

The Efficacy and Safety of Standardized Allergen-Removed *Rhus verniciflua* Extract as Maintenance Therapy after First-Line Chemotherapy in Patients with Advanced Non-Small Cell Lung Cancer

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Abstract: Chemotherapy improves the survival of patients with advanced non-small cell lung cancer (NSCLC), but tumor progression is often inevitable. Strategies are needed to improve the therapeutic efficacy of chemotherapy. Over recent years, there has been increasing interest in the role of maintenance therapy after first-line chemotherapy. We investigated the efficacy and safety of standardized allergen-removed *Rhus verniciflua* Stokes extract (aRVS) as maintenance therapy in patients with non-progressive disease following first-line chemotherapy. We reviewed the medical records of 33 patients with advanced NSCLC, who started treatment with aRVS in a state of tumor regression or stable disease after completion of four or six cycles of induction chemotherapy at the Integrative Cancer Center, Kyung Hee University Hospital at Gangdong from June 2006 to April 2012. The primary objective of this study was progression-free survival (PFS) of aRVS as maintenance therapy. Secondary

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objectives included assessments of disease control rate (DCR), overall survival (OS), and the safety of aRVS treatment. The median PFS was 5.2 months with a 6- and 12-month PFS rate of 40.6% and 12.9%, respectively. The DCR was 93.9% and the median OS was 34.8 months. The overall survival rates at 12, 24, and 36 months were 84.2%, 76.7% and 49.9%, respectively. We observed no hematologic toxicity, nephrotoxicity, or hepatotoxicity during aRVS treatment. In conclusion, maintenance therapy with aRVS for patients with advanced NSCLC is well-tolerated and offers encouraging improved PFS and OS compared with historical controls. Our data provide further evidence that aRVS may be used beyond disease progression in this clinical setting.

Keywords: Standardized Allergen-Removed *Rhus verniciflua* Stokes Extract; Advanced Non-Small Cell Lung Cancer; Maintenance Therapy; Herbal Medicine.

Introduction

The standard of care for the treatment of patients with advanced non-small cell lung cancer (NSCLC) includes four to six cycles of first-line platinum-based doublet chemotherapy, and it is recommended that patients wait until the disease progresses further before administering second-line anticancer systemic therapy (Schiller *et al.*, 2002; Socinski *et al.*, 2002; Sandler *et al.*, 2006; Scagliotti *et al.*, 2008; Pirker *et al.*, 2009; Reck *et al.*, 2009). Although palliative chemotherapy for advanced NSCLC offers symptomatic relief and a modest improvement in survival, the efficacy of current standard chemotherapy combinations appears to reach a therapeutic plateau of about 12 months of median survival (Schiller *et al.*, 2002; Pfister *et al.*, 2004; Sandler *et al.*, 2006; NSCLC Meta-Analyses Collaborative Group, 2008; Scagliotti *et al.*, 2008; Pirker *et al.*, 2009).

The duration of response or disease stabilization after first-line chemotherapy is brief (median duration: two to three months), and the majority of patients experience disease progression (Brodowicz *et al.*, 2006; Ciuleanu *et al.*, 2009; Fidias *et al.*, 2009). Over recent years, there has been increasing interest in the role of maintenance therapy in advanced NSCLC (Cappuzzo *et al.*, 2010; Gervais *et al.*, 2011; Behera *et al.*, 2012; Paz-Ares *et al.*, 2012; Perol *et al.*, 2012; Zhang *et al.*, 2012). Investigations have established the role of maintenance therapy in patients with advanced NSCLC after first-line chemotherapy (Ciuleanu *et al.*, 2009; Cappuzzo *et al.*, 2010; Cohen *et al.*, 2010a,b). A key consideration for maintenance therapy is to utilize a well-tolerated agent with a relatively low risk of cumulative toxicities (Ciuleanu *et al.*, 2009; Perol *et al.*, 2012). From this point of view, a natural product could be a suitable candidate for maintenance therapy.

Rhus verniciflua Stokes (RVS), the lacquer tree, is an indigenous East Asian plant that has been used as an anti-cancer treatment in traditional Korean medicine since the 15th century (Her *et al.*, 1597; Kim, 2000). Preclinical studies demonstrated that RVS extract exhibits anti-proliferative and apoptotic activities in various human cancer cell lines via activation of caspase-9 and inhibition of the PI3K/Akt/PKB pathway (Lee *et al.*, 2003; Jang *et al.*, 2005; Kim *et al.*, 2006, 2008b, 2009). Standardized allergen-removed *Rhus verniciflua* Stokes extract (aRVS) was suggested as a potential anti-cancer treatment in

several clinical studies (Lee *et al.*, 2009a,b, 2010a,b, 2011; Cheon *et al.*, 2011). In addition, it was experimentally proven to inhibit vascular endothelial growth factor (VEGF) and was recently shown to have an inhibitory effect on matrix metalloproteinase-2 (MMP2) and matrix metalloproteinase-9 (MMP9) activities in a human fibrosarcoma cell line (Sminova *et al.*, 2002; Choi *et al.*, 2006, 2012; Moon *et al.*, 2010). In advanced NSCLC, favorable outcomes have been shown in two reports (Lee *et al.*, 2009b; Cheon *et al.*, 2011). Based on its efficacy in NSCLC and negligible toxicity profile, we postulated that maintenance therapy with aRVS would improve progression-free survival for patients with advanced NSCLC.

The aim of this study was to assess the potential benefit and toxicity of aRVS as maintenance therapy after first-line chemotherapy in patients with advanced NSCLC.

Patients and Methods

This retrospective study was approved by Kyung Hee University Hospital at Gangdong, Kyung Hee University (KHNMC) Institutional Review Board.

Patient Selection

This study included patients with recurrent or metastatic NSCLC treated with aRVS at the Integrative Cancer Center, Kyung Hee University Hospital at Gangdong, Korea, between June 2006 and April 2012. Patients were eligible if they met the following criteria: age 18 years or older with histologically or cytologically confirmed recurrent or metastatic NSCLC for which they had completed four or six cycles of first-line chemotherapy with documented radiographic evidence of a complete response (CR) or a partial response (PR) or stable disease (SD). Additional inclusion criteria were measurable or evaluable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), (Therasse *et al.*, 2000) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, and adequate hematologic, hepatic and renal functions. Patients with brain metastases were eligible if the metastases were stable and successfully treated with local therapy. Patients with hospital visits simply for counseling without taking aRVS, or other clinically significant cancers within five years were not eligible.

Evaluation of Clinical and Tumor Characteristics

The following demographic and clinicopathological information was retrospectively obtained from reviews of the medical records at the Integrative Cancer Center, Kyung Hee University Hospital at Gangdong: age, gender, performance status, smoking history, tumor histology, status of primary NSCLC and metastatic site, history of prior treatment, response and regimens of first line chemotherapy, and the treatment after the failure of aRVS. NSCLC staging was determined according to the American Joint Committee on Cancer criteria (7th edition, 2010).

Standardized Allergen-Removed Rhus verniciflua Stokes Extract

aRVS was manufactured by Kyung Hee University Medical Center according to the method described in Korean Patent No. 0504160. RVS stalks, which were 10 years old and grown in Wonju, Republic of Korea, were dried without direct contact to sunlight and chopped. The stalks were roasted in an iron pot at 100–240°C for 3–5 minutes to remove allergens. Treated stalks were extracted twice with a 10-fold volume of water at 90°C to 95°C for six hours. The extract were filtered with Whatman grade GF/B glass microfiber filter paper and concentrated under vacuum to remove water. The concentrate was lyophilized to a brownish powder. The extraction yield from 100 g of chopped stalks was 3.3 g. The quality of the extract was tested and controlled according to the guidelines of the Korean Food and Drug Administration (KFDA) and high performance liquid chromatography showed that the RVS extract contained fustin, fisetin, sulfuretin, butein, and other compounds. The content of fustin and fisetin was more than 13% (w/w) and 2% (w/w), respectively.

Treatment

For patients with response or SD, aRVS was administered until disease progression or unacceptable toxicity occurred. Patients who wanted to continue aRVS despite of progressive disease (PD) were maintained on aRVS.

All patients were recommended an initial dose of aRVS of 1350 mg/day (450 mg three times a day) orally, which was based on the 10 established formularies of Korean medical volumes approved by the KFDA. Patients were allowed to receive full concomitant palliative supportive care therapies, including acupuncture, moxibustion, and intermittent use of other herbal medicine during aRVS treatment.

Assessment of Toxicity and Tumor Response

Toxicity was analyzed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Tumor response was measured according to the RECIST criteria version 1.0, every 6–8 weeks (Therasse *et al.*, 2000).

Endpoints and Statistics

The primary endpoint of this study was progression-free survival (PFS) with secondary endpoints being disease control rate (DCR), overall survival (OS), and safety. PFS was defined as the time from the first day of treatment with aRVS to the first documentation of disease progression, or death from any cause. OS was defined as the time from the first day of treatment with aRVS to the time of death from any cause, or to the last follow-up date the patient was known to be alive. If patients experienced progression of disease prior to their first scan for response evaluation, the last follow-up date was used for PFS. Survival was calculated by the Kaplan-Meier method and statistically compared using the log rank

test. All statistical analyses were conducted using SPSS 16.0 statistical software. *p* values less than 0.05 were considered statistically significant.

Results

Thirty-three patients were included. The median follow-up for survival was 33.6 months.

Clinicopathological Characteristics of Patients

Patient demographics and clinicopathological characteristics are summarized in Table 1. The median age for the treated sample was 52 years (range, 32 to 84 years), and 15 patients (45.5%) were female. Other prevalent characteristics at baseline included patients over 65 years (27.3%), adenocarcinoma histology (84.8%), ECOG performance status of two (15.2%), brain metastases (15.2%), and bone metastases (33.3%). In total, 15 (45.5%) patients had received gemcitabine and platinum first-line chemotherapy and 10 (30.3%) had received pemetrexed and cisplatin; 18 (54.5%) had achieved PR and 15 (45.5%) achieved SD with previous first-line chemotherapy.

Treatment Administration

aRVS was administered for a median duration of 10.9 months (range: 1.2–37.8 months). No patient required dose reductions or interruptions.

Documented post-study (post-aRVS) treatments were reported in 25 patients (89.3%). Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) was the most commonly selected agent (20 patients). The remaining five patients received conventional cytotoxic chemotherapies. Of patients with documented PD, 23 (82.1%) received aRVS continuously based upon the decision of the patient or physician. The median duration of aRVS beyond PD was 12.8 months (3.0 to 34.9 months). Twenty-two patients received aRVS in combination with chemotherapy.

Adverse Events

Toxicity was evaluated in all patients and is summarized in Table 2. All patients tolerated aRVS very well without any grade 3 or 4 adverse events. There were no withdrawals or deaths due to adverse events, regardless of causality.

Response and Survival

A summary of the best overall response during aRVS treatment is given in Table 3. All 33 patients were assessable for treatment response. No patient had CR or PR, and 31 patients had SD (93.9%) as their best response to aRVS. Two patients (6.1%) had PD and the DCR was therefore 93.9%. Twenty-eight progressions had occurred, and 12 of them had died at the time of our analysis. Figure 1 shows Kaplan-Meier curves for OS and PFS for all

Table 1. Patient Baseline Characteristics

Variable		Number of Patients (%)
Gender	Male	18 (54.5)
	Female	15 (45.5)
Age	Median (range)	52 (32–84)
	< 65 years	24 (72.7)
	≥ 65 years	9 (27.3)
Performance status	ECOG 0	1 (3.0)
	ECOG 1	27 (81.8)
	ECOG 2	5 (15.2)
Smoking status	Current smoker or ever smoked	16 (48.5)
	Never smoked	17 (51.5)
Tumor histology	Adenocarcinoma	28 (84.8)
	Non-adenocarcinoma*	5 (15.2)
Disease stage at initial diagnosis	I	7 (21.2)
	II	0
	III	0
	IV (M1a)	13 (39.4)
	IV (M1b)	13 (39.4)
Current disease status	Recurrent	7 (21.2)
	Metastatic	26 (78.8)
Prior chemotherapy regimen	Gemcitabine plus platinum	15 (45.5)
	Pemetrexed plus cisplatin	10 (30.3)
	Paclitaxel plus platinum	5 (15.2)
	Concurrent chemoradiation (docetaxel/cisplatin, cisplatin, docetaxel)	3 (9.1)
Response to first line-chemotherapy at study initiation	CR	0
	PR	18 (54.5)
	SD	15 (45.5)
Prior radiation		13 (39.4)
Prior radiation organ	Brain	4 (12.1)
	Lung	5 (15.2)
	Bone	6 (18.2)
Number of metastatic site	One	15 (45.5)
	Two	12 (36.4)
	Three	5 (15.2)
	Four or more	1 (3.0)
Metastatic site	Brain	5 (15.2)
	Lung to lung	16 (48.5)
	Bone	11 (33.3)
	Liver	1 (3.0)
	Adrenal gland	0 (0.0)
	Pleura	14 (42.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; SD, stable disease; *, 4 squamous cell, 1 large cell, 1 large cell neuroendocrine, 1 pleomorphic.

Table 2. Adverse Events of aRVS (*n* = 33)

Variable	Grade 1 or 2 No. (%)	Grade 3 or 4 No. (%)	Total No. (%)
Dyspepsia	2 (6.1)	0	2 (6.1)
Nausea/Vomiting	0	0	0
Insomnia	1 (3.0)	0	1 (3.0)
Skin itching	1 (3.0)	0	1 (3.0)
Skin rash	0	0	0
AST/ALT	0	0	0
Bilirubin	0	0	0
Creatinine	0	0	0
Neutropenia	0	0	0
Thrombocytopenia	0	0	0

Notes: Abbreviations: aRVS, standardized allergen-removed *Rhus verniciflua* Stokes extract; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Best Response to Treatment

Total (<i>n</i> = 33)	
PR	0 (0.0)
SD	31 (93.9)
PD	2 (6.1)

Notes: Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease.

33 patients. The median PFS was 5.2 months (95% CI, 4.0 to 6.4 months) with a 6- and 12-month PFS rate of 40.6% and 12.9%, respectively. The median OS was 34.8 months. The survival rates at 12, 24, and 36 months were 84.2%, 76.7%, and 49.9%, respectively. The median PFS and the median OS were not significantly different in their response (PR versus SD) to induction therapy (data not shown).

The median OS was longer for the group with aRVS continuation compared to the aRVS discontinuation beyond PD (34.8 months vs. 25.1 months), but this is not statistically significant ($p = 0.27$).

Discussion

In the current study, we demonstrated that maintenance therapy with aRVS in patients with advanced NSCLC compares favorably to historical controls (Table 4). Table 4 shows the brief outcomes of previous maintenance studies and this study. The median PFS of 5.2 months in this study compares favorably to the median PFS of 12.4 weeks–4.8 months in previous maintenance studies (Ciuleanu *et al.*, 2009; Cappuzzo *et al.*, 2010; Paz-Ares *et al.*,

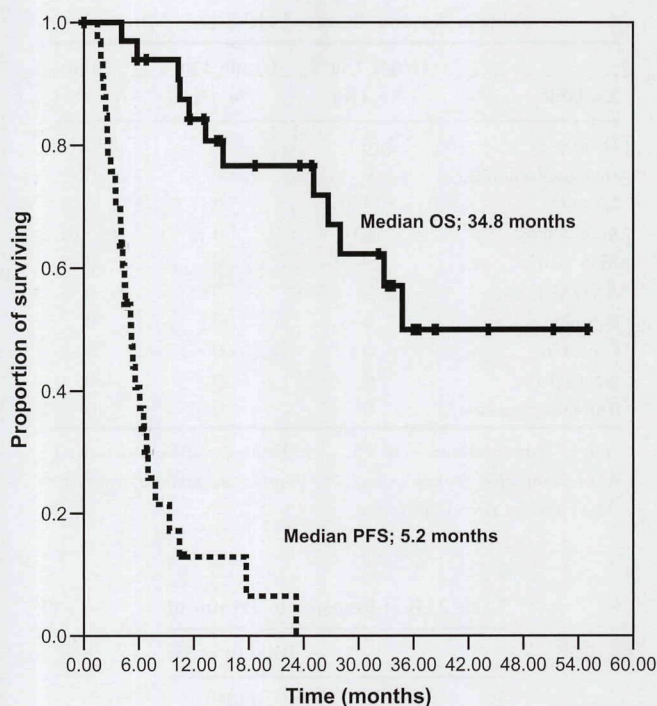


Figure 1. Overall survival and progression-free survival curves of all patients. OS, overall survival time; PFS, progression-free survival time.

2012; Zhang *et al.*, 2012). The median OS of 34.8 months was also higher than the median OS of 12.0–18.7 months in maintenance pemetrexed, erlotinib, and gefitinib studies (Ciuleanu *et al.*, 2009; Cappuzzo *et al.*, 2010; Paz-Ares *et al.*, 2012; Zhang *et al.*, 2012). This study is, to our knowledge, the first to show the potential efficacy of an herbal product. aRVS-related toxicities were nearly absent except for a few mild cases of dyspepsia.

The efficacy of first- and second-line treatments for NSCLC was established from clinical research (Shepherd *et al.*, 2000, 2005; Schiller *et al.*, 2002; Hanna *et al.*, 2004; Thatcher *et al.*, 2005; Kim *et al.*, 2008a). However, efficacy benefits have tended to plateau and there is a need for improvement in the clinical outcomes of patients with advanced NSCLC (Schiller *et al.*, 2002; Pfister *et al.*, 2004; Sandler *et al.*, 2006; Scagliotti *et al.*, 2008; Pirker *et al.*, 2009; Reck *et al.*, 2009). Maintenance therapy, either by continuing with an agent that was part of first-line therapy or by administering a different agent upon completion of first-line therapy, is defined as the continuation of a treatment after achieving a clinical response that is comparable to the state previous to chemotherapy, including disease stabilization (Behera *et al.*, 2012; Gridelli *et al.*, 2012). The objective with maintenance therapy is to increase the duration of disease control and, ultimately, improve survival.

Ciuleanu and colleagues showed the benefit of pemetrexed switch maintenance therapy for advanced non-squamous NSCLC patients after induction with a platinum doublet

Table 4. Comparison of Reports of Variable Maintenance Treatment Regimens in Advanced NSCLC Patients

Study	Regimen	N	MA	Adeno (%)	ECOG 2 (%)	DCR (%)	PFS/TTP (m)	MST (m)	PST (%)
JMEN (Ciuleanu <i>et al.</i> , 2009)	Pemetrexed plus BSC	441	60.6	50	0	52	4.3	13.4	51
(switch maintenance)	BSC	222	60.4	48	0	33	2.6	10.6	67
SATURN (Cappuzzo <i>et al.</i> , 2010)	Erlotinib plus BSC	438	60	47	0	60.6	3.1	12.8	71
	BSC	451	60	44	0	50.8	2.8	11.1	72
PARAMOUNT (Paz-Ares <i>et al.</i> , 2012)	Pemetrexed plus BSC	359	61	85	<1	72	4.1	13.9	64
(continuous maintenance)	BSC	180	62	88	1	60	2.8	11.0	72
INFORM (Zhang <i>et al.</i> , 2012)	Gefitinib plus BSC	148	55	71	2	72	4.8	18.7	43
	BSC	148	55	70	3	51	2.6	16.9	62
Current study	aRVS	33	52	84.8	15.2	93.9	5.2	34.8	89.3

Notes: Abbreviations: N, number; MA, median age; Adeno, adenocarcinoma; ECOG Eastern Cooperative Oncology Group; DCR, disease control rate; PFS, progression-free survival; TTP, time to progression; MST, median survival time; m, months; PST, post-study treatments received; BSC, best supportive care; aRVS, standardized allergen-removed *Rhus verniciflua* Stokes extract; CTx, chemotherapy.

(PFS; 4.3 versus 2.6 months; hazard ratio [HR] = 0.50; $p < 0.0001$, OS; 13.4 versus 10.6 months, HR = 0.79, $p = 0.012$). (Ciuleanu *et al.*, 2009) In the phase III SATURN study, erlotinib significantly extended PFS (12.3 weeks versus 11.1 weeks, HR = 0.71, $p < 0.0001$) and OS (12 months versus 11 months, HR = 0.81, $p < 0.0088$) compared with the placebo in patients with advanced NSCLC after platinum-based chemotherapy (Cappuzzo *et al.*, 2010). Both pemetrexed and erlotinib have been approved by the United States Food and Drug Administration for maintenance therapy of advanced NSCLC (Gridelli *et al.*, 2009, 2012; Cohen *et al.*, 2010a,b). In the PARAMOUNT trial, continued maintenance with pemetrexed significantly prolonged PFS (4.1 versus 2.8 months, HR 0.62, 95% CI 0.49–0.79, $p = 0.00006$) and OS (16.9 versus 14.0 months, HR 0.78, 95% CI 0.64–0.96, $p = 0.0195$) compared with the placebo (Paz-Ares *et al.*, 2012). In the INFORM trial, maintenance gefitinib after first-line platinum-based chemotherapy in advanced NSCLC patients was associated with a significant improvement in PFS compared with the placebo (4.8 versus 2.6 months; HR 0.42, 95% CI 0.33–0.55, $p < 0.0001$) (Zhang *et al.*, 2012). Several other agents have been investigated as continuation maintenance therapy (Pino *et al.*, 2008; Fidias *et al.*, 2009; Gridelli *et al.*, 2009; Patel *et al.*, 2009; Gervais *et al.*, 2011; Perol *et al.*, 2012).

Another important consideration with the use of maintenance therapy is the potential impact on the patient's quality of life. The availability of better tolerated drugs has made

the maintenance strategy a feasible option because, previously, prolongation of first-line platinum doublet therapy led to cumulative toxicity issues that precluded use of this approach. The safety results in the aRVS group of this study were consistent with the previously reported safety profile of aRVS (Lee *et al.*, 2009a, 2011; Cheon *et al.*, 2011). The incidence of drug-related adverse events was negligible. These symptoms spontaneously diminished without reducing the dosage of aRVS. None of the patients discontinued treatment or needed dose modifications due to adverse events of the aRVS extract. Although pemetrexed or EGFR TKI has favorable toxicity, some drug-related grade 3–4 adverse events were reported (Ciuleanu *et al.*, 2009; Cappuzzo *et al.*, 2010; Paz-Ares *et al.*, 2012). The excellent safety of aRVS qualifies it as a suitable candidate for maintenance therapy.

A relevant number of patients who intended to receive second-line treatment actually will not be able to receive it, due to worsening conditions, disease progression, or death. In maintenance studies, about 50–70% of patients receive post-study chemotherapy (Brodowicz *et al.*, 2006; Ciuleanu *et al.*, 2009; Fidias *et al.*, 2009; Cappuzzo *et al.*, 2010; Paz-Ares *et al.*, 2012; Zhang *et al.*, 2012). In actual clinical practice, a much lower rate of patients who experience an objective response or disease stabilization after first-line chemotherapy receive second-line therapy. In the current study, 25 patients (89.3%), a higher proportion compared with other trials, received active therapies after PD. This higher rate of post-PD treatment may prolong survival time. aRVS prolonged PFS (5.2 months) without worsening the patient's quality of life due to its rare toxicity, and it may enable more patients to have the opportunity to have additional lines of chemotherapy.

The development of resistance to treatment remains an important problem in cytostatic targeted agents. When there is disease progression while the patient is on cytostatic agents, it is debatable whether the patient should continue the cytostatic agent alongside a change in other systemic therapies, or discontinue the agent altogether (Grothey *et al.*, 2008; Jahanzeb, 2009; Campiglio *et al.*, 2011). In this study, the continuation of aRVS (median duration of 12.8 months after PD), which was observed in 82.1% of patients who experienced PD, is one possible explanation for the longer-than-expected median OS observed in the study sample. We recognize that our study is limited by its retrospective nature and the lack of a comparable control group who did not continue aRVS after progression. Nevertheless, the median OS of 34.8 months of this study, which was longer than expected, suggests that continued aRVS beyond PD may be beneficial to maximize the clinical outcomes from aRVS in advanced NSCLC patients. Continuation of aRVS was not associated with a significant improvement in OS but a trend towards improved OS (34.8 months vs. 25.1 months).

Although this study included younger patients and a higher proportion of adenocarcinoma patients than other trials, 15% of the patients had ECOG PS 2 and molecularly unselected patients were included. This suggests that our results cannot be explained by the selection of patients with better than usual prognostic factors.

aRVS is a standardized, quality-controlled herbal medicine. For clinical use, RVS itself has been limited because it contains a toxic allergen, urushiol (Powell and Barrett, 1986).

Therefore, standardized aRVS was developed. Based on the traditional medical literature, preclinical and abundant clinical observations, aRVS has been prescribed primarily for cancer patients (Her, 1597; Lee *et al.*, 2009a, 2011; Moon *et al.*, 2010; Cheon *et al.*, 2011; Choi *et al.*, 2012). aRVS was reported to significantly inhibit vascular endothelial growth factor-induced proliferation in human umbilical vein endothelial cells at nontoxic concentrations, despite its weak cytotoxicity against human umbilical vein endothelial cells (Choi *et al.*, 2006). Human fibrosarcoma HT1080 cell invasion was also reduced by aRVS in a dose-dependent manner, suggesting that the decrease is a consequence, at least in part, of reduced activities of both MMP-2 and MMP-9 (Moon *et al.*, 2010). Fisetin (3,7,30,40-tetrahydroxyflavone), a flavonoid from RVS, was also proven to inhibit the metastatic ability of PC-3 prostate cancer cells by reducing MMP-2 and MMP-9 expression through suppression of PI3K/Akt and JNK signaling pathways (Chien *et al.*, 2010). These findings suggest that aRVS is a candidate for the treatment of cancer metastasis. Previously, we showed the efficacy and safety of aRVS in 40 patients with previously treated advanced NSCLC (Cheon *et al.*, 2011).

The limitation of our study is that it is a single institution, single treatment arm, and retrospective review that included only 33 patients. Moreover, this study does not have control groups. As such, comparison of efficacy endpoints achieved with other regimens in other studies may be highly biased by patient selection. Therefore, it is hard to draw such a conclusion that aRVS could be considered first-line maintenance therapy. Despite these limitations, maintenance therapy with aRVS was associated with excellent toxicity and relatively long survival compared with previously proven trials. This study provides a sound basis for conducting clinical trials with aRVS as maintenance therapy in NSCLC in view of its promising efficacy and negligible toxicity.

Author Disclosure Statement

The authors have no conflicting financial interests to disclose.

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