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Previous Immune Checkpoint Inhibitor Treatment to Increase the Efficacy of Docetaxel and Ramucirumab Combination Chemotherapy

DAIJIRO HARADA[1], KENJI TAKATA[2], SHUNTA MORI[1], TOSHIYUKI KOZUKI[1], YOSHIKA TAKECHI[3], SATOKO MORIKI[3], YUMI ASAKURA[3], TAKAYUKI OHNO[3] and NAOYUKI NOGAMI[1]

[1]*Department of Thoracic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan;*
[2]*Department of Respiratory Medicine, National Hospital Organization Okayama Medical Center, Okayama, Japan;*
[3]*Department of Pharmacy, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan*

Abstract. *Background/Aim: For immune checkpoint inhibitor (ICI)-pretreated patients, docetaxel and ramucirumab (DOC+RAM) combination therapy may be more effective compared to patients not receiving ICI treatment. Patients and Methods: From June 2013 to July 2018, 39 patients with advanced/recurrent non-small cell lung cancer underwent DOC+RAM therapy. We analyzed the efficacy and safety of DOC+RAM therapy based on the presence (pre-ICI+) or absence (pre-ICI–) of ICI pretreatment history. Results: Of the 39 patients treated with DOC+RAM, we identified 18 (46%) pre-ICI+ patients. Overall response rates for DOC+RAM concerning pre-ICI+ and pre-ICI– patients were 38.9% vs. 19.0%, respectively. Median progression-free survival (PFS) was 5.7 vs. 2.3 months [hazard ratio(HR)=0.36; 95% confidence interval (CI)=0.16–0.80]. Adverse events such as fever, myalgia, arthritis, pleural effusion, and pneumonitis tended to be increased in pre-ICI+ patients. Conclusion: Despite increased toxicity concerns, DOC+RAM therapy in pre-ICI+ patients showed a trend for tumor regression improvement and statistically significant prolongation of PFS.*

Lung cancer is one of the leading causes of mortality worldwide. Immune checkpoint inhibitor (ICI) monotherapy or combination chemotherapy with cytotoxic agents has been developed for patients with advanced non-small cell lung cancer (NSCLC). However, median progression-free survival (PFS) is limited (1, 2). Applying more effective sequential chemotherapy is important for the prolongation of life. Recently, salvage cytotoxic chemotherapy after ICI treatment has been reported to increase antitumor effects (3-6). Moreover, it has been suggested that the efficacy of sequential cytotoxic chemotherapy may improve both the overall response rate (ORR) and PFS, regardless of the efficacy of previous ICI treatment and programmed death-ligand 1 (PD-L1) expression (4). Some studies have reported that activation of the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) inhibitory (VEGF/VEGFR) signal is one of the ICI resistant mechanisms, and that combination therapy of a VEGF/VEGFR inhibitor with ICI had a synergistic and improved antitumor effect (7). It has also been reported that using docetaxel with ramucirumab, a VEGFR inhibitor combination therapy (DOC+RAM) for ICI-treated patients may be more effective than for patients in historical case controls (6). Therefore, we conducted a retrospective comparative study on the efficacy and toxicity of DOC+RAM therapy at our hospital.

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Correspondence to: Daijiro Harada, MD, Ph.D., Department of Thoracic Oncology, National Hospital Organization Shikoku Cancer Center, 160 Minami-Umemoto-machi, Matsuyama-shi, Ehime 791-0280, Japan. Tel: +81 899991111, Fax: +81 899991100, e-mail: h401068@yahoo.co.jp

Key Words: Non-small cell lung cancer, cytotoxic chemotherapy, previous immune checkpoint inhibitor treatment.

Patients and Methods

We retrospectively reviewed the medical records of patients with advanced or recurrent NSCLC who had undergone DOC+RAM therapy at our hospital from June 2013 to July 2018. In total, 39 patients were analyzed, and we compared the efficacy and safety of this therapy based on the presence (pre-ICI+) or absence (pre-ICI–) of an ICI pretreatment history. In this study, it was not relevant whether ICI treatment was immediately undertaken prior to the DOC+RAM therapy. We applied the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to determine efficacy. For evaluation of toxicity, we used the Common Terminology Criteria for Adverse Events (CTCAEs) version 4.0. Overall survival (OS) was defined as the interval from the initial day of DOC+RAM treatment to death from any cause. PFS was defined as the interval from the initial day of chemotherapy to disease progression or

death. Comparisons for categorical variables such as ORRs and disease control rates (DCRs) were performed using Fisher's exact test. Survivals were assessed using the Kaplan–Meier method and determined using the log-rank test. In addition, a multivariate Cox regression model was used to examine factors that may influence survival in relation to DOC+RAM therapy. For the multivariate analysis, hazard ratios (HRs) were estimated using a stepwise selection method. For all analyses, a *p*-value of <0.05 indicated a statistically significant difference.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it involves a modified version of R commander designed to add statistical functions frequently used in biostatistics.

This study was conducted with approval obtained from institutional ethics review boards of the national hospital organization Shikoku Cancer Center, Matsuyama, Japan [2019-12].

Results

Patient characteristics. Patient characteristics are listed in Table I. Of the 39 patients treated with DOC+RAM, 18 (46%) patients were pretreated with ICI (pre-ICI+). The male-to-female ratio and the squamous cell carcinoma ratio were higher in the pre-ICI+ patients. Conversely, *EGFR* mutation-positivity was found to be higher in the pre-ICI– patients.

Efficacy and survival analysis. The ORRs for the pre-ICI+ and pre-ICI– patients were 38.9% (95%CI=17.3–64.3%) *vs*. 19.0% (95%CI=5.4-41.9%), respectively, (p=0.29) (Figure 1a). The DCRs were 83.3% (95%CI=58.6–96.4%) *vs*. 57.1% (95%CI=34.0-78.2%), respectively, (p=0.096) (Figure 1b). Previous treatment with ICI led to an increased response to DOC+RAM therapy. PFS was significantly longer in pre-ICI+ patients than in pre-ICI– patients, and the median PFS (mPFS) was 5.7 (95%CI=2.1-9.9) *vs*. 2.3 (95%CI=1.7-4.4) months, respectively, (p=0.020) (Figure 2a). Median survival time (MST) was 13.8 (95%CI=10.2–NA) *vs*. 10.5 (95%CI=6.7-13.1) months (p=0.065) (Figure 2b).

We conducted a univariate and multivariate analysis of PFS and OS, respectively. The individual clinical factors and biomarkers analyzed in the study are shown in Table II. Considering the distribution of the characteristics, we adopted six factors: pre-ICI, sex, smoking status, existence of a driver mutation [an epidermal growth factor receptor (*EGFR*) mutation and anaplastic lymphoma kinase (*ALK*) transfusion], age (≥70 years and <70 years), and stage (recurrence or not), as independent variables to evaluate univariate and multivariate analysis for PFS and OS. Performance status (PS) is regarded as a predictive factor of the effect of cytotoxic agents and was not adopted because most patients were had a 0 or 1 status in both groups. In addition, PD-L1 expression, considered as a predictive biomarker associated with ICI treatment effects, was also not adopted because the relevant data were not available for >50% of patients in both groups. The univariate analysis demonstrated that pre-ICI treatment was the sole factor that correlated with a prolonged PFS using DOC+RAM therapy, with statistical significance. Furthermore, using a backward stepwise selection method with *p*-values, pre-ICI+ was the only independent predictive

Table I. *Characteristics of the study patients*.

	Pre-ICI+ (n=18)		Pre-ICI– (n=21)	
Characteristic	n	(%)	n	(%)
Median age, (range)	66.5 (54-78)		65 (50-76)	
Median treatment line, (range)	3 (2-5)		3 (2-5)	
Gender				
Male	15	(83.3)	10	(47.6)
Female	3	(16.7)	11	(52.4)
ECOG PS				
0	1	(5.6)	2	(9.5)
1	16	(88.9)	16	(76.2)
2	1	(5.6)	2	(9.5)
3	0	(0)	1	(4.8)
Disease stage				
IIIB	3	(16.7)	1	(4.8)
IV	11	(61.1)	14	(66.7)
Recurrence	4	(22.2)	6	(28.6)
Histology				
Adenocarcinoma	13	(72.2)	20	(95.2)
Squamous	5	(27.8)	0	(0)
Large cell	0	(0)	1	(4.8)
Smoking status				
Non-smoker	2	(11.1)	7	(33.3)
Smoker/ever smoker	16	(88.9)	14	(66.7)
PD-L1 status				
<1%	4	(22.2)	6	(28.6)
1-49%	3	(16.7)	3	(14.3)
≥50%	1	(5.6)	1	(4.8)
Unknown	10	(55.6)	11	(52.4)
EGFR mutation				
Negative	15	(83.3)	13	(61.9)
Positive	2	(11.1)	8	(38.1)
Not evaluated	1	(5.6)	0	(0)
ALK transfusion				
Negative	17	(94.4)	16	(76.2)
Positive	0	(0)	1	(4.8)
Not evaluated	1	(5.6)	4	(19.0)
Previous ICI Tx			-	-
Nivolumab	11	(61.1)		
Pembrolizumab	1	(5.6)		
Atezolizumab	1	(5.6)		
ICI + Chemo	5	(27.8)		

ALK: Anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR: epidermal growth factor receptor; ICI: immune checkpoint inhibitor; ICI + Chemo: ICI plus cytotoxic agent combination chemotherapy PD-L1: programmed death-ligand 1; Tx: treatment.

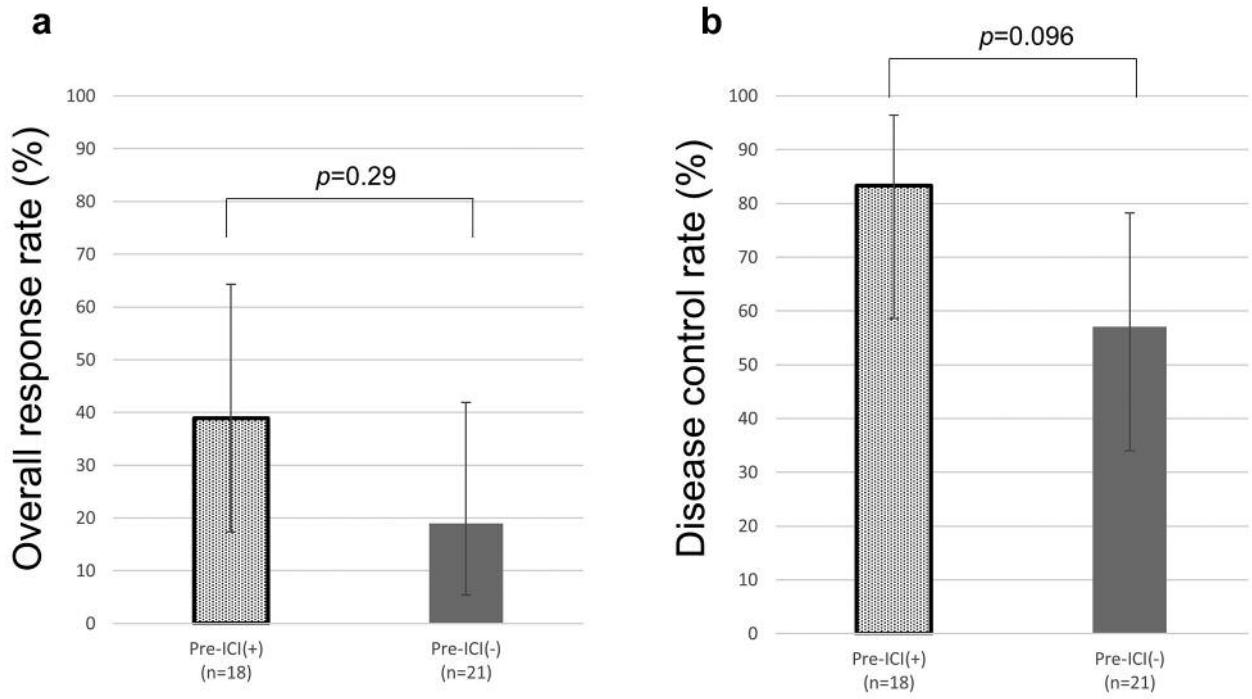

Figure 1. *a: Overall response rate. The ORRs in pre-ICI+ and pre-ICI– were 38.9% (95%CI=17.3-64.3%) vs. 19.0% (95%CI=5.4-41.9%), respectively, (p=0.29). b: Disease control rate. The DCRs were 83.3% (95%CI=58.6-96.4%) vs. 57.1% (95%CI=34.0-78.2%), respectively, (p=0.096). CI: Confidence interval; DCR: disease control rate; ICI: immune checkpoint inhibitor; ORR: overall response rate.*

factor of PFS (HR=0.42; 95%CI=0.21-0.89; p=0.024) in the multivariate analysis (Table II). However, pre-ICI+ was not an independent predictive factor of OS in the univariate and multivariate analyses (Table III). OS rates were also better in pre-ICI+ patients. In addition, there were five patients who underwent ICI plus cytotoxic agent combination chemotherapy (ICI+Chemo), and the efficacy tended to be similar (data not shown).

Safety. The dose of DOC was reduced in 33% of patients in both groups because of toxicity. Eight pre-ICI+ patients (44%) and 17 (81%) pre-ICI– patients discontinued DOC+RAM therapy because of disease progression, while ten patients (56%) and three patients (14%) discontinued DOC+RAM therapy because of adverse events, respectively.

Adverse events (AEs) are listed in Table IV. All patients experienced varying grades of AEs after the administration of DOC+RAM. The incidence of any grade of AEs, such as nausea, diarrhea, constipation, fatigue, peripheral neuropathy, fever, myalgia, arthritis, oral mucositis, pleural effusion, edema, and pneumonitis, was higher in pre-ICI+ patients. However, neutropenia and hypertension were higher in pre-ICI– patients. The incidence of ≥grade 3 anorexia and pneumonitis was higher in pre-ICI+ patients. There were no grade 5 AEs in either group.

With regard to ramucirumab-related toxicity, the frequency of proteinuria, hypertension, and hemorrhagic AEs is shown in Table IV. Concerning other AEs ≥grade 3, a grade 3 lung infection (n=1) and a grade 3 thromboembolic event (n=1) occurred in the pre-ICI+ patient group. Grade 3 palmar-plantar erythrodysesthesia syndrome (n=1) and grade 3 heart failure (n=1) occurred in the pre-ICI– patient group. Among the pre-ICI+ patients, three patients developed pneumonitis, two of whom had grade 3 pneumonitis.

Discussion

This retrospective study showed a statistically significant prolonged PFS and a trend towards an improved ORR, DCR, and OS, using DOC+RAM therapy in ICI pretreated patients compared with those without ICI treatment, for patients with previously treated NSCLC. According to the results of the multivariate analysis, pre-ICI+ therapy was found to be a factor that positively influenced the efficacy of DOC+RAM therapy.

Shiono *et al*. showed that, after nivolumab treatment, DOC+RAM therapy is highly effective (6). The ORR of DOC+RAM was reported to be 60%, and the PFS and OS were 169 and 343 days, respectively. Tamura *et al*. also indicated that the effectiveness of docetaxel with or without

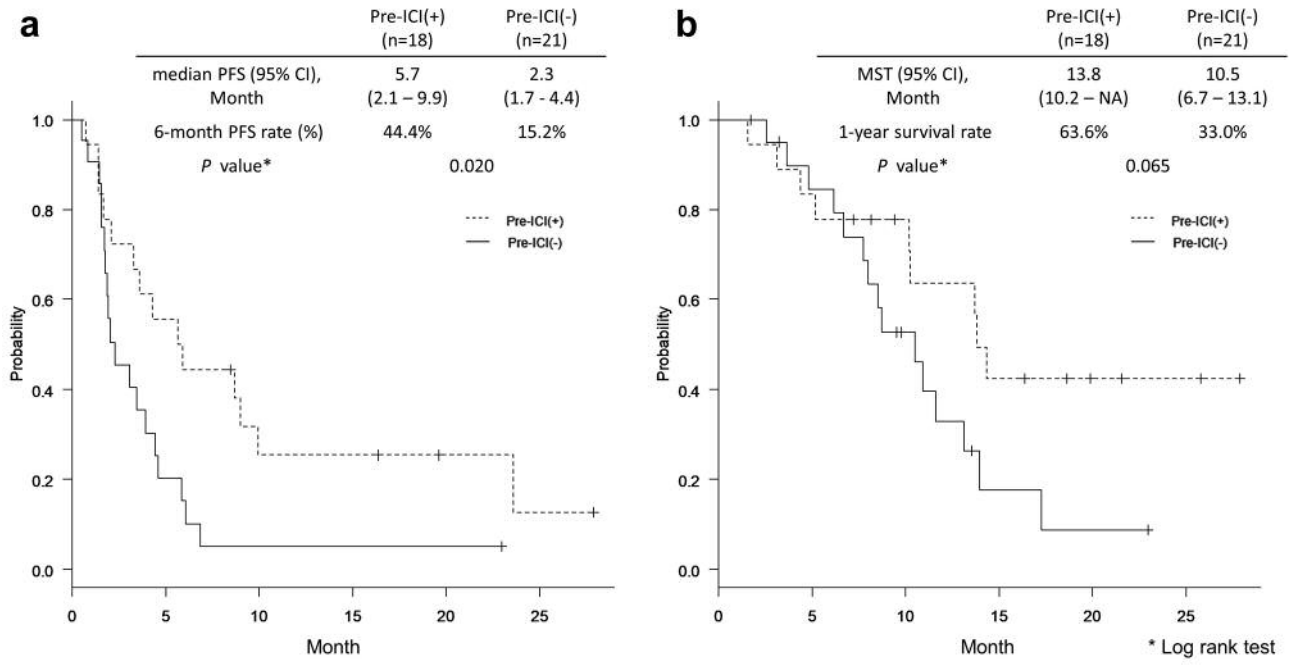

Figure 2. *Progression-free survival and overall survival. a: Progression-free survival. Pre-ICI+ group had a prolongation of the progression-free survival time with statistical significance. b: Overall survival time of the pre-ICI+ group tended to be longer. CI: Confidence interval; HR: hazard ratio; ICI: immune checkpoint inhibitor; MST: median survival time; PFS: progression-free survival; OS: overall survival.*

ramucirumab or S1 therapy after nivolumab might be enhanced (5, 8), and our results are consistent with their findings.

Two hypotheses can be considered to explain why the efficacy of DOC+RAM after ICI treatment increased. One possibility is that previous ICI treatment produced beneficial changes in the efficacy of cytotoxic chemotherapy in the tumor and/or its microenvironment and, as a result, the efficacy increased. The other possibility is that DOC+RAM therapy overcame the resistance mechanism of ICI. However, both possibilities are closely related, and the former can be considered implicit in the latter.

The main mechanism through which cytotoxic chemotherapy promotes tumor immunity is by inducing immunogenic cell death as part of its intended therapeutic effect and by disrupting the mechanisms through which tumors evade immune recognition. The mechanisms of these actions have been reported to include the elimination of myeloid-derived suppressor cells and T-regulatory cells, the induction of expression of costimulatory molecules, enhancement of antigen presentation and processing, and tumor cell death (3, 9). Recently, clinical studies have shown that ICI plus platinum doublet cytotoxic chemotherapy significantly improves efficacy compared to ICI treatment, suggesting a synergistic effect between the cytotoxic chemotherapy and ICI treatment (1).

It has been also suggested that antiangiogenic agents stimulate the immune system and, conversely, immunotherapy also has an antiangiogenic action (10). Four key mechanisms, namely, inhibition of dendritic cell maturation, reduction of T-cell tumor infiltration, promotion of inhibitory cells in the tumor microenvironment (7, 11, 12), and inhibition of T-cell development from hematopoietic progenitor cells (12) are considered to be related to VEGF–mediated immunosuppression (7). Regarding the mechanism of both ICI natural and acquired resistance, it has also been suggested that these VEGF/VEGFR immunosuppressive pathways may be involved in the resistance (13). Although ICI and RAM (a VEGFR inhibitor) were not concurrently administered in this study, when taking into consideration the possibility that the pharmacological action of ICI continues for a long time even after discontinuation of ICI treatment (14), there is a possibility that sequential therapy with the VEGFR inhibitor might be related to restoring the acquired resistance of ICI. We suggest that VEGF/VEGFR inhibitor combination chemotherapy relieves the suppression of tumor immunity, a mechanism of acquired resistance of ICI, and thereby not only enhances the antitumor effect of the sequential chemotherapy but also achieves a long-term response, which is specific to ICI.

Overall, pre-ICI+ patients had many AEs, particularly diarrhea, peripheral neuropathy, fever, myalgia, arthritis, pleural

Table II. *Univariate and multivariate analysis of PFS.*

	n	Univariate		Multivariate	
		HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Pre-ICI					
Negative	21	Ref	0.023	Ref	0.012
Positive	18	0.43 (0.21-0.89)		0.36 (0.16-0.80)	
Gender					
Male	25	Ref	0.662	Ref	0.442
Female	14	0.85 (0.41-1.77)		0.68 (0.25-1.82)	
Smoking status					
Non-smoker	9	Ref	0.750	Ref	0.286
smoker	30	1.14 (0.51-2.54)		1.79 (0.61-5.22)	
Driver mutations					
Negative	28	Ref	0.305	Ref	0.108
Positive	11	1.47 (0.70-3.09)		2.20 (0.84-5.72)	
Age					
<70	28	Ref	0.325	Ref	0.040
≥70	11	1.46 (0.69-3.09)		2.63 (1.05-6.62)	
Stage					
Stage III, IV	29	Ref	0.272	Ref	0.141
Recurrence	10	0.62 (0.27-1.45)		0.51 (0.20-1.25)	

CI: Confidence interval; HR: hazard ratio; ICI: immune checkpoint inhibitor; PFS: progression-free survival; Ref: referent.

Table III. *Univariate and multivariate analysis of OS.*

	n	Univariate		Multivariate	
		HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Pre-ICI					
Negative	21	Ref	0.071	Ref	0.061
Positive	18	0.46 (0.20-1.07)		0.41 (0.16-1.04)	
Gender					
Male	25	Ref	0.884	Ref	0.646
Female	14	0.94 (0.41-2.18)		0.74 (0.20-2.69)	
Smoking status					
Non-smoker	9	Ref	0.907	Ref	0.945
Smoker	30	0.95 (0.39-2.30)		1.04 (0.30-3.69)	
Driver mutations					
Negative	28	Ref	0.756	Ref	0.929
Positive	11	1.15 (0.48-2.73)		1.05 (0.33-3.34)	
Age					
<70	28	Ref	0.918	Ref	0.525
≥70	11	1.05 (0.39-2.86)		1.45 (0.46-4.52)	
Stage					
Stage III, IV	29	Ref	0.297	Ref	0.437
Recurrence	10	0.56 (0.19-1.65)		0.62 (0.19-2.05)	

CI: Confidence interval; HR: hazard ratio; ICI: immune checkpoint inhibitor; OS: overall survival; Ref: referent.

effusion, and pneumonitis. Among these, some AEs tended to be more frequent than those reported to have occurred in a DOC+RAM prospective trial undertaken in Japan (JVCG). These included fever, myalgia, arthritis, pleural effusion, and pneumonitis. We considered that these AEs may have occurred because the effects of prior ICI pharmacology remained during the DOC+RAM therapy period (8). Some of these AEs are recognized as immune-related AEs (irAEs) in ICI treatment. We

Table IV. *Adverse events*.

Adverse event (CTCAE v 4.0)	Pre-ICI(+) (n=18)		Pre-ICI(–) (n=21)	
	Total n (%)	Grade 3≤ n (%)	Total n (%)	Grade 3≤ n (%)
Neutropenia	6 (33)	1 (5.6)	12 (57)	9 (42.9)
Anemia	0 (0)	0 (0)	1 (4.8)	1 (4.8)
Thrombocytopenia	14 (78)	1 (5.6)	17 (81)	1 (4.8)
Febrile neutropenia	0 (0)	0 (0)	3 (14)	3 (14)
AST/ALT increase	2 (11)	0 (0)	4 (19)	0 (0)
Anorexia	11 (61)	3 (17)	12 (57)	1 (4.8)
Nausea	5 (28)	0 (0)	2 (9.5)	0 (0)
Diarrhea	4 (22)	0 (0)	2 (9.5)	0 (0)
Constipation	2 (11)	0 (0)	0 (0)	0 (0)
Fatigue	14 (78)	0 (0)	11 (52)	0 (0)
Peripheral neuropathy	4 (22)	1 (5.6)	1 (4.8)	0 (0)
Rash	1 (5.6)	0 (0)	2 (9.5)	1 (4.8)
Dysgeusia	2 (11)	0 (0)	1 (4.8)	0 (0)
Fever	9 (50)	0 (0)	8 (38)	0 (0)
Myalgia	7 (39)	0 (0)	2 (9.5)	0 (0)
Arthritis	6 (33)	0 (0)	1 (4.8)	0 (0)
Oral mucositis	14 (78)	2 (11)	13 (62)	5 (24)
Pleural effusion	4 (22)	1 (5.6)	1 (4.8)	1 (4.8)
Edema	5 (28)	0 (0)	3 (14)	0 (0)
Pneumonitis	3 (17)	2 (11)	1 (4.8)	0 (0)
Hypoxia	1 (5.6)	1 (5.6)	0 (0)	0 (0)
Ramucirumab related toxicity				
Proteinuria	8 (44)	0 (0)	10 (48)	0 (0)
Hypertension	1 (5.6)	0 (0)	4 (19)	1 (4.8)
Hemorrhagic AEs	3 (17)	0 (0)	5 (24)	1 (4.8)
• epistaxis	2 (11)		3 (14)	
• tracheal hemorrhage			1 (4.8)	
• gastrointestinal hemorrhage			1 (4.8)	1 (4.8)
• oral hemorrhage	1 (5.6)			

AEs: Adverse events; ALT: alanine amino transferase; AST: aspartate amino transferase; CTCAE: common terminology criteria for adverse event; ICI: immune checkpoint inhibitor.

suggested that irAEs in regard to ICI treatment occurred later, or that the DOC+RAM treatment had induced the pharmacological effects of ICI, resulting in the onset of irAEs. As the VEGF/VEGFR inhibitor-specific AEs (bleeding, proteinuria, and hypertension) of the DOC+RAM therapy had not increased (Table IV), it may not be considered that the total AEs of the DOC+RAM therapy had increased. Some studies have reported that the efficacy also improved if there were many irAEs during the ICI treatment (15). Considering these findings, the same tendency was seen in this observational study.

There were several limitations to our study. First, because this was a retrospective study, this study had a short observation period and small patient numbers; therefore, a prospective study is recommended. Second, we did not analyze whether pre-ICI + was a predictive factor in DOC+RAM therapy or whether DOC alone would have provided a similar result; therefore, we consider that this issue requires further research.

Conclusion

Despite increased toxicity concerns, DOC+RAM therapy in pre-ICI+ patients showed a trend for tumor regression improvement and statistically significant prolongation of PFS. Considering that combination chemotherapies with ICI as a first-line chemotherapy are likely to be widely used, DOC+RAM therapy might become an even more valuable treatment regimen in treatment sequencing.

Conflicts of Interest

Daijiro Harada has been paid lecture fees to participate in a speakers' bureau by Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb Company, Yakult Honsha Co., Ltd., Kyowa Hakko Kirin Co., Ltd., AstraZeneca K.K., Nippon Boehringer Ingelheim Co., Ltd. and Eli Lilly Japan. Toshiyuki Kozuki has received honoraria outside the current work from Chugai Pharmaceutical, AstraZeneca, Eli Lilly

Japan, Boehringer–Ingelheim, Ono Pharmaceutical, Bristol-Myers Squibb Company, Taiho Pharmaceutical, MSD K.K., Pfizer Inc. Japan, and Kyowa Hakko Kirin, and research funding from Chugai Pharmaceutical, AstraZeneca, MSD K.K., and Eli Lilly Japan. Naoyuki Nogami has received honoraria from Astellas Pharma, AstraZeneca, Ono Pharmaceutical, Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Boehringer Ingelheim and Pfizer. The remaining Authors declare that they have no competing interests regarding this study.

Authors' Contributions

Daijiro Harada, Kenji Takata, Toshiyuki Kozuki and Naoyuki Nogami were involved in study concept and design. Daijiro Harada, Kenji Takata, Shunta Mori, Yoshika Takechi, Satoko Moriki, Yumi Asakura and Takayuki Ohno involved in data acquisition. Analysis and interpretation of data was done by Daijiro Harada, Toshiyuki Kozuki and Naoyuki Nogami. Manuscript writing was made by Daijiro Harada, Toshiyuki Kozuki and Naoyuki Nogami. All Authors reviewed and approved the final manuscript.

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