Effect of *Astragalus Membranaceus* on Patients with Metastatic Non-Small Cell Lung Cancer: A Retrospective Cohort Study

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OBJECTIVE
Astragalus membranaceus root extract (AMe) has been shown to have immunomodulatory effects on macrophages and Th1 type immune responses. Our goal was to determine whether AMe improves the overall survival (OS) of patients with metastatic non-small cell lung cancer (NSCLC).

METHODS
The medical charts of metastatic NSCLC were retrospectively reviewed. Histological subtype, performance status, age, gender, smoking status, comorbidities, chemotherapeutics, and erlotinib that were part of any type of treatment were recorded.

RESULTS
The median age of the patients was 61. The median follow-up period was longer for Group A (AMe users) than Group C (control group) (18 vs. 11 months, p<0.001). At the time of analysis, 83.8% of the patients had died. Univariate analysis showed that OS was significantly longer in Group A than Group C (21±4.2 vs. 11±0.9 months, p=0.004). In addition to AMe usage, female gender, smoking status, presence of hypertension, and erlotinib usage also had significant impacts on OS (p<0.05 for all variables). The multivariate analysis showed that only AMe (hazard ratio [HR]: 0.46, 95% CI: 0.27-0.76, p=0.003) and erlotinib (HR: 0.45, 95% CI: 0.22-0.89, p=0.02) usage were correlated with significantly longer OS.

CONCLUSION
Taking AMe during systemic anti-cancer treatment may significantly prolong OS of patients with metastatic NSCLC.

Keywords: *Astragalus membranaceus*; Herb; Mortality; Non-small cell lung cancer; Overall survival; Traditional Chinese medicine.

Introduction

Cancers of the lung and bronchus are the most common causes of cancer death. Patients with advanced non-small cell lung cancer (NSCLC) are treated with standard therapies such as chemotherapy (CT), immunotherapy, radiation therapy, or with combination of them.[1,2] *Astragalus membranaceus* root extract (AMe) has a long history of medicinal use in Chinese herbal medicine as part of herbal mixtures to treat reduced vitality, which has symptoms such as fatigue, diarrhea, and lack of appetite. AMe, which has im-

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munomodulatory effects on macrophages and Th1 type immune responses, has been widely studied for its capability for immunopotentiation, apoptosis induction, and inhibition of inflammation and immunorestorative activity.[3-6] *In vitro* analysis has shown that AMe increases resistance to the immunosuppressive effects of CT drugs, stimulates macrophages to produce interleukin-6 (IL-6), and increases tumor necrosis factor.[7]

Astragalus saponin IV which is one of the active parts of AMe has been demonstrated that enhances chemosensitivity to cisplatin by inhibiting B7-H3.[5,8] B7-H3 is a member of the B7 family and broadly expressed on the transcriptional level in lymphoid and non-lymphoid organs. It complicates the immune response by regulating costimulatory and coinhibitory pathways. The anti-cancer effect of AMe extract is not only through its immunomodulatory effect but also through growth pathways, and perhaps some epigenetic effects. In a meta-analysis of 17 randomized studies with 1552 patients, *Astragalus*-based traditional Chinese medicine used with CT was associated with significantly increased overall survival (OS) and overall tumor response rates.[9]

This study aimed to determine whether AMe improves the survival results of patients with metastatic NSCLC, especially in patients with European descent.

Materials and Methods

The medical charts of patients who were admitted to Istanbul University, Institute of Oncology, Outpatient Medical Oncology Clinic between January 2017 and June 2017 to receive therapy for metastatic NSCLC were retrospectively assessed. The treatment principles of our institution are decided according to the current guidelines, after discussion with the multidiscipline team after each patient's visit. Of note, in our country, immunotherapies do not on the cover of governmental insurance, so immunotherapeutic agents cannot be used in our unit. Many patients have a tendency to use herbal replacements, and mostly immunologically based supportive treatments may make sense. When the patient conveys such a request in our clinic, we suggested the use of AMe, which has enough data about the use with targeted drugs and CT in previous publications. The suggested daily dose was 2-3 tablets of 250 mg AMe (Solgar, NJ, USA) minimum for 6 months.

We retrospectively collected the patients with minimum 6 months on *Astragalus* supplements during CT and targeted therapy. We record all medicine history along with supplement usage of patients at every visit

routinely. The supplement had to be started with the first treatment cycle and used for at least 6 months. The patients who used minimum 6 months without other supplements and patients with no supplements as control group are included in the study. The exclusion criteria included being younger than 18 years old, using other group of herbal medicine, AM usage <6 months. Furthermore, patients with inadequate follow-up and had major record deficit in the file are excluded from the study. Each patient's informed consent was obtained before searching medical records for study either on phone call or at visit, informed consent was obtained from legal heir of patients who were death at the time of analysis. The study was approved by Istanbul University, Institute of Oncology, Institutional Review Board (Number: 70973125-604.01.01).

SPSS for Windows version of SPSS 20.0 (Chicago, IL., USA) was employed for data analysis and probability values <0.05 were considered statistically significant. The following variables were considered confounding factors in multivariate models: (1) Histological subtype, (2) high-risk comorbidities, (3) age, (4) gender, (5) smoking history, (6) performance status, and (7) cancer treatments (intravenous CT, oral CT, and targeted therapies) after diagnosis. The follow-up duration was calculated from the date of the diagnosis to the date of death or last follow-up visit. The OS was defined as the time of diagnosis to the date of death. Quantitative data were presented as the means with standard errors, medians with minimums and maximums. The results of qualitative analyses were presented as frequencies and percentages. Relationships and comparisons of several clinical variables were evaluated through Pearson Chi-square. Fisher's exact test was used where Pearson Chi-square test was inapplicable. We compared the OS of patients in Groups A and C using Kaplan-Meier estimates and the log-rank test for univariate analyses. Cox regression analysis was used to determine the association of AM usage and OS in the multivariate analysis.

Results

Characteristics of Study Subjects
A total of 117 metastatic NSCLC patients included this study who mostly were male gender (n: 109, 93.2%). Four patients in the two groups were female and the majority of patients had non-squamous histology. Thirty-four patients (Group A) using AMe during systemic anti-cancer treatment were compared with 83 controls (Group C) that did not use AMe and another herbal supplement following NSCLC diagnosis. The median

Ak et al.
Astragalus Extract as Complementary Therapy for Lung Cancer

217

age of the patients was 61 (range: 42-81) and all patients were administered systemic treatment (CT or erlotinib). About 96% of patients received platin-based CT. There were no records that suggesting the side effect of the supplement, but these data did not indicate Grade 1 toxicities for laboratory results and toxicities that the patient did not complain since the assessments of patients were recorded before study. As for systemic treatments, patients had received, there were no differences in the proportion of patients with regard to comorbidities, type of intravenous CT, and oral targeted therapies. Only three patients from the control group and two patients from the AMe group did not receive platinum-based therapy. The histological subtype, performance status, age, gender, smoking status, comorbidities, usage of CT agents, and erlotinib were similar in Groups A and C (Table 1).

Survival Results and Adjusted Hazard Ratio (HR) for Death between AMe Users and Control Group
The median follow-up period was significantly longer for A group than C group (18 vs. 11 months, p<0.001). At the time of the analysis, 83.8% of the patients had died; 71 in Group C and 27 in Group A. In the univariate analysis, the median OS was significantly longer in Group A than Group C (21±4.2 vs. 11±0.9 months, p=0.004) (Fig. 1). In addition to AMe usage, female gender, smoking status, presence of hypertension, and erlotinib usage also had a significant impact on OS (p<0.05 for all) (Table 2).

In the multivariate analysis, only AMe and erlotinib were associated with significant increases to OS. After adjusting for age, comorbidities, and conventional treatments, the Cox proportional hazard modeling revealed that the overall HR of death was 0.46 (95% CI: 0.27-0.76, p=0.003) in AMe users, compared with the control group (Table 3).

Discussion

With an increasing number of cancer patients seeking an improved quality of life, complementary and alternative therapies are becoming more common. According to the National Health Insurance database in Taiwan, the three most commonly prescribed herbs for cancer patients were *Hedyotis diffusa, Scutellaria barbata*, and AM.[10] Immune restorative effects of AMe on cancer patients were demonstrated in 1983 by Sun et al. first.[11] A number of studies deal with AMe's immunostimulatory and anti-cancer mechanisms. AME induces Ig production of murine B cells and improves white blood cell counts, the thymus index, the spleen index, CD4+/CD8+ ratio, TNF, IFN-, IL-2, and IL-17A

Table 1 Patient characteristics and comparison of AMe and control groups

	Variables group (%)	Control AMe group (%)	p
Age (years, median)	61	60.5	0.48*
Age			
≤60	39 (47)	17 (50)	0.76
>60	44 (53)	17 (50)	
Gender			
Male	79 (95.2)	30 (88.2)	0.22**
Female	4 (4.8)	4 (11.8)	
PS			
ECOG 0–1	69 (84.1)	30 (88.2)	0.77**
ECOG ≥2	13 (15.9)	4 (11.8)	
Smoking			
No	10 (12)	8 (23.5)	0.11
Yes	73 (88)	26 (76.5)	
Histologic subtype			
Non-squamous	57 (68.7)	21 (61.8)	0.47
Squamous	26 (31.3)	13 (38.2)	
Hypertension			
No	51 (61.4)	15 (44.1)	0.08
Yes	32 (38.6)	19 (55.9)	
IHD			
No	63 (75.9)	27 (79.4)	0.68
Yes	20 (24.1)	7 (20.6)	
DM			
No	71 (85.5)	27 (79.4)	0.41
Yes	12 (14.5)	7 (20.6)	
Gemcitabine			
No	27 (32.5)	8 (23.5)	0.33
Yes	56 (67.5)	26 (76.5)	
Pemetrexed			
No	63 (75.9)	22 (64.7)	0.21
Yes	20 (24.1)	12 (35.3)	
Taxane			
No	26 (31.3)	11 (32.4)	0.91
Yes	57 (68.7)	23 (67.6)	
Etoposite			
No	77 (92.8)	30 (88.2)	0.47**
Yes	6 (7.2)	4 (11.8)	
Erlotinib			
No	64 (77.1)	25 (73.5)	0.68
Yes	19 (22.9)	9 (26.5)	
Platinum			
No	3 (3.6)	2 (5.9)	0.62**
Yes	80 (96.4)	32 (94.1)	
Vinorelbine			
No	67 (80.7)	30 (88.2)	0.32
Yes	16 (19.3)	4 (11.8)	
Follow-up period (months) (median± SE) (range)	11±15.6 (0–93)	18±23 (5–102)	<0.001*
Last status			
Exitus	71 (85.5)	27 (79.4)	0.41
Alive	12 (14.5)	7 (20.6)	

Chi-squared test; *Mann–Whitney U-test; **Fisher's exact test. AMe: Astragalus membranaceus extract; PS: Performance status; ECOG: Eastern cooperative oncology group; IHD: Ischemic heart disease; DM: Diabetes mellitus; SE: Standard error

Fig. 1. The Kaplan–Meier plots of overall survival for patients who used Astragalus membranaceus root.
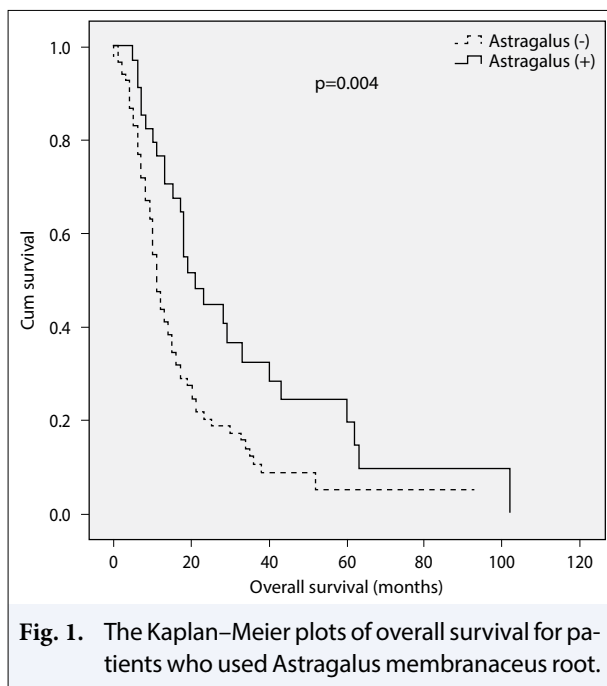
in mice with lung cancer.[12,13] Furthermore, AMe was found to be a potent immunomodulatory agent because it stimulated macrophages, so it could also be used as an immunotherapeutic vaccine adjuvant.[14]

The anti-cancer effect of AMe extract is not only through the immunomodulatory effect but also through growth pathways and perhaps through epigenetic effects. AMe inhibits cell proliferation and induces cell apoptosis through the PI3K/AKT/mTOR and ERK signaling pathways.[15-17] Furthermore, AMe modulated the invasiveness and angiogenesis of gastric adenocarcinoma cells through the way of metastatic proteins metalloproteinase (MMP)-2 and MMP-9.[4] This suggests that AMe may inhibit tumors' metastatic capabilities.

Our patient population is really in search of herbal treatments. Actually, this leads to the use of treatments of unknown origin that may cause serious side effects in patients. A long time we have met with very serious side effects that resulted from herbal medicine. Moreover, these searches sometimes led to the financial exploitation of our patients by malicious people. So based on literature, we recommended to AMe with commercial available form that has rational to offer to our patients who were seeking herbal supplement treatment advice to be clear to what they used. All studies that previously mentioned revealed questions about survival effect of supplement in our cohort, so we held this study. Although there are publications that suggest otherwise,[18] we have many more data that

Table 2 Univariate analysis of OS

Variables	No. of events/ no. of total	Median±SE	p*
Age			
≤60	44/56	15±2.2	0.36
>60	54/61	13±1.8	
Gender			
Male	93/109	13±1.3	0.035
Female	5/8	33±13.7	
PS			
ECOG 0–1	85/99	13±1.5	0.62
ECOG ≥2	13/18	16±8.5	
Smoking			
No	13/18	34±19	0.002
Yes	85/99	12±1.3	
Histologic subtype			
Non-squamous	65/78	15±1.6	0.16
Squamous	33/39	10±1.7	
Gemcitabine			
No	24/35	14±1.8	0.7
Yes	74/82	13±1.7	
Pemetrexed			
No	73/85	11±1.7	0.07
Yes	25/32	18±3.8	
Taxane			
No	31/37	14±2.4	0.77
Yes	67/80	13±2.1	
Etoposite			
No	88/107	13±1.4	0.76
Yes	10/10	18±1.6	
Erlotinib			
No	76/89	11±1.1	<0.001
Yes	22/28	28±6	
Platinum			
No	5/5	15±8.7	0.73
Yes	93/112	13±1.7	
Vinorelbine			
No	79/97	14±1.4	0.31
Yes	19/20	11±3.4	
Hypertension			
No	54/66	12±1.6	0.015
Yes	44/51	17±3.4	
IHD			
No	73/90	13±2.5	0.84
Yes	25/27	14±1.9	
DM			
No	82/98	14±1.6	0.49
Yes	16/19	12±1.3	
AMe			
No	71/83	11±0.95	0.004
Yes	27/34	21±4.28	

Kaplan-Meier estimator, *Log-rank test. OS: Overall survival; PS: Performance status; ECOG: Eastern cooperative oncology group; IHD: Ischemic heart disease; DM: Diabetes mellitus; AMe: Astragalus membranaceus extract; SE: Standard error

Ak et al.
Astragalus Extract as Complementary Therapy for Lung Cancer

219

Table 3 Multivariate analysis of OS

Variables	HR	95% CI	p
Age>60 versus ≤60 years	1.39	0.9-2.15	0.12
Gender: Female versus male	0.54	0.2-1.46	0.22
Smoking: (+) versus (-)	1.06	0.46-2.4	0.89
HT: (+) versus (-)	0.76	0.47-1.26	0.29
IHD: (+) versus (-)	0.9	0.52-1.56	0.71
DM: (+) versus (-)	1.43	0.77-2.65	0.25
Gemcitabine: (+) versus (-)	0.75	0.42-1.33	0.32
Pemetrexed: (+) versus (-)	1.15	0.67-1.97	0.61
Taxane: (+) versus (-)	0.95	0.56-1.62	0.86
Etoposite: (+) versus (-)	0.88	0.41-1.88	0.75
Erlotinib: (+) versus (-)	0.45	0.22-0.89	0.02
Platinum: (+) versus (-)	1.03	0.34-3.17	0.94
Vinorelbine: (+) versus (-)	1.61	0.9-2.9	0.1
AMe: (+) versus (-)	0.46	0.27-0.76	0.003
ECOG-PS: 2-4 versus 0-1	0.91	0.47-1.75	0.78
Histology: Squamous versus non-squamous	1.27	0.75-2.14	0.36

HR: Hazard ratio; CI: Confidence interval; HT: Hypertension; IHD: Ischemic heart disease; DM: Diabetes mellitus; AMe: Astragalus Membranaceus extract; ECOG-PS: Eastern cooperative oncology group performance status scale

show longer OS with the combination of CT and AMe for lung cancer patients.[7,8] In a large meta-analysis of 34 randomized studies, *Astragalus*-based traditional Chinese medicine increased effectiveness of platinum-based CT. Twelve studies (940 patients) reported reduced risk of death within 12 months and 30 studies (2472 patients) reported improved tumor response. [7] Our data also showed that AMe increases OS despite different types of regimens, though this may be because near all of our patients used cisplatin doublets. As with CT, *Astragalus* and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor have an additive effect on EGFR mutant lung cancer, according to current literature.[19,20] Consistent with these data, our results showed survival advantages of AMe in combination with erlotinib or CT. Although our population is relatively low, it may be a key population since other studies held in Asian countries.

Cancer patients frequently receive cardiovascular medications, including renin-angiotensin system blockers (RASBs), because cardiovascular diseases are common in the population. RASBs may provide synergistic effects with systemic cancer treatment by reducing angiotensin 2-mediated cell proliferation and angiogenesis.[21-23] Although, it lost significance in multivariate analysis, we also found that hypertensive patients using anti-hypertensive drugs showed significantly longer OS (p<0.05). In the multivariate analysis,

p value was very close to the significance level (p=0.08), which may be due to the low number of cases.

There is little possibility for complete remission in metastatic lung cancer patients with CT alone. Immunotherapy may offer the best chance for a complete response.[2] The intersection of immune surveillance by tumor growth and development has led to significant therapeutic progress that is currently being studied in various cancer types, including lung cancer. Based on Phase III studies that show shown longer OS, Phase II studies have been approved for inhibitory antibodies PD-1 (pembrolizumab and nivolumab) and PD-L1 (atezolizumab, avelumab, and durvalumab). [7] Although immunotherapy is standard of care in lung cancer patients, immunotherapeutic agents are not covered by Turkish state insurance policy as many other middle- and low-income countries. This situation leads clinicians in our country to use complementary immunogenic therapies based on the scientific basis.

There are some limitations of this study that should be mentioned. Since this is a retrospective study, patient selection bias and time trend bias are inevitable. Another major limitation pertains to un availability of immunotherapies in our patient population that resulted better survival than conventional therapies we used. Although, we aimed to assess the effect of AMe, we cannot rule out imbalances or the heterogeneity of the treatment regimens utilized and toxicities of the systemic anti-cancer treatment that may have effect on survival results. Furthermore, again in this retrospective analysis, adverse events and toxicities that did not recorded could not be irrefutable.

Conclusion

Astragalus-based traditional Chinese medicine may have a potential clinical efficacy in the treatment of advanced NSCLC. More rationally designed trials are needed to investigate tumor response, survival, and quality of life of NSCLC patients using AMe. *Astragalus* extract may consider as a supportive care agent in metastatic NSCLC patients.

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Ak et al.
Astragalus Extract as Complementary Therapy for Lung Cancer

221

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