Original Article

Utility of atezolizumab plus bevacizumab, carboplatin, and paclitaxel combination for the treatment of advanced non-squamous non-small cell lung cancer patients with malignant pleural effusion

Kakeru Hisakane[1]^, Kenichiro Atsumi[1], Masahiro Seike[2], Takashi Hirose[1]

[1]Department of Pulmonary Medicine and Medical Oncology, Nippon Medical School Tamanagayama Hospital, Tokyo, Japan; [2]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

Contributions: (I) Conception and design: K Hisakane, T Hirose; (II) Administrative support: K Hisakane, K Atsumi, T Hirose; (III) Provision of study materials or patients: K Hisakane, K Atsumi, T Hirose; (IV) Collection and assembly of data: K Hisakane, K Atsumi, T Hirose; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kakeru Hisakane, MD, PhD. Department of Pulmonary Medicine and Medical Oncology, Nippon Medical School Tamanagayama Hospital, 1-7-1, Nagayama, Tama-city, 206-8512, Tokyo, Japan. Email: hisa079kane@nms.ac.jp.

Background: Malignant pleural effusion (MPE) remains a negative prognostic factor in non-small cell lung cancer (NSCLC), even after the emergence of immune checkpoint inhibitors. Vascular endothelial growth factor (VEGF) plays a pivotal role in the pathogenesis of MPE. Bevacizumab, a humanized monoclonal antibody against VEGF, is a key agent for patients who develop MPE. However, it is unclear whether MPE is a poor prognostic factor in patients with advanced non-squamous NSCLC receiving treatment with the atezolizumab plus bevacizumab, carboplatin, and paclitaxel (ABCP) regimen. Moreover, the effect of ABCP on MPE control is unknown. This study aimed to elucidate the efficacy and safety of ABCP for non-squamous NSCLC patients with MPE.

Methods: We retrospectively analyzed consecutive patients with advanced non-squamous NSCLC who received treatment with ABCP (January 2019–September 2023). Patients were divided into two groups (non-MPE and MPE), and treatment outcomes were compared. In the MPE group, treatment efficacy for MPE control and toxicity were evaluated.

Results: Of the 46 patients enrolled, 17 and 29 were included in the non-MPE and MPE groups, respectively. The objective response and disease control rates were not significantly different between the non-MPE and MPE groups (76.5% *vs.* 51.7%, P=0.13; 88.2% *vs.* 82.8%, P>0.99; respectively). Similarly, the median progression-free survival and median overall survival were not significantly different (9.9 *vs.* 10.1 months, P=0.87; 16.0 *vs.* 19.9 months, P=0.87, respectively). In the MPE group, 25 patients (86.2%) achieved MPE control lasting >8 weeks from the initiation of treatment with ABCP; the median progression-free survival without an unequivocal increase in MPE was 15.0 months. The incidence rates of grade ≥3 non-immune- and immune-related adverse events were 83% and 17%, respectively. There was no treatment-related death.

Conclusions: The ABCP regimen may be a promising treatment option for non-squamous NSCLC patients with MPE.

Keywords: Atezolizumab plus bevacizumab, carboplatin and paclitaxel (ABCP); immune checkpoint inhibitor (ICI); malignant pleural effusion (MPE); non-small cell lung cancer (NSCLC); vascular endothelial growth factor (VEGF)

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^ ORCID: 0000-0002-9108-2050.

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Introduction

Malignant pleural effusion (MPE) is found in approximately 10–40% of non-small cell lung cancer (NSCLC) cases and is associated with poor prognosis (1-3). Vascular endothelial growth factor (VEGF) plays a crucial role in the development of MPE (4-7). Prior to the advent of immune checkpoint inhibitors (ICIs), several phase 2 trials were conducted to evaluate the efficacy of platinum-combination chemotherapy plus bevacizumab (a humanized anti-VEGF monoclonal antibody) in the treatment of advanced non-squamous NSCLC patients with MPE. In these studies, the rate of MPE control ranged approximately 80–90% (8-10). Therefore, bevacizumab is considered a key agent for patients with advanced non-squamous NSCLC who develop MPE.

Multiple treatment regimens consisting of ICIs with or without platinum-combination chemotherapy have been approved as standard therapy for advanced NSCLC (11). Atezolizumab [anti-programmed cell death-ligand 1 (anti-PD-L1) antibody] plus bevacizumab, carboplatin, and paclitaxel (ABCP) is a representative regimen combining an ICI and a VEGF inhibitor (12). MPE remains an unfavorable prognostic factor in patients with advanced NSCLC treated with therapies including ICIs (13-15). Prognostic analysis of advanced NSCLC patients with MPE treated with immunochemotherapy with or without bevacizumab failed to reveal a benefit of adding bevacizumab on survival (15,16). Consequently, it has been suggested that the synergistic effect of bevacizumab and ICIs may be limited in patients with NSCLC who suffer from MPE. However, in these studies, various regimens were used and few patients received bevacizumab-containing therapy.

To the best of our knowledge, the prognostic impact of MPE in patients with advanced non-squamous NSCLC treated with ABCP, as well as the controlling effect of this regimen on MPE, remain uncertain. Therefore, we conducted a retrospective study to elucidate the efficacy and safety of ABCP in patients with advanced non-squamous NSCLC who develop MPE. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-347/rc).

Highlight box

Key findings

- The presence of malignant pleural effusion (MPE) was not identified as an unfavorable predictor of response to treatment with atezolizumab plus bevacizumab, carboplatin and paclitaxel (ABCP) and survival in patients with advanced non-squamous non-small cell lung cancer (NSCLC). In addition, the ABCP regimen exerted short- and long-term effects on the control of MPE.

What is known and what is new?

- MPE is an unfavorable prognostic factor in NSCLC. Following the emergence of immune checkpoint inhibitors (ICIs), retrospective studies have shown that MPE remains a poor prognostic factor in NSCLC patients treated with ICI alone or ICI plus chemotherapy.
- This study demonstrated that the ABCP regimen was an effective and safe treatment for patients with advanced non-squamous NSCLC even in the presence of MPE. In particular, the control effect of MPE by the ABCP regimen in the short and long term was encouraging.

What is the implication, and what should change now?

- ABCP may be an optimal regimen for patients with NSCLC suffering from MPE. Prospective clinical trials with larger cohorts are warranted to address this clinical hypothesis.

Methods

Patient selection and treatment

We enrolled consecutive patients with stage IV or recurrent non-squamous NSCLC who received treatment with ABCP at Nippon Medical School Tamanagayama Hospital (Tama, Japan) between January 2019 and September 2023. Patients who underwent ABCP therapy in the second- or later-line settings were also eligible for enrollment. The dosage and administration schedule of each drug were based on the protocol of the IMpower 150 study (12). Dose reduction, omission, postponement, and discontinuation of the treatment were decided by the treating physician according to the condition of the patient. All clinical data were retrieved from the medical records of patients. The treatment outcomes were compared between patients with and without MPE. The presence of MPE at the initiation of treatment with ABCP was confirmed by chest computed tomography. Patients who exhibited positive pleural fluid cytology results, exudative pleural effusion, or presented with pleural nodules and nodular pleural thickening along with pleural effusion on a computed tomography scan were diagnosed with MPE. Informed consent for participation in this study was provided by the patients through an opt-out method. This study was approved by the Ethics Committee of Nippon Medical School Tamanagayama Hospital (approval number: F-2023-

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086). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study assessments

Tumor response was determined according to The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Objective response and disease control rates were defined as the proportions of patients achieving complete response or partial response, and complete response, partial response, or stable disease, respectively. MPE control rate was defined as the percentage of patients without an unequivocal increase in MPE for 8 weeks after the initiation of treatment with ABCP. This rate was assessed only in patients with MPE at baseline (10,17). Unequivocal increase in MPE was defined as equivalent to progressive disease in RECIST (version 1.1). The assessment of unequivocal increase in MPE compared with baseline was performed using chest X-ray or computed tomography. Progression-free survival (PFS) was defined as the period from the initiation of treatment with ABCP until disease progression, death from any cause, or last follow-up. Pleural progression-free survival (PPFS), defined as the period from the initiation of treatment with ABCP until an unequivocal increase in MPE, death from any cause, or last follow-up, was assessed only in patients with MPE at baseline (10,17). Overall survival (OS) was defined as the period from the initiation of treatment with ABCP until death from any cause or last follow-up. Data regarding outcomes (i.e., death, disease progression, or unequivocal increase in MPE) were censored at the date of the last follow-up. The date of data cut-off was December 31, 2023. Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events version 5.0. In addition, data concerning immune-related adverse events (irAEs) of all grades and non-irAEs of grade ≥3 were extracted.

Statistical analysis

All comparisons between proportions were evaluated with the Pearson's χ^2 test or Fisher's exact test, as appropriate. Kaplan-Meier plots were employed for survival analyses; differences in survival were compared with the log-rank test. Multivariate analyses for survival were performed using the Cox proportional hazards model with variables. P values <0.05 represented statistical significance. All statistical analyses were conducted using the JMP software (version 11; SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 46 patients were included in this study. Patient characteristics are shown in *Table 1*. Overall, the median age was 70 years; 36 (78%) and 10 (22%) patients were male and female, respectively; 38 (83%) patients had an Eastern Cooperative Oncology Group performance status (PS) 0–1. Histologically, the majority of cases (91%) were adenocarcinomas. Among the patients, 14 (30%) and 1 (2%) had epidermal growth factor receptor (*EGFR*) mutation and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) rearrangement, respectively. Of note, 11 (24%) patients experienced disease recurrence (post surgery in 10 cases, post chemoradiotherapy in 1 case). Finally, 21 (46%) patients received the ABCP regimen as 2nd- or later-line therapy. Next, we divided the entire population into two groups according to the presence of MPE. MPE was found in 29 patients (63%). There were no significant differences in clinical factors between the two groups, except for the status of disease (*Table 1*). In the MPE group, drainage of MPE at the initiation of treatment with ABCP was performed in 15 patients (52%). Pleurodesis prior to the administration of ABCP was not performed in any of the patients.

Comparison of treatment efficacy and survival based on the presence of MPE

Tumor responses to treatment with ABCP are listed in *Table 2*. The objective response and disease control rates were not significantly different between the non-MPE and MPE groups (76.5% *vs.* 51.7%, P=0.13; 88.2% *vs.* 82.8%, P>0.99, respectively). The median follow-up time was 11.1 months (range, 0.4–53.8 months). Similarly, there were no statistically significant differences in PFS (median: 9.9 *vs.* 10.1 months, P=0.87) (*Figure 1A*) and OS (median: 16.0 *vs.* 19.9 months, P=0.87) (*Figure 1B*).

Factors predicting survival in patients with MPE

Table 3 shows the results of the multivariate analyses of valuables for PFS and OS in the MPE group. Eastern Cooperative Oncology Group PS was identified as an independent prognostic factor for PFS and OS, whereas the other factors were not correlated with survival.

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Table 1 Patient characteristics

Parameter	All patients (N=46)	Non-MPE group (N=17)	MPE group (N=29)	P value
Age, years, median [range]	70 [45–80]	69 [45–76]	72 [46–80]	
Age				0.75
<65 years	16 [35]	5 [29]	11 [38]	
≥65 years	30 [65]	12 [71]	18 [62]	
Sex				0.72
Male	36 [78]	14 [82]	22 [76]	
Female	10 [22]	3 [18]	7 [24]	
Smoking history				0.16
Ever	34 [74]	15 [88]	19 [66]	
Never	12 [26]	2 [12]	10 [34]	
ECOG performance status				0.97
0	10 [22]	4 [24]	6 [21]	
1	28 [61]	10 [58]	18 [62]	
2	8 [17]	3 [18]	5 [17]	
Histology				0.62
Adenocarcinoma	42 [91]	15 [88]	27 [93]	
Other	4 [9]	2 [12]	2 [7]	
PD-L1 tumor proportion score				0.33
<1%	16 [35]	9 [52]	7 [24]	
1–49%	16 [35]	4 [24]	12 [41]	
≥50%	9 [19]	1 [6]	8 [28]	
Unknown	5 [11]	3 [18]	2 [7]	
EGFR mutation				0.14
Positive	14 [30]	5 [29]	9 [31]	
Negative	31 [68]	11 [65]	20 [69]	
Unknown	1 [2]	1 [6]	0 [0]	
EML4-ALK rearrangement				0.13
Positive	1 [2]	0 [0]	1 [3]	
Negative	43 [94]	15 [88]	28 [97]	
Unknown	2 [4]	2 [12]	0 [0]	
Disease stage				0.02
IVA	17 [37]	4 [24]	13 [45]	
IVB	18 [39]	5 [29]	13 [45]	
Recurrence	11 [24]	8 [47]	3 [10]	
Treatment line of ABCP				0.56
1st	25 [54]	8 [47]	17 [59]	
2nd or later	21 [46]	9 [53]	12 [41]	

Data are presented as numbers (%), unless otherwise indicated. MPE, malignant pleural effusion; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; *EGFR*, epidermal growth factor receptor; *EML4-ALK*, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; ABCP, atezolizumab plus bevacizumab, carboplatin, and paclitaxel.

Table 2 Best response to treatment

Response	Non-MPE group (N=17)	MPE group (N=29)	P value
Complete response, N	3	2	
Partial response, N	10	13	
Stable disease, N	2	9	
Progressive disease, N	1	3	
Not evaluated, N	1	2	
Objective response rate, %	76.5	51.7	0.13
Disease control rate, %	88.2	82.8	>0.99

MPE, malignant pleural effusion.

Treatment efficacy for the control of MPE

Among 29 patients in the MPE group, the MPE control rate was 86.2% (25/29). MPE control was not achieved in only four (13.8%) patients; interestingly, the MPE control rate was not evaluable in those patients. Of those, three patients expired within 8 weeks after initiating treatment with ABCP due to primary disease, primary disease with bacterial pneumonia, or coronavirus disease-2019, respectively. The remaining patient was transferred to a different hospital at their request, and progress was unknown; hence, the data of this patient were censored. In other words, the MPE control rate was 100% in the 25 patients who were evaluable. Fifteen (52%) patients had confirmed progressive disease (PD) by the last-follow up. At the time of PD, MPE was controlled in eight (53%) patients, an unequivocal increase in MPE was observed in five (33%) patients, and no evaluation of MPE was recorded in the remaining two (13%) patients.

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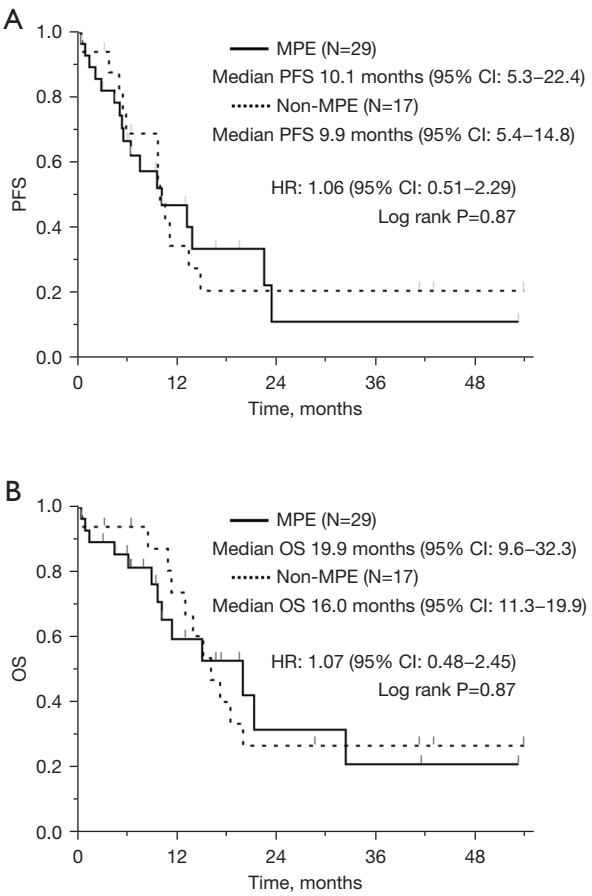

Figure 1 Kaplan-Meier curves for PFS (A) and OS (B) according to the presence of MPE. MPE, malignant pleural effusion; PFS, progression-free survival; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Pleurodesis was performed in two (7%) patients. The time from the initiation of treatment with ABCP to pleurodesis was 7.6 and 16.5 months, respectively. The median PPFS in the MPE group was 15.0 months (*Figure 2*).

Treatment toxicity in patients with MPE

AEs related to treatment with ABCP in the MPE group are summarized in *Table 4*. The incidence rate of grade 3 or 4 non-irAEs was 83%. Grade 3 or 4 neutropenia and febrile neutropenia occurred in 48% and 17% of patients, respectively. Other grade 3 or 4 non-irAEs were as follows: anemia (7%); decreased appetite (7%); and proteinuria (3%). In total, irAEs of any grade occurred in 38% of patients. The incidence rate of grade 3 irAEs was 17%. Grade 3 pneumonitis, rash, increased alanine aminotransferase, and increased aspartate aminotransferase occurred in 7%, 3%, 3%, and 3% of patients, respectively. There was no occurrence of grade 4 irAEs. The rate of steroid use due to irAEs was 10%. Moreover, the rate of treatment discontinuation due to AEs was 10%. There was no occurrence of treatment-related death in this study.

Discussion

In our study, the presence of MPE was not identified as an unfavorable predictor of response to treatment with ABCP and survival in patients with advanced non-squamous NSCLC. Moreover, the ABCP regimen exerted short- and long-term effects on the control of MPE. Importantly, the toxicity of this therapy in patients with MPE was acceptable.

Recent retrospective studies revealed that MPE affected poor outcomes in patients with advanced NSCLC receiving ICI treatment with or without chemotherapy (13-15). However, only a small number of patients were treated with a bevacizumab-containing regimen (i.e., ABCP); furthermore, prognostic analysis was not specifically performed for the patient populations in these studies. To our knowledge, the present study is the first to demonstrate that the effect of the ABCP regimen may not be diminished by the presence of MPE. In the previous studies, for patients with MPE, there was no significant difference in survival between the bevacizumab-containing immunochemotherapy group and non-bevacizumab immunochemotherapy group (15,16). These findings indicated that the synergetic effect of bevacizumab and ICIs may be limited; however, to date, there is no basic research directly supporting this hypothesis. In addition, at present, there are no clinical trials demonstrating the superiority of ABCP over other immunochemotherapy regimens without bevacizumab in NSCLC patients with or without MPE.

Tumor angiogenesis decreases anti-tumor immune factors [e.g., T cell infiltration by high interstitial fluid pressure from leaky nascent vessels and loose pericyte coverage, T cell extravasation by adhesion molecules, PD-L1 expression, interleukin 6 (IL6) and IL10, and dendritic cell maturation] and increases pro-tumor immune factors [e.g., regulatory T (Treg) cell recruitment, M2-like tumor-associated macrophage enrichment, and effector $CD8^+$ T cell apoptosis by Fas ligand (FASLG) on the tumor endothelial barrier], thereby inducing the development of an immunosuppressive microenvironment (18). VEGF is a key pro-angiogenic molecule secreted by tumor cells and involved in several of the immune steps noted above. For example, VEGF

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Table 3 Multivariate analyses of factors for progression-free survival and overall survival in patients with MPE

Parameter	N	Progression-free survival		Overall survival	
		HR (95% CI)	P value	HR (95% CI)	P value
Age			0.32		0.82
<65 years	11	0.47 (0.08–2.01)		0.82 (0.12–3.99)	
≥65 years	18	–		–	
Sex			0.83		0.11
Male	22	1.15 (0.30–4.49)		4.05 (0.73–30.6)	
Female	7	–		–	
Smoking history			0.68		0.43
Ever	19	1.29 (0.38–4.37)		1.73 (0.44–7.76)	
Never	10	–		–	
ECOG performance status			0.007		0.042
0–1	24	0.11 (0.02–0.52)		0.13 (0.01–0.93)	
2	5	–		–	
PD-L1 tumor proportion score[†]			0.44		0.47
<50%	19	1.80 (0.40–9.34)		1.77 (0.37–10.3)	
≥50%	8	–		–	
EGFR or *ALK* gene alteration			0.45		0.21
Yes	10	1.98 (0.35–16.1)		4.31 (0.47–107)	
No	19	–		–	
Treatment line of ABCP			0.30		0.23
1st	17	0.35 (0.05–2.92)		0.16 (0.01–4.25)	
2nd or later	12	–		–	
Drainage of MPE at the initiation of treatment with ABCP			0.59		0.71
Yes	16	1.40 (0.42–5.28)		1.28 (0.36–5.16)	
No	13	–		–	

[†], the PD-L1 status of two patients was unknown. MPE, malignant pleural effusion; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death-ligand 1; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; ABCP, atezolizumab plus bevacizumab, carboplatin, and paclitaxel.

modulates the expression of inhibitory checkpoints [e.g., programmed cell death 1 (PD-1), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), T-cell immunoglobulin mucin family member 3 (Tim-3), and lymphocyte-activation gene 3 (Lag-3)] on intratumoral $CD8^+$ T cells (19). VEGF blockade reduces Treg cell proliferation in the peripheral blood of patients with metastatic colorectal cancer (20). VEGF impedes the functional maturation of dendritic cells in human cancer (21). Based on the interaction between angiogenesis and tumor immunity, anti-VEGF could enhance the effect of ICIs. Several clinical trials, including the IMpower 150 study, have shown that this combination strategy is promising for the treatment of cancer (12,18). The exploratory analysis of the IMpower 150 trial demonstrated survival benefits in the ABCP treatment arm compared with the BCP (bevacizumab, carboplatin, and paclitaxel) treatment arm among patients with *EGFR* mutations and liver metastases (22). *EGFR* mutation is linked to VEGF

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expression in lung cancer (23). The reduced efficacy of ICIs in the treatment of liver metastasis is associated with the immune suppression caused by Treg cells (24). Based on these findings, it is hypothesized that the ABCP regimen may exert a sufficient anti-tumor effect even in the immunosuppressive microenvironment. MPE is generated by integrated interactions between tumor cells and host cells (e.g., macrophages, mesothelial cells, and lymphocytes) (25). VEGF is released from tumor cells and innate immune cells (e.g., natural killer cells and tumor-associated macrophages), contributing to the development of MPE through vascular permeability and angiogenesis (6,7,26). Several suppressive innate and adaptive immune signaling pathways have been identified in the microenvironment of MPE (26). In fact, previous clinical studies have shown only a minimal effect of ICI monotherapy (intravenous or intrapleural) in NSCLC patients with MPE (13,14,27). The mechanism through which VEGF is involved in the formation of an immunosuppressive microenvironment in the presence of MPE remains elusive. However, considering that VEGF is a core molecule in the pathogenesis of MPE, the combination of bevacizumab and ICIs appears a reasonable strategy for the treatment of patients who develop MPE, which was validated by the present findings.

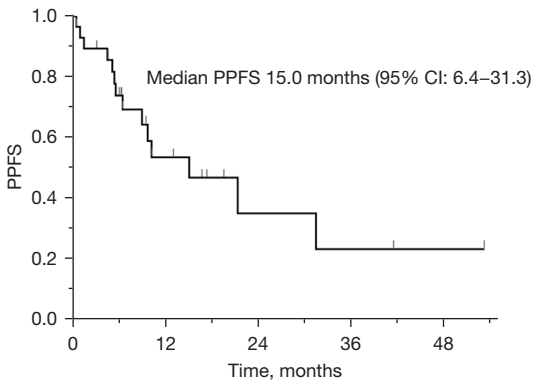

Figure 2 Kaplan-Meier curves for PPFS in patients with MPE. CI, confidence interval; MPE, malignant pleural effusion; PPFS, pleural progression-free survival.

In the multivariate analyses, PD-L1 status was not associated with survival in patients with MPE. PD-L1 expression is a versatile predictor for ICI response in clinical settings (28). However, ICI monotherapy or ICIs plus chemotherapy for NSCLC patients with MPE showed low efficacy even in those with high PD-L1 expression (≥50%) (14,15). Interestingly, previous evidence indicated that the

Table 4 Adverse events in patients with MPE (N=29)

Toxicity	Grade 1, N	Grade 2, N	Grade 3, N	Grade 4, N	Grade ≥3, N [%]
Non-irAEs (grade ≥3)					
All			13	11	24 [83]
Neutropenia			3	11	14 [48]
Febrile neutropenia			5	0	5 [17]
Anemia			2	0	2 [7]
Decreased appetite			2	0	2 [7]
Proteinuria			1	0	1 [3]
irAEs (any)					
All	0	6	5	0	5 [17]
Pneumonitis	0	0	2	0	2 [7]
Rash	0	2	1	0	1 [3]
Increased alanine aminotransferase	0	0	1	0	1 [3]
Increased aspartate aminotransferase	0	0	1	0	1 [3]
Hypothyroidism	0	3	0	0	0 [0]
Diarrhea	0	1	0	0	0 [0]

MPE, malignant pleural effusion; irAE, immune-related adverse event.

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PFS and OS of patients with MPE receiving ICIs plus chemotherapy tended to be shorter in patients with high PD-L1 expression (≥50%) than in those with low PD-L1 expression (<50%) (statistical analysis was not performed) (15). Nevertheless, this trend was not observed in our analysis. Hence, PD-L1 expression may be less important in determining the selection of treatment regimens for patients with MPE. Our results suggested that the ABCP regimen may exert a therapeutic effect in the presence of MPE regardless of PD-L1 status.

In this study, the ABCP regimen showed effectiveness in controlling MPE. The definition of MPE control rate and patient background in NSCLC patients treated with bevacizumab-containing therapy vary between studies; nonetheless, the reported MPE control rate ranges 80–95% (8-10,16,17,29). Our results were broadly consistent with those previously reported. In addition, more than half of the patients had retained MPE control at the time of RECIST PD, thus leading to a longer PPFS compared with PFS. This finding has been reported in patients with NSCLC receiving bevacizumab-containing regimens without ICI (9,29). MPE control is essential for preventing the deterioration of symptoms and quality of life of the patients, as well as for maintaining a good PS (10). Poor PS is a strong unfavorable prognostic factor in patients with MPE (30,31). In our analysis, poor PS was associated with shorter survival. Two of five patients with poor PS (i.e., 2) experienced early death (i.e., <8 weeks); of note, the MPE control rate was not evaluated in those patients. Conversely, the other three patients achieved MPE control. Further investigations are warranted to evaluate the effectiveness of the ABCP regimen in controlling MPE in patients with poor PS.

Drainage of MPE is required for symptomatic MPE as palliative care. Pleurodesis is considered in case lung re-expansion is achieved with drainage of MPE (32). However, pleurodesis is associated with several demerits, including pain, fever, acute respiratory distress syndrome, and a certain risk of failure (33,34). Therefore, our policy is to avoid pleurodesis as much as possible in patients who can be treated with anti-cancer drugs (particularly angiogenesis inhibitors). Indeed, pleurodesis prior to treatment with ABCP was not performed in any of the patients in this study. Subsequently, only two patients underwent pleurodesis at their terminal state. In the multivariate analysis, patients who required drainage of MPE at the initiation of treatment with ABCP were not associated with shorter survival. We emphasize that pleurodesis is not necessary before the initiation of ABCP due to the reliable MPE control effect of this treatment.

In the present study, the toxicity of the ABCP regimen among patients in the MPE group was tolerable. The toxicity profile in the non-MPE group was generally similar to that in the MPE group (Table S1). Concerning the hematological toxicity, the rates of grade ≥3 neutropenia and febrile neutropenia were relatively high compared with those reported in the IMpower 150 trial (12). This may be because the present study included more elderly patients and patients with poor PS. The rates of other AEs were not significantly different between the present study and the IMpower 150 trial (12).

This study has certain limitations. Firstly, this was a retrospective study involving a small number of cases. Secondly, some patients with relatively short follow-up periods were included in this analysis. Thirdly, the diagnosis of MPE was not confirmed by pathological analysis in all patients. However, some patients did not have sufficient pleural fluid volume to allow safe and adequate drainage. Moreover, the diagnostic accuracy of pleural fluid cytology is limited (32). Thus, prospective clinical trials assessing the significance of the ABCP regimen in patients with MPE are warranted.

Conclusions

This study revealed that the ABCP regimen may be an effective and safe treatment for patients with advanced non-squamous NSCLC even in the presence of MPE. In particular, the control effect of MPE by the ABCP regimen in the short and long term was encouraging. Almost all patients were able to avoid pleurodesis. Hence, the ABCP regimen may be a promising treatment option for non-squamous NSCLC patients with MPE.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-347/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-347/coif). K.H. reports personal fees from AstraZeneca, MSD, Kyorin Pharmaceutical, Chugai Pharmaceutical, and Daiichi-Sankyo, outside the submitted work. M.S. reports grants from Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Nippon Kayaku, and Kyowa Hakko Kirin; and personal fees from AstraZeneca, MSD, Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Pfizer, Novartis, Takeda Pharmaceutical, Kyowa Hakko Kirin, Nippon Kayaku, Daiichi-Sankyo, Merck Biopharma, and Amgen, outside the submitted work. T.H. reports grants from Chugai Pharmaceutical, Nippon Boehringer Ingelheim, and Taiho Pharmaceutical; and personal fees from Chugai Pharmaceutical, AstraZeneca, MSD, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Eli Lilly, Taiho Pharmaceutical, Daiichi-Sankyo, Takeda Pharmaceutical, Pfizer, and Novartis, outside the submitted work. The other author has 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Nippon Medical School Tamanagayama Hospital, Tokyo, Japan ethics committee (No. F-2023-086). Informed consent for participation in this study was provided by the patients through an opt-out method.

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References

1. Morgensztern D, Waqar S, Subramanian J, et al. Prognostic impact of malignant pleural effusion at presentation in patients with metastatic non-small-cell lung cancer. J Thorac Oncol 2012;7:1485-9.
2. Porcel JM, Gasol A, Bielsa S, et al. Clinical features and survival of lung cancer patients with pleural effusions. Respirology 2015;20:654-9.
3. Ryu JS, Ryu HJ, Lee SN, et al. Prognostic impact of minimal pleural effusion in non-small-cell lung cancer. J Clin Oncol 2014;32:960-7.
4. Yano S, Shinohara H, Herbst RS, et al. Production of experimental malignant pleural effusions is dependent on invasion of the pleura and expression of vascular endothelial growth factor/vascular permeability factor by human lung cancer cells. Am J Pathol 2000;157:1893-903.
5. Ishimoto O, Saijo Y, Narumi K, et al. High level of vascular endothelial growth factor in hemorrhagic pleural effusion of cancer. Oncology 2002;63:70-5.
6. Chen Y, Mathy NW, Lu H. The role of VEGF in the diagnosis and treatment of malignant pleural effusion in patients with non-small cell lung cancer (Review). Mol Med Rep 2018;17:8019-30.
7. Zhao J, Liu B, Liu N, et al. The role of angiogenesis in malignant pleural effusion: from basic research to clinical application. Am J Cancer Res 2022;12:4879-91.
8. 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.
9. Usui K, Sugawara S, Nishitsuji M, et al. A phase II study of bevacizumab with carboplatin-pemetrexed in non-squamous non-small cell lung carcinoma patients with malignant pleural effusions: North East Japan Study Group Trial NEJ013A. Lung Cancer 2016;99:131-6.
10. Noro R, Kobayashi K, Usuki J, et al. Bevacizumab plus chemotherapy in nonsquamous non-small cell lung cancer patients with malignant pleural effusion uncontrolled by tube drainage or pleurodesis: A phase II study North East Japan Study group trial NEJ013B. Thorac Cancer 2020;11:1876-84.
11. Singh N, Jaiyesimi IA, Ismaila N, et al. Therapy for Stage IV Non-Small-Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline, Version 2023.1. J Clin Oncol 2023;41:e51-62.

12. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.
13. Shibaki R, Murakami S, Shinno Y, et al. Malignant pleural effusion as a predictor of the efficacy of anti-PD-1 antibody in patients with non-small cell lung cancer. Thorac Cancer 2019;10:815-22.
14. Epaillard N, Benitez JC, Gorria T, et al. Pleural effusion is a negative prognostic factor for immunotherapy in patients with non-small cell lung cancer (NSCLC): The pluie study. Lung Cancer 2021;155:114-9.
15. Nishimura T, Ichihara E, Yokoyama T, et al. The Effect of Pleural Effusion on Prognosis in Patients with Non-Small Cell Lung Cancer Undergoing Immunochemotherapy: A Retrospective Observational Study. Cancers (Basel) 2022;14:6184.
16. Kawachi H, Tamiya M, Taniguchi Y, et al. Efficacy of Immune Checkpoint Inhibitor With or Without Chemotherapy for Nonsquamous NSCLC With Malignant Pleural Effusion: A Retrospective Multicenter Cohort Study. JTO Clin Res Rep 2022;3:100355.
17. 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.
18. Yi M, Jiao D, Qin S, et al. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. Mol Cancer 2019;18:60.
19. Voron T, Colussi O, Marcheteau E, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. J Exp Med 2015;212:139-48.
20. Terme M, Pernot S, Marcheteau E, et al. VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. Cancer Res 2013;73:539-49.
21. Gabrilovich DI, Chen HL, Girgis KR, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nat Med 1996;2:1096-103.
22. Nogami N, Barlesi F, Socinski MA, et al. IMpower150 Final Exploratory Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in Key NSCLC Patient Subgroups With EGFR Mutations or Metastases in the Liver or Brain. J Thorac Oncol 2022;17:309-23.
23. Hung MS, Chen IC, Lin PY, et al. Epidermal growth factor receptor mutation enhances expression of vascular endothelial growth factor in lung cancer. Oncol Lett 2016;12:4598-604.
24. Lee JC, Mehdizadeh S, Smith J, et al. Regulatory T cell control of systemic immunity and immunotherapy response in liver metastasis. Sci Immunol 2020;5:eaba0759.
25. Stathopoulos GT, Kalomenidis I. Malignant pleural effusion: tumor-host interactions unleashed. Am J Respir Crit Care Med 2012;186:487-92.
26. Murthy P, Ekeke CN, Russell KL, et al. Making cold malignant pleural effusions hot: driving novel immunotherapies. Oncoimmunology 2019;8:e1554969.
27. Tsimafeyeu I, Goutnik V, Shrainer I, et al. Multicenter phase 2 study of intrapleural nivolumab in patients with metastatic non-small cell lung cancer and pleural effusion. Am J Cancer Res 2023;13:1103-6.
28. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
29. Tao H, Meng Q, Li M, et al. Outcomes of bevacizumab combined with chemotherapy in lung adenocarcinoma-induced malignant pleural effusion. Thorac Cancer 2018;9:298-304.
30. Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax 2014;69:1098-104.
31. Zhang T, Chen X, Wan B, et al. Development of RECLS score to predict survival in lung cancer patients with malignant pleural effusion. Transl Lung Cancer Res 2021;10:1318-26.
32. Gonnelli F, Hassan W, Bonifazi M, et al. Malignant pleural effusion: current understanding and therapeutic approach. Respir Res 2024;25:47.
33. Shinno Y, Kage H, Chino H, et al. Old age and underlying interstitial abnormalities are risk factors for development of ARDS after pleurodesis using limited amount of large particle size talc. Respirology 2018;23:55-9.
34. Bhatnagar R, Piotrowska HEG, Laskawiec-Szkonter M, et al. Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions: A Randomized Clinical Trial. JAMA 2020;323:60-9.

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