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Impact of previous anti-angiogenesis treatment in nivolumab-treated advanced non-small cell lung cancer

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Abstract

Aim: To investigate how previous systemic therapy such as anti-angiogenesis can influence cancer immunotherapy for non-small cell lung cancer (NSCLC).

Methods: A total of 134 patients with advanced NSCLC who were treated with nivolumab were retrospectively reviewed. Correlation between status of prior anti-angiogenesis treatment and clinical characteristics were determined. Impact of prior anti-angiogenesis on therapeutic outcome of nivolumab was investigated for tumor efficacy such as progression-free survival (PFS).

Results: Sixteen patients were treated with at least one anti-angiogenesis agent prior to nivolumab. The prior use of anti-angiogenesis agent was associated with stage IV disease, non-squamous histology, and two or more lines of systemic therapy. Median PFS was significantly shorter in the prior anti-angiogenesis group than in no prior anti-angiogenesis group (8.3 *vs.* 11.3 weeks, log-rank $P = 0.006$). Multivariate analyses demonstrated that only prior anti-angiogenesis status was associated with worse PFS. There is also a slight trend for worse disease control rate ($P = 0.101$, Fisher's exact test) and overall survival ($P = 0.200$, log-rank) in prior anti-angiogenesis group.

Conclusion: This retrospective study suggests that prior anti-angiogenesis treatment negatively impacts the therapeutic outcome of immunotherapy in advanced NSCLC.

Keywords: Non-small cell lung cancer, nivolumab, angiogenesis, immunotherapy

INTRODUCTION

Systemic treatment for advanced cancer had been primarily cytotoxic chemotherapy until modern systemic modalities were recently developed. Now we know that targeted therapies for selected advanced cancer such as oncogene-driven malignancy provide better outcomes than traditional chemotherapy. For instance, small molecule kinase inhibitors are available for advanced non-small cell lung cancer (NSCLC) with a somatic mutation in the catalytic domain of epidermal growth factor receptor gene (EGFR) or gene rearrangement in anaplastic leukemic kinase gene (ALK)[1-4]. More recently, inhibitors for immune checkpoints that negatively regulate anti-cancer immunity have become clinically available with improved survival outcome for the treatment of advanced NSCLC, head/neck, melanoma, bladder, and renal cell carcinomas[5-11].

The mortality rate for lung cancer, however, has not changed dramatically over the last several decades[12]. Although recently developed cancer immunotherapy, such as anti-PD-1 therapy, has made a significant impact on daily practice for advanced NSCLC, most patients who are treated with such agents still succumb to the disease within five years[13]. Continued efforts to enhance activity of cancer immunotherapy are required to further improve outcome.

Recently researchers have been conducting clinical trials to determine if the combination of immunotherapy and other treatments may have additive clinical activity in this disease. Anti-angiogenesis agents such as bevacizumab have been developed and achieved regulatory approval for several cancer types[14,15]. These agents are also being investigated in various diseases in combination with immunotherapy[16]. Rationale for the combination is that suppression of neoangiogenesis, remodeling on distorted microvasculature, and resultant improved tumor perfusion are expected to enhance anti-cancer immunity[16]. Because bevacizumab has a relatively long half-life (approximately 20 days) and lasting biological effect[15], previous anti-angiogenesis treatment might positively influence the efficacy of anti-cancer immunotherapy. Several studies have indicated that withdrawal of anti-angiogenesis agents results in an increase in tumor aggressiveness due to rebound angiogenesis in the tumor microenvironment[17,18]. We therefore conducted a retrospective study to determine if prior use of anti-angiogenesis therapy can impact progression-free survival in advanced NSCLC patients who were treated with anti-PD-1 therapy.

METHODS

Patient selection

A total of 801 advanced and metastatic NSCLC patients were registered at University of Kansas Cancer Center between January 2015 and June 2016. Review of their medical records identified 141 patients who were treated with at least one dose of the anti-PD-1/PD-L1 inhibitors at University of Kansas Cancer Center. A majority (n = 133) of patients were treated with nivolumab alone, whereas others were treated with nivolumab and atezolizumab (n = 1), atezolizumab alone (n = 1), pembrolizumabalone (n = 4), or other investigational agentalone (n = 2). All of these agents were intravenously given every two weeks (nivolumab) or every three weeks (atezolizumab and pembrolizumab) according to standard dosing schedules.

Because most patients were treated with nivolumab (n = 134), we decided to focus on patients who received it for recurrent or metastatic disease. They were grouped based on presence or absence of previous anti-angiogenesis treatment which included bevacizumab and ramcirumab. None of the patients received other anti-angiogenesis agents prior to nivolumab. Information about clinical demographics was collected as well. The two groups (prior anti-angiogenesis *vs.* no prior anti-angiogenesis) were compared for the differences in clinical demographics and outcome. Tumor response was determined according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and disease control rate (DCR) was defined as the sum of

complete response, partial response, and stable disease rates. Due to retrospective analysis, repeat imaging to confirm response was not always performed. Progression-free survival (PFS) was determined by duration from the start of nivolumab to disease progression or death of any cause. Definition of disease progression for the purpose of determining PFS was based on RECIST 1.1 criteria and/or on the clinical grounds (i.e., clinical progression without formal radiologic assessment if patients were unable to perform re-staging).

Statistical analysis

The Kaplan-Meier curves were applied and the differences were assessed using the log-rank test. Univariate and multivariable Cox proportional hazard models were used in order to assess the effects of variable(s) on PFS of the patients. Association between anti-angiogenesis treatment and other clinical features were carried out using Chi-squared or Fisher's exact test. JMP software version 14 (SAS Institute, Cary, NC, USA) was used to perform statistical analyses. For all statistical tests, significance was considered to be achieved when two-sided *P* value was less than 0.05. This study was reviewed and approved by University of Kansas Medical Center Institutional Review Board.

RESULTS

Patient characteristics according to previous anti-angiogenesis treatments are shown in Table 1. Of the 134 patients who received nivolumab, the individual dose was 3 mg/kg or 240 mg flat for 30 and 104 patients, respectively. Sixteen patients received at least one dose of anti-angiogenesis agents prior to nivolumab. They were previously treated with bevacizumab alone (n = 11), ramucirumab alone (n = 4), or both (n = 1). The number of doses for anti-angiogenesis agents ranged between one and 13 with a median of six. In seven of those, no other systemic therapy was given between anti-angiogenesis regimen and nivolumab. Of the 134 patients, seven patients completed PD-L1 immunohistochemistry with tumor material. Only two were tested positive (≥ 1%).

As of June 10, 2017, a total of 31 patients are still being treated with nivolumab; one in the prior anti-angiogenesis and 30 in the no prior anti-angiogenesis group. Because of the inherent limitation of retrospective review, many patients were lost to follow-up after progression on nivolumab. Only six patients in the no prior anti-angiogenesis group received an anti-angiogenesis agent after progression on nivolumab, whereas none did in prior anti-angiogenesis group.

Patients in the prior anti-angiogenesis group had significantly higher likelihood of having stage IV disease, non-squamous histology, and two or more lines of systemic therapy prior to nivolumab as compared to the no anti-angiogenesis group. The difference in histology is expected because current regulatory approval for bevacizumab, which is used in most patients in this group, is indicated for only non-squamous NSCLC. There was no pseudoprogression in either group.

PFS and overall survival (OS) were investigated according to known prognostic factors as well as prior anti-angiogenesis status. Kaplan-Meier analyses demonstrated that the prior anti-angiogenesis group had a statistically shorter PFS as compared to the no prior anti-angiogenesis group, whereas no other factors demonstrated statistical difference (log rank P = 0.006, Figures 1 and 2A). Multivariate analysis for PFS showed that previous anti-angiogenesis remained statistically significant when other factors are being considered [Table 2]. There is no dose-response relationship between the number of doses of anti-angiogenesis agent and PFS [Figure 2B]. There is a trend in favor of the no anti-angiogenesis group in OS [Table 2] and DCR [Table 3], although the difference was not significant.

DISCUSSION

Discovery of immune checkpoints and development of agents to enhance T cell function has led to a drastic change in the management of advanced cancer, resulting regulatory approvals for several immunotherapy

Table 1. Patient characteristics and correlation with previous anti-angiogenesis treatment (*n* = 134)

Characteristics	Anti-angiogenesis *n* (%)		Total	*P* value
	Yes	No		
Total	16 (100)	118 (100)	134	
Age				0.173
< 70	10 (63)	92 (78)	102 (76)	
≥ 70	6 (37)	26 (22)	32 (24)	
Stage at diagnosis				0.001
III	0 (0)	45 (38)	45 (34)	
IV	16 (100)	73 (62)	89 (66)	
Histology				0.002
Nonsquamous	15 (94)	63 (53)	78 (58)	
Squamous	1 (6)	55 (47)	56 (42)	
Sex				0.427
Male	11 (69)	67 (57)	78 (58)	
Female	5 (31)	51 (43)	56 (42)	
ECOG Performance Status				0.360
0-1	14 (88)		103 (77)	
2+	2 (12)		31 (23)	
EGFR status				1.000
Positive	0 (0)		5 (4)	
Negative/unknown	16 (100)		129 (94)	
No. of nivolumab doses				
Range (median)	1-35 (4.5)		1-59 (5)	0.208*
Dose of nivolumab				0.523
240 mg flat	2 (12)	28 (24)	30 (22)	
3 mg/kg	14 (88)	90 (76)	104 (78)	
Reason for discontinuation				0.408**
PD/Death	15 (94)	74 (63)	89 (66)	
AE	0 (0)	8 (7)	104 (78)	
Lost follow-up	0 (0)	5 (4)	89 (66)	
Ongoing	1 (7)	30 (25)	31 (23)	
Others	0 (0)	1 (1)	1 (1)	
No. of systemic chemotherapy lines				< 0.0001
1	6 (38)	103 (87)	109 (81)	
2+	10 (62)	15 (13)	25 (19)	

*Mann-Whitney *U* test; **Among those who discontinued nivolumab, there was no significant correlation between pre-angiogenesis status and frequency of PD/death. ECOG: eastern cooperative oncology group; EGFR: epidermal growth factor receptor; PD: progressive disease; AE: adverse events

agents. Researchers are looking to potentiate T cell-mediated anti-tumor activity by adding agents with different mechanisms of action. For instance, cytotoxic chemotherapy, targeted agents, and anti-angiogenesis agents are being combined with anti-PD-1/PD-L1 inhibitors in ongoing clinical trials[16]. Except for one regimen which was recently approved via the accelerated approval process and still needing larger confirmatory studies[19], no combination regimen including immunotherapy is indicated for any human cancer. Patients with advanced cancer definitely require further development in systemic treatment which exceeds the current efficacy of single agent immunotherapy.

Targeting tumor neoangionegesis has been extensively investigated over the last few decades. Several agents have achieved regulatory approval in the treatment of advanced cancer[15,20-25]. In contrast to vascular endothelial growth factor receptor (VEGFR) kinase inhibitors for renal cell and hepatocellular carcinomas[20-23], monoclonal antibodies directed against VEGF/VEGFR are indicated for several cancer types only in combination with systemic chemotherapy[15,24]. For the treatment of advanced NSCLC, bevacizumab and ramucirumab are approved when combined with carboplatin-based regimens or docetaxel, respectively[15,24]. No anti-angiogenesis agent as monotherapy is indicated for NSCLC. Several studies with anti-angiogenesis agents have resulted in unexpected severe toxicity and a detrimental outcome for squamous NSCLC patients[26,27]. These findings indicate that anti-angiogenesis needs to be not only given in selected populations (i.e., non-squamous) but combined with agents with other mechanisms of action, because anti-angiogenesis by itself has only modest activity.

Table 2. Univariate and Multivariate analyses for prognostic factors on PFS and OS in NSCLC patients treated with nivolumab

Factor	PFS		OS	
	Univariate analysis HR (95%CI) *P* value	Multivariate analysis HR (95%CI) *P* value	Univariate analysis HR (95%CI) *P* value	Multivariate analysis HR (95%CI) *P* value
Age (< 70 *vs*. ≥ 70)	0.882 (0.698-1.136)	0.938 (0.729-1.228)	0.858 (0.659-1.146)	0.952 (0.710-1.277)
	0.31909	0.633	0.288	0.744
Stage at diagnosis (III *vs*. IV)	0.829 (0.652-1.038)	0.849 (0.651-1.099)	0.988 (0.766-1.258)	0.959 (0.724-1.271)
	0.104	0.216	0.923	0.772
Histology	0.939 (0.762-1.163)	0.841 (0.659-1.077)	0.788 (0.621-0.100)	0.727 (0.549-0.964)
(nonsquamous *vs*. squamous)	0.561	0.168	0.050	0.027
Sex (female *vs*. male)	0.810 (0.650-1.002)	0.826 (0.660-1.026)	0.829 (0.645-1.054)	0.817 (0.636-1.048)
	0.052	0.084	0.127	0.107
Performance Status *vs*. 2+)	0.902 (0.710-1.172)	0.877 (0.680-1.155)	0.767 (0.591-1.019)	0.716 (0.538-0.952)
	0.425	0.340	0.066	0.028
No. of systemic treatment	0.848 (0.668-1.100)	0.967 (0.733-1.303)	0.893 (0.679-1.212)	0.983 (0.705-1.371)
(0-1 *vs*. 2+)	0.205	0.820	0.451	0.919
Previous anti-angiogenesis	1.466 (1.087-1.913)	1.444 (1.009-2.029)	1.277 (0.867-1.771)	1.506 (0.979-2.316)
(yes *vs*. no)	0.014	0.044	0.200	0.074

Table 3. Best objective response according to prior anti-angiogenesis treatment

	Total *n* (%)	Prior anti-angiogenesis agent		*P* value
		Yes	No	
	134 (100)	16 (100)	118 (100)	
ORR (CR + PR)	11 (8)	1 (6)	10 (8)	1.00
Non-ORR	123 (92)	15 (94)	108 (92)	
SD	43 (32)	2 (13)	41 (35)	
PD	40 (30)	7 (44)	33 (28)	
NE	40 (30)	6 (38)	34 (29)	
DCR (CR + PR + SD)	54 (40)	3 (19)	51 (43)	0.101
Others (PD + NE)	80 (60)	13 (81)	67 (57)	

ORR: overall response rate; CR: complete response; PR: partial response; SD: stable disease; NE: not evaluable; DCR: disease control rate

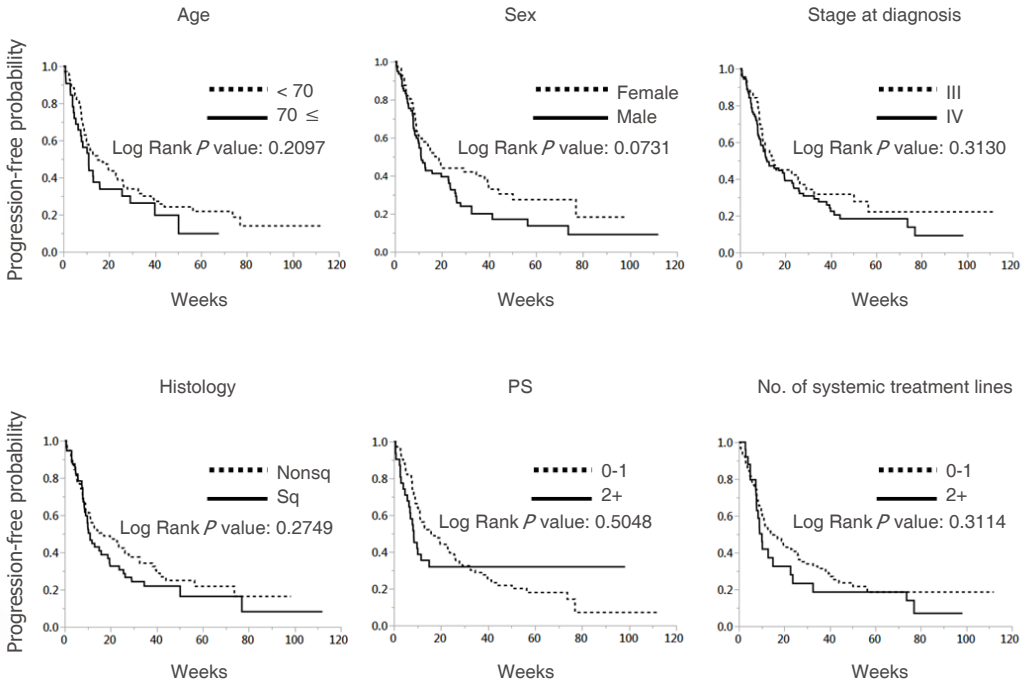

Figure 1. Progression-free survival according to clinical characteristics. Progression-free survival curves were plotted according to six clinical characteristics. log-rank tests were used for statistical analysis

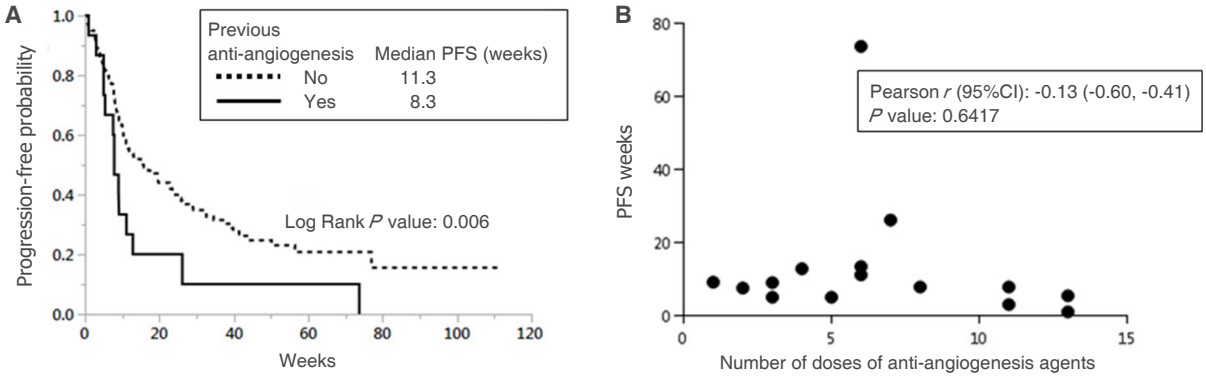

Figure 2. Impact of previous anti-angiogenesis treatment on progression-free survival. A: Progression-free survival curves were plotted according to prior anti-angiogenesis treatment; B: Relationship between number of prior anti-angiogenesis doses and progression-free survival on nivolumab

In addition to their modest clinical activity, the use of anti-angiogenesis agents in advanced cancer raised other concerns for researchers. Preclinical studies demonstrated that use and subsequent withdrawal of anti-VEGF agents could develop rebound tumor vascularization[17]. Others also reported induction of angiogenesis-related cytokines and epithelial-mesenchymal transition which enhance cancer invasiveness and eventual metastasis[28-31]. Clinical studies in patients with colorectal cancer also showed that continuation of bevacizumab beyond first progression was associated with prolonged overall survival, suggesting a detrimental withdrawal effect of anti-angiogenesis in humans as well[32].

Despite the abovementioned negative aspects for anti-angiogenesis agents, preclinical studies demonstrated therapeutic synergism between anti-angiogenesis and immunotherapy[33,34]. Targeting VEGF enhanced IFNγ-mediated upregulation of PD-L1 which in turn led to disease relapse in glioblastoma models. This negative effect of anti-angiogenesis treatment was nullified by dual blockade of the VEGF and PD-1/PDL1 signaling[34]. Supported by these preclinical observations, combination strategy using anti-angiogenesis agents and immune checkpoint inhibitors are actively tested in a number of clinical trials[35].

In this retrospective study, 16 (11.9%) of 134 patients who were treated nivolumab received anti-angiogenesis agents previously. This infrequent use of anti-angiogenesis agents in the first-line systemic therapy seems consistent with the study reported by Zhu *et al.*[36], where only 21.2% of stage IV NSCLC patients in their large SEER-Medicare analysis received bevacizumab in the first-line systemic therapy.

This study also showed that previous use of anti-angiogenesis agents was associated with significantly worse PFS. Overall response rate (ORR) and OS in the prior anti-angiogenesis group were also inferior to those in the no prior anti-angiogenesis group, although the differences were not statistically significant. Despite a relatively small number of patients in the prior anti-angiogenesis group, univariate and multivariate analyses demonstrated that prior anti-angiogenesis status is a poor prognostic factor independently for PFS. This detrimental effect of prior anti-angiogenesis on nivolumab treatment might be explained by withdrawal effect of anti-angiogenesis as discussed above. Consistent with this study, there are other similar clinical observations reported in the literature. A small retrospective study of 16 patients with glioblastoma reported a disappointing clinical effect when nivolumab was given after progression on bevacizumab[37]. A recent case series revealed that three patients with renal cell carcinoma with two or more lines of systemic anti-angiogenesis treatment developed rapid disease progression while on nivolumab treatment[38]. These patients received prior VEGFR TKIs prior to initiation of nivolumab. Moreover, in the pivotal phase III trial which led to Food and Drug Administration (FDA) approval of nivolumab for renal cell carcinoma, the difference in OS between the nivolumab and the control arms was not statistically significant when patients with two or more previous anti-angiogenesis agents were selected for subset analysis[11]. Although these observations,

including this study, are still hypothesis-generating, the potential negative effect of prior anti-angiogenesis treatment warrants further investigation.

Retrospective observational studies such as this always have limitations. Various unappreciated biases exist in all retrospective studies. For instance, several patients in each group have never undergone formal re-staging but were considered as clinical progression which determined PFS. This single institution retrospective study needs to be validated by larger prospective and/or retrospective studies. Subset analyses within prior anti-angiogenesis group showed that there was no correlation between PFS and number of doses of anti-angiogenesis agents [Figure 2B] or interval from the last administration of anti-angiogenesis agent to first dose of nivolumab (data not shown). We acknowledge that these subset analyses require a larger sample size in order to establish clinical significance.

This retrospective study suggests that preceding anti-angiogenesis treatment has detrimental effect on subsequent treatment outcome of immunotherapy in NSCLC. This phenomenon might be associated with rebound tumor angiogenesis due to withdrawal of anti-angiogenesis treatment. This hypothesis needs to be confirmed by studies with a larger patient sample.

DECLARATIONS

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Authors' contributions

Concept, design, clinical studies, data acquisition, data analysis: Komiya T
Literature search: Komiya T, Huang CH, Neupane P, Williamson SK
Statistical analysis: Komiya T, Chalise P
Manuscript preparation, manuscript editing, and manuscript review: Komiya T, Huang CH, Neupane P, Williamson SK, Chalise P

Data source and availability

Data and survey materials are available upon request from the corresponding author.

Financial support and sponsorship

None.

Conflicts of interest

The authors have no conflict of interest.

Patient consent

Informed consent was exempted by institutional IRB.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval from institutional IRB was obtained.

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