed by MPE (71 cases), brain metastasis (60 cases), and liver metastasis (38 cases).

Treatment efficacy in all patients

In all patients, the ORR, DCR, and progressive disease rate were 25.2%, 63.9%, and 36.1%, respectively. At the time of analysis, the PFS was based on 195 events (82.3% maturity), whereas the OS was based on 148 events (62.4% maturity). The median follow-up time in censored patients was 12.5 months (range, 3.1–42.6 months). The median PFS was

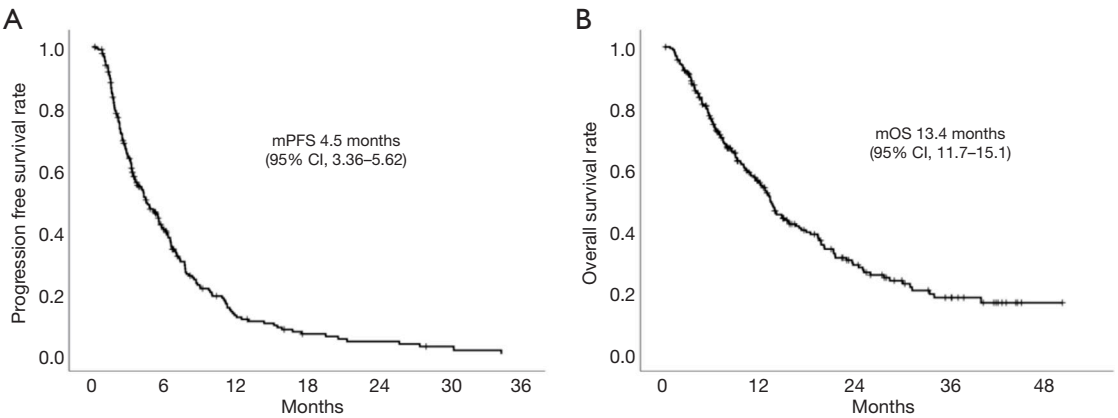

Figure 1 Kaplan-Meier survival curves of PFS and OS in all patients treated with DOC plus RAM. (A) The median PFS was 4.5 (95% CI, 3.36–5.62) months and (B) the median OS was 13.4 (95% CI, 11.7–15.1) months. PFS, progression-free survival; OS, overall survival; DOC, docetaxel; RAM, ramucirumab; CI, confidence interval.

4.5 (95% CI, 3.36–5.62) months (*Figure 1A*) and the median OS was 13.4 (95% CI, 11.7–15.1) months (*Figure 1B*).

The log-rank test revealed no differences in the median PFS of patient treated with DOC plus RAM in terms of age (<75 *vs.* ≥75) (*Figure 2A*), sex (male *vs.* female) (*Figure 2B*), and smoking status (non-smoker *vs.* smoker) (*Figure 2C*). Conversely, the median PFS in ECOG-PS groups (0–1 *vs.* 2–4) were significantly different [5.46 (95% CI: 4.42–6.51) *vs.* 2.79 (95% CI: 2.18–3.39) months; P<0.001] (*Figure 2D*).

Treatment efficacy by metastatic site

The ORR and DCR are listed by metastatic site in *Figure 3*. The ORR of DOC plus RAM for MPE was relatively low, and DOC plus RAM seemed to be unable to decrease pleural effusion. However, about 50% of patients were able to prevent an increase in pleural effusion. The ORR and DCR for lung and liver metastasis were higher than those in all patients, showing 30.3% and 77.5%, and 48.6% and 71.4%, respectively. The ORR and DCR for brain metastasis were almost the same as those of all patients. Of 60 patients with brain metastases, 52 patients (86.7%) received palliative treatment in addition to DOC plus RAM. Among these, five patients underwent surgery and 48 received radiation therapy, with one patient receiving both therapies.

The log-rank test revealed no differences in the median PFS of patients who received DOC plus RAM concerning MPE (positive *vs.* negative) (*Figure 4A*), lung metastasis (positive *vs.* negative) (*Figure 4B*) and liver metastasis (positive *vs.* negative) (*Figure 4C*). The median PFS of patients with brain metastasis (positive *vs.* negative) was significantly different [3.14 (95% CI: 2.38–3.90) *vs.* 5.14 (95% CI: 4.25–6.03) months; P=0.002] (*Figure 4D*).

Association between patient characteristics and progression free survival

The results of the Cox proportional hazards model for predicting the PFS in patients treated with DOC plus RAM are shown in *Table 2*. In the univariate analysis, ECOG-PS (0–1 *vs.* 2–4, HR: 1.76, 95% CI: 1.24–2.50, P=0.002) and brain metastasis (negative *vs.* positive, HR: 1.63, 95% CI: 1.19–2.25, P=0.003) were significantly associated with poorer PFS. Similarly, in the multivariate analysis, ECOG-PS (0–1 *vs.* 2–4, HR: 1.66, 95% CI: 1.14–2.40, P=0.008) and brain metastasis (negative *vs.* positive, HR: 1.71, 95% CI: 1.23–2.37, P=0.001) were identified as independent factors significantly associated with poorer PFS.

In the univariate and multivariate analyses for predicting the OS, ECOG-PS (0–1 *vs.* 2–4, HR: 2.02, 95% CI: 1.37–2.97, P=0.001) and MPE (negative *vs.* positive, HR: 1.63, 95% CI: 1.15–2.31, P=0.007) were significant poor prognostic factors, whereas brain metastasis was not consistently identified as a poor prognostic factor of OS (Table S2).

Discussion

Our study provides the most comprehensive set of data regarding the efficacy of DOC plus RAM in previously treated patients with NSCLC in a clinical setting. To the best of our knowledge, this is the first study that elucidates

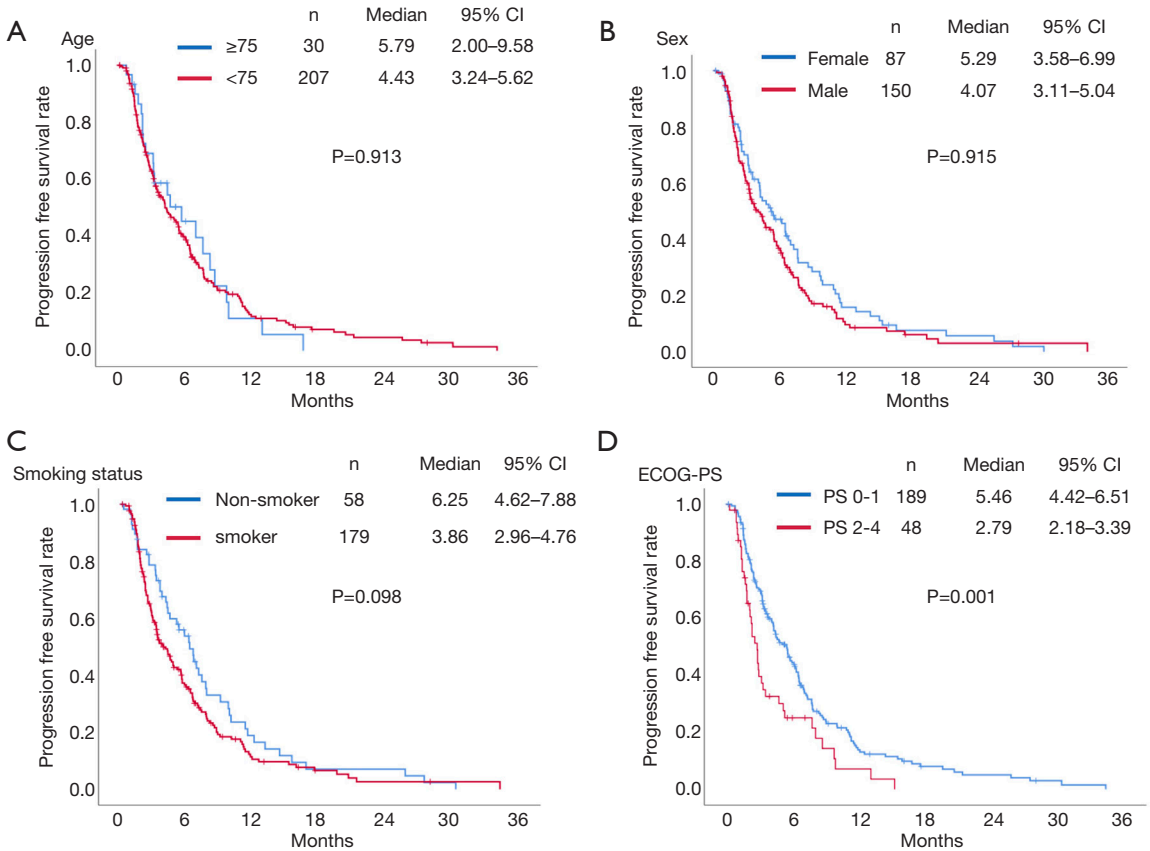

Figure 2 Kaplan-Meier survival curves of PFS. There were no significant differences in the median PFS of patient treated with DOC plus RAM in terms of (A) age, (B) sex, and (C) smoking status; (D) Poor PS group had shorter PFS compared to good PS group significantly [2.79 (95% CI: 2.18–3.39) *vs.* 5.46 (95% CI: 4.42–6.51) months; P<0.001]. PFS, progression-free survival; DOC, docetaxel; RAM, ramucirumab; PS, performance status; CI, confidence interval.

the relationship between metastatic site and therapeutic efficacy. Our findings demonstrate that poor ECOG-PS (≥2) and brain metastasis were independent factors significantly associated with a shorter PFS in patients who received DOC plus RAM. Furthermore, no differences in the PFS between patients with and without MPE and lung metastasis were found. There are several possible explanations as to why these differences in the PFS were observed in our study.

Although there are no reports on the efficacy of DOC plus RAM for patients with poor ECOG-PS, there are various reports about the efficacy and safety of DOC alone in ECOG-PS 2 patients. These studies have made its use controversial because of the significant increase in febrile neutropenia (23-25). Although the 2018 National Comprehensive Cancer Network Guidelines recommend DOC plus RAM treatment in previously treated patients with ECOG-PS 0–2 with NSCLC, ECOG-PS 2 patients were not included in the REVEL trial and there is no evidence that demonstrates the efficacy and safety in ECOG-PS 2 patients (26). We first showed that poor ECOG-PS was a significant and independent factor associated with a shorter PFS and OS. Although the number of treatment cycles was not collected, there was no significant difference in the discontinuation rate due to adverse events between good and poor PS patients. Nevertheless, the shorter survival of poor PS patients may result from the tumor burden at the start of DOC plus RAM. Therefore, further investigations on poor PS populations are needed.

The most common sites of metastatic disease in patients with NSCLC have been reported to be the bone, lungs, liver, brain, and adrenal glands (27,28). The MPE, occurring in approximately 15.0% of patients with NSCLC,

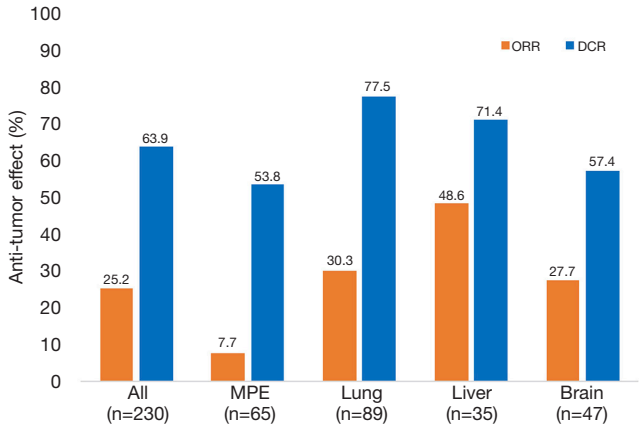

Figure 3 The ORR and DCR on each metastatic site. The ORR for MPE was 7.7%, relatively low. The ORR and DCR for lung and liver metastasis were higher than those in all patients, showing 30.3% and 77.5%, and 48.6% and 71.4%, respectively. The ORR and DCR for brain metastasis were almost the same as those of all patients. ORR, overall response rate; DCR, disease control rate; MPE, malignant pleural effusion.

also affects patient management and quality of life and is a prognostic factor for poor survival (29,30). NSCLC patients with MPE or liver metastasis have a poorer prognosis than patients without MPE or liver metastasis (14,30,31). Brain metastasis is also considered a poor prognostic factor in NSCLC patients; therefore, patients with brain metastasis have often been an excluded from clinical trials (32). BEV has been reported to be effective for metastatic sites, such as the MPE, lung, liver, and brain by binding to serum VEGF-A and inhibiting the binding of VEGF-A and VEGFR (14-18,20,33,34). Although RAM also inhibits VEGF-A/VEGFR signaling using a method similar to BEV (i.e., by binding to VEGFR2), the relationship between these metastatic sites and RAM efficacy is unknown.

Our study revealed that brain metastasis was a factor associated with poor PFS. This is similar to previously reported data that patients with brain metastasis have a poorer prognosis than those without brain metastasis (34). Subsequently, the blocking of VEGFR2 alone may be a weak preventive strategy against angiogenesis in the

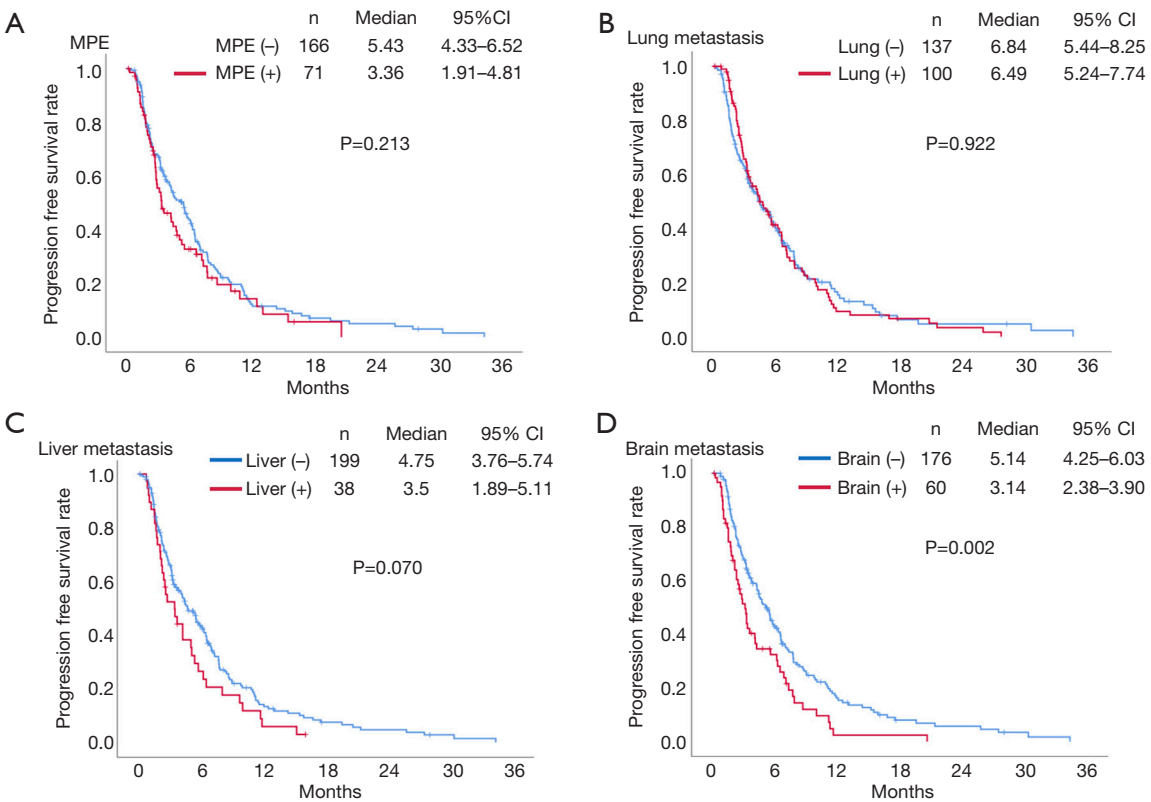

Figure 4 Kaplan-Meier survival curves of PFS. There were no significant differences in the median PFS of patient treated with DOC plus RAM in terms of (A) MPE, (B) lung metastasis, and (C) liver metastasis; (D) patients with brain metastasis had shorter PFS compared to patients without brain metastasis significantly [3.14 (95% CI: 2.38–3.90) *vs.* 5.14 (95% CI: 4.25–6.03) months; P=0.002]. PFS, progression-free survival; DOC, docetaxel; RAM, ramucirumab; MPE, malignant pleural effusion; CI, confidence interval.

Table 2 Univariate and multivariate analysis of PFS in patients treated with DOC plus RAM

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, years				
<75	1		1	
≥75	0.98 (0.63–1.51)	0.914	1.00 (0.64–1.57)	0.992
Sex				
Male	1		NA	
Female	0.83 (0.62–1.10)	0.197	NA	NA
ECOG-PS				
0–1	1		1	
2–4	1.76 (1.24–2.50)	0.002	1.66 (1.14–2.40)	0.008
Smoking status				
Non-smoker	1		NA	
Smoker	1.31 (0.95–1.83)	0.103	NA	NA
MPE				
(–)	1		1	
(+)	1.22 (0.89–1.67)	0.215	1.13 (0.82–1.55)	0.458
Lung metastasis				
(–)	1		1	
(+)	1.01 (0.76–1.35)	0.922	0.99 (0.74–1.32)	0.928
Liver metastasis				
(–)	1		1	
(+)	1.40 (0.97–2.03)	0.073	1.34 (0.90–1.98)	0.145
Brain metastasis				
(–)	1		1	
(+)	1.63 (1.19–2.25)	0.003	1.71 (1.23–2.37)	0.001

PFS, progression-free survival; DOC, docetaxel; RAM, ramucirumab; ECOG-PS, Eastern Cooperative Oncology Group-performance status; MPE, malignant pleural effusion; HR, hazard ratio; CI, confidence interval.

brain. According to existing research, in tissues with high vascular density, such as the brain, tumors grow not only by angiogenesis, but also by vessel co-option, which is a non-angiogenic process through which tumor cells utilize pre-existing tissue blood vessels. However, the same study also shows that blocking VEGF-A resulted in the undetectability of tumors (35). These observations may contribute to the difference of efficacy between BEV and RAM in treating brain metastasis in mouse models. Although the reason brain metastasis was not a poor prognostic factor of OS remains unclear, the number of prior treatments and the treatment regimen before and after administration may be involved.

Although there were no differences in the PFS and OS between patients with and without lung and liver metastasis in our study, the ORR and DCR for lung and liver metastasis were higher than those for all patients. There are several reasons as follows: VEGFR2 is constitutively phosphorylated, especially in the liver, lungs, and kidneys *in vivo*, and highly expressed in surgically resected lung specimen of NSCLC (36,37). It has been reported that VEGFR2 antibody inhibited the growth of lung metastasis of renal cell carcinoma by 26% (38). VEGFR2 is also up-regulated in patients with hepatocellular carcinoma and induces angiogenesis with consecutive endothelial growth in

the hepatic sinusoids (39). Clinically, RAM was approved for patients with hepatocellular carcinoma who were previously treated with sorafenib on the basis of the REACH-2 trial results in 2019 (40). Although further studies are required to determine whether DOC plus RAM improves the PFS and OS in patients with lung or liver metastasis, according to our data on anti-tumor effects, the therapy may be effective for patients with rapid progression of lung or liver metastasis. Recently, some studies have showed the efficacy of combination therapies of DOC and anti-angiogenic agents after ICIs. Brueckl *et al.* demonstrated the high response rate and long-term survival of DOC plus RAM followed immediately after ICIs (41). Grohé *et al.* also revealed the combination therapy of DOC plus nintedanib, triple angiokinase inhibitor after ICIs showed the clinical benefit in the prospective study (42). Our study included 40% of patients who received immunotherapy as the previous therapy, which may have affected the ORR and DCR for lung and liver metastasis.

MPE was associated with the low response and significantly shortened the OS. Generally, VEGF-A/VEGFR2 signaling increases vascular permeability and promotes pleural effusion retention. VEGF-A/VEGFR1 signaling may also contribute to tumor-associated angiogenesis (43). Unlike BEV, RAM does not block the VEGF-A/VEGFR1 pathway. As a result, MPE may hardly have been decreased, which may have affected poor OS. However, about 50% of patients were able to prevent an increase in pleural effusion, and therefore MPE was likely not a significant poor prognostic factor of PFS. Furthermore, regarding the clinical efficacy of MPE, results of prospective studies such as the PLEURAM study are expected in the future (44).

This study has several limitations. First, biases are inevitable due to the retrospective study design, including selection bias. However, confounding effects were adjusted for using multivariate models. Second, data on first-line and further lines of treatments before DOC plus RAM were not analyzed. Therefore, the OS may not have been evaluated accurately. Third, the efficacy of DOC plus RAM on metastatic sites was not directly compared to that of DOC monotherapy in this study. Therefore, it is difficult to elucidate the efficacy of RAM alone for each metastatic site. Further comparative studies are needed to validate our findings.

In conclusion, a poor ECOG-PS and brain metastasis were independently associated with poor PFS in patients with NSCLC treated with DOC plus RAM in a clinical setting. Careful monitoring is required for patients with these factors. Although DOC plus RAM did not prolong the PFS of patients with lung metastasis, and liver metastasis, the ORR and DCR for lung and liver metastasis were higher than those of all patients. DOC plus RAM could be an optimal therapy for patients with previously treated NSCLC who have lung and liver metastasis. Further studies are warranted to confirm the results of our study.

Acknowledgments

We thank all the patients who participated in this study.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tlcr-20-1263

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tlcr-20-1263

Peer Review File: Available at http://dx.doi.org/10.21037/tlcr-20-1263

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-1263). AT reports personal fees from Chugai Pharmaceutical, grants and personal fees from AstraZeneka, personal fees from Boehringer Ingelheim, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Bristol-Myers Squibb, personal fees from MSD, personal fees from Taiho, personal fees from Pfizer, personal fees from Eli Lilly, personal fees from Kissei, outside the submitted work. S.A reports grants and personal fees from AstraZeneca, grants and non-financial support from F. Hoffmann-La Roche, grants and personal fees from Ono, grants and personal fees from Taiho, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Pfizer, grants and personal fees from Bristol-Myers Squibb, personal fees from Hisamitsu, grants and personal fees from MSD, grants and personal fees from Eli Lilly, grants and personal fees from Chugai, personal fees from Kyowa Hakko Kirin, grants and personal fees from Merck, outside the submitted work. MT reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Bristol-

Myers Squibb, personal fees from Chugai Pharmaceutical, personal fees from AstraZeneca, personal fees from Taiho Pharmaceutical, personal fees from Eli Lilly, personal fees from Asahi Kasei Pharmaceutical, personal fees from MSD, outside the submitted work. HS reports personal fees from Chugai Pharmaceutical, personal fees from MSD, personal fees from AstraZeneca, outside the submitted work. TH reports grants and personal fees from Ono Pharmaceutical Co. Ltd, grants and personal fees from Lilly Japan Co. Ltd, grants and personal fees from AstraZeneca Co. Ltd, grants and personal fees from Taiho Pharmaceutical Co. Ltd, grants and personal fees from Chugai Pharmaceutical Co. Ltd., grants from Merck Serono Co. Ltd., grants from Boehringer Ingelheim, grants and personal fees from MSD Oncology Co. Ltd, outside the submitted work. The other 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. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013). This study was reviewed and approved by the Institutional Review Board at the Osaka International Cancer Institute (IRB No.20098), the Osaka Habikino Medical Center (IRB No.1046), the Osaka General Medical Center (IRB No.2020-060), and the National Hospital Organization Kinki-Chuo Chest Medical Center (IRB No.2020-034). Consent to participate was waived by the ethics board.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.
2. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382:41-50.
3. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
4. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-2301.
5. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
6. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-103.
7. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
8. Kudoh S, Takeda K, Nakagawa K, et al. Phase III study of docetaxel compared with vinorelbine in elderly patients with advanced non-small-cell lung cancer: results of the West Japan Thoracic Oncology Group Trial (WJTOG 9904). J Clin Oncol 2006;24:3657-63.
9. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014;384:665-73.
10. Yoshimura A, Yamada T, Okuma Y, et al. Retrospective analysis of docetaxel in combination with ramucirumab for previously treated non-small cell lung cancer patients. Transl Lung Cancer Res 2019;8:450-60.
11. Shiono A, Kaira K, Mouri A, et al. Improved efficacy of ramucirumab plus docetaxel after nivolumab failure in previously treated non-small cell lung cancer patients. Thorac Cancer 2019;10:775-81.
12. Harada D, Takata K, Mori S, et al. Previous Immune Checkpoint Inhibitor Treatment to Increase the Efficacy of Docetaxel and Ramucirumab Combination Chemotherapy. Anticancer Res 2019;39:4987-93.
13. Sakaguchi T, Furuya N, Ito K, et al. The efficacy and safety of ramucirumab plus docetaxel in older patients with advanced non-small cell lung cancer. Thorac Cancer 2020;11:1559-65.
14. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A

Crucial Target for Anti- and Pro-Angiogenic Therapies. Genes Cancer 2011;2:1097-105.
15. Tamiya M, Tamiya A, Yamadori T, et al. Phase2 study of bevacizumab with carboplatin-paclitaxel for non-small cell lung cancer with malignant pleural effusion. Med Oncol 2013;30:676.
16. Kitamura K, Kubota K, Ando M, et al. Bevacizumab plus chemotherapy for advanced non-squamous non-small-cell lung cancer with malignant pleural effusion. Cancer Chemother Pharmacol 2013;71:457-61.
17. Masago K, Fujimoto D, Fujita S, et al. Response to bevacizumab combination chemotherapy of malignant pleural effusions associated with non-squamous non-small-cell lung cancer. Mol Clin Oncol 2015;3:415-9.
18. Brodsky SV, Mendelev N, Melamed M, Ramaswamy G. Vascular density and VEGF expression in hepatic lesions. J Gastrointestin Liver Dis 2007;16:373-7.
19. Park YN, Kim YB, Yang KM, Park C. Increased expression of vascular endothelial growth factor and angiogenesis in the early stage of multistep hepatocarcinogenesis. Arch Pathol Lab Med 2000;124:1061-5.
20. Seo Y, Baba H, Fukuda T, Takashima M, Sugimachi K. High expression of vascular endothelial growth factor is associated with liver metastasis and a poor prognosis for patients with ductal pancreatic adenocarcinoma. Cancer 2000;88:2239-45.
21. Wong WB, Wu N, Yang E, Davies J, Chae YK. Real-World Clinical and Economic Outcomes and the Role of Bevacizumab in Patients With Non-Small-Cell Lung Cancer With Liver Metastases. J Oncol Pract 2019;15:e878-87.
22. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
23. Ozawa K, Minami H, Sato H. Logistic regression analysis for febrile neutropenia (FN) induced by docetaxel in Japanese cancer patients. Cancer Chemother Pharmacol 2008;62:551-7.
24. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol 2014;90:190-9.
25. Califano R, Griffiths R, Lorigan P, et al. Randomised phase II trial of 4 dose levels of single agent docetaxel in performance status (PS) 2 patients with advanced non-small cell lung cancer (NSCLC): DOC PS2 trial. Manchester lung cancer group. Lung Cancer 2011;73:338-44.
26. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Non–Small-Cell Lung Cancer, version 8. 2020. Available online: https://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf, accessed at 22 October 2020.
27. Hess KR, Varadhachary GR, Taylor SH, et al. Metastatic patterns in adenocarcinoma. Cancer 2006;106:1624-33.
28. Quint LE, Tummala S, Brisson LJ, et al. Distribution of distant metastases from newly diagnosed non-small cell lung cancer. Ann Thorac Surg 1996;62:246-50.
29. Morgensztern D, Waqar S, Subramanian J, Trinkaus K, Govindan R. Prognostic impact of malignant pleural effusion at presentation in patients with metastatic non-small-cell lung cancer. J Thorac Oncol 2012;7:1485-9.
30. Sugiura S, Ando Y, Minami H, Ando M, Sakai S, Shimokata K. Prognostic value of pleural effusion in patients with non-small cell lung cancer. Clin Cancer Res 1997;3:47-50.
31. Ren Y, Dai C, Zheng H, et al. Prognostic effect of liver metastasis in lung cancer patients with distant metastasis. Oncotarget 2016;7:53245-53.
32. Edelman MJ, Belani CP, Socinski MA, et al. Outcomes associated with brain metastases in a three-arm phase III trial of gemcitabine-containing regimens versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. J Thorac Oncol 2010;5:110-6.
33. Hiratsuka S, Nakamura K, Iwai S, et al. MMP9 induction by vascular endothelial growth factor receptor-1 is involved in lung-specific metastasis. Cancer Cell 2002;2:289-300.
34. Masuda C, Sugimoto M, Wakita D, et al. Bevacizumab suppresses the growth of established non-small-cell lung cancer brain metastases in a hematogenous brain metastasis model. Clin Exp Metastasis 2020;37:199-207.
35. Leenders WP, Küsters B, Verrijp K, et al. Antiangiogenic therapy of cerebral melanoma metastases results in sustained tumor progression via vessel co-option. Clin Cancer Res 2004;10:6222-30.
36. Maharaj AS, Saint-Geniez M, Maldonado AE, D'Amore PA. Vascular endothelial growth factor localization in the adult. Am J Pathol 2006;168:639-48.
37. Ding M, Liu L, Hu C, Liu Y, Qiao Y, Jiang X. Expression of VEGFR2 and NRP-1 in non-small cell lung cancer and their clinical significance. Chin J Cancer Res 2014;26:669-77.
38. Lee YJ, Karl DL, Maduekwe UN, et al. Differential effects of VEGFR-1 and VEGFR-2 inhibition on tumor metastases based on host organ environment. Cancer Res 2010;70:8357-67.

39. Bösmüller H, Pfefferle V, Bittar Z, et al. Microvessel density and angiogenesis in primary hepatic malignancies: Differential expression of CD31 and VEGFR-2 in hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Pathol Res Pract 2018;214:1136-41.
40. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:282-96.
41. Brueckl WM, Ficker JH, Zeitler G. Clinically relevant prognostic and predictive markers for immune-checkpoint-inhibitor (ICI) therapy in non-small cell lung cancer (NSCLC). BMC Cancer 2020;20:1185.
42. Grohé C, Gleiber W, Haas S, et al. Nintedanib plus docetaxel after progression on immune checkpoint inhibitor therapy: insights from VARGADO, a prospective study in patients with lung adenocarcinoma. Future Oncol 2019;15:2699-706.
43. Lacal PM, Graziani G. Therapeutic implication of vascular endothelial growth factor receptor-1 (VEGFR-1) targeting in cancer cells and tumor microenvironment by competitive and non-competitive inhibitors. Pharmacol Res 2018;136:97-107.
44. Takemoto S, Fukuda M, Yamaguchi H, et al. Phase II study of ramucirumab and docetaxel for previously treated non-small cell lung cancer patients with malignant pleural effusion: Protocol of PLEURAM study. Thorac Cancer 2020;11:389-93.

Cite this article as: Matsumoto K, Tamiya A, Matsuda Y, Taniguchi Y, Atagi S, Kawachi H, Tamiya M, Tanizaki S, Uchida J, Ueno K, Yanase T, Suzuki H, Hirashima T. Impact of docetaxel plus ramucirumab on metastatic site in previously treated patients with non-small cell lung cancer: a multicenter retrospective study. Transl Lung Cancer Res 2021;10(4):1642-1652. doi: 10.21037/tlcr-20-1263

Supplementary

Table S1 Front-line treatment of DOC plus RAM

	N (%)
Chemotherapy	115 (48.5)
Platinum doublets	53 (22.4)
Platinum doublets plus bevacizumab	42 (17.7)
Monotherapy	20 (8.4)
EGFR inhibitors	27 (11.4)
Erlotinib	4 (1.7)
Afatinib	6 (2.5)
Osimerutinib	17 (7.2)
Immunotherapy (monotherapy)	80 (33.7)
Nivolumab	52 (21.9)
Pembrolizumab	16 (6.8)
Atezolizumab	10 (4.2)
Durvalumab	2 (0.8)
Chemotherapy plus immunotherapy	13 (5.5)
Pembrolizumab	9 (3.8)
Atezolizumab	4 (1.7)
Experimental therapy	2 (0.9)

DOC, docetaxel; RAM, ramucirumab; EGFR, epidermal growth factor receptor.

http://dx.doi.org/10.21037/tlcr-20-1263

Table S2 Univariate and multivariate analysis of OS in patients treated with DOC plus RAM

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age				
<75	1		NA	
≥75	1.13 (0.70–1.84)	0.610	NA	NA
Sex				
Male	1		NA	
Female	0.74 (0.53–1.04)	0.087	NA	NA
ECOG-PS				
0–1	1		1	
2–4	2.37 (1.64–3.42)	0.001	2.02 (1.37–2.97)	0.001
Smoking status				
Non-smoker	1		1	
Smoker	1.57 (1.06–2.34)	0.025	1.61 (1.06–2.45)	0.026
MPE				
(–)	1		1	
(+)	1.76 (1.25–2.47)	0.001	1.63 (1.15–2.31)	0.007
Lung metastasis				
(–)	1		1	
(+)	0.97 (0.70–1.35)	0.862	1.03 (0.73–1.45)	0.869
Liver metastasis				
(–)	1		1	
(+)	1.46 (0.96–2.23)	0.075	1.23 (0.79–1.90)	0.356
Brain metastasis				
(–)	1		1	
(+)	1.27 (0.88–1.82)	0.198	1.30 (0.91–1.87)	0.153

OS, overall survival; DOC, docetaxel; RAM, ramucirumab; ECOG-PS, Eastern Cooperative Oncology Group-performance status; MPE, malignant pleural effusion; HR, Hazard Ratio; CI, confidence interval.

http://dx.doi.org/10.21037/tlcr-20-1263