2009. Vol.30. No.6. *112-117*
The Journal of Korean Oriental Medicine

Case Report

The Concurrent Use of *Rhus verniciflua* Stokes as Complementary Therapy with Second or More Line Regimens on Advanced Non-small-cell Lung Cancer: Case Series

Sang-Hun Lee[1], Kyung-Suk Kim[1], Won-Cheol Choi[2], Seong-Woo Yoon[1]

[1]Department of Internal Medicine,
[2]Department of Clinical Oncology, M·μ Integrative Cancer Center,
East-West Neo Medical Center, College of Oriental Medicine, Kyunghee University

Objective: *Rhus verniciflua* Stokes (RVS) has anticancer effect confirmed by preclinical studies and historical records. We thus tried to evaluate retrospectively the effect of RVS as a complementary medicine for patients with advanced non-small-cell lung cancer (NSCLC) showing refractory to conventional chemotherapy.
Patients and Methods: From June 1, 2006 to June 30, 2007, patients with advanced NSCLC who received both the standardized RVS extract and a standard course of second or more line therapy such as pemetrexed (Alimta®), erlotinib (Tarceva®), and gefitinib (Iressa®) were checked. A total of 13 patients were eligible for the final analysis after fulfilling inclusion/exclusion criteria. Time to progression (TTP) of these patients treated with the standardized RVS extract was checked in the aftercare period.
Results: Patients received RVS treatment for a median period of 296 (range 84-698) days. The median TTP was 220.5 (range 36-489) days, and three patients (23.1%) had TTP values of 15 more months. No significant side effects from RVS treatment have been observed.
Conclusion: The standardized RVS extract might have synergetic effects by assisting apoptosis in advanced NSCLC with concurrent standard therapy agents, since it prolonged TTP without significant adverse effects. This study suggests that the standardized RVS extract is beneficial to patients with chemotherapy-refractory NSCLC. Further clinical trials and preclinical studies are necessary to determine the efficacy and safety of the standardized RVS extract in NSCLC.

Key Words : *Rhus verniciflua* Stokes; flavonoids; antineoplastic agents; non-small cell lung carcinoma

Introduction

Lung cancer is the leading cause of cancer death worldwide. About two thirds of patients with non-small-cell lung cancer (NSCLC) constituting 75% to 80% of all new cases were of the advanced stage disease, which cannot be resected at initial presentation[1)]. Available conventional treatments offer only palliative systemic therapy for patients with advanced NSCLC such as stage IIIB or IV. In spite of chemotherapy with targeted therapy agents such as the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, survival outcomes are still disappointing[2)]. Drug resistance and toxicity remain as major obstacles to the successful outcome of chemotherapeutic agents, especially for treatment of lung cancer.

• Received : 17 April 2009 • Revised : 1 June 2009 • Accepted : 1 June 2009
• Correspondence to : Seong-Woo Yoon
Department of Internal Medicine, M · μ Integrative Cancer Center, East-West Neo Medical Center, College of Oriental Medicine, Kyunghee University, 149 Sangil-dong, Gangdong-Ku, Seoul, 134-727 Republic of Korea
Tel : +82-2-4406218, Fax : +82-2-4407287, Email : stepano212@daum.net

Complementary therapy is urgently needed to reduce side effects and/or to potentiate chemotherapeutic agents.

We previously reported that stabilization of NSCLC disease progression is possible using the standardized *Rhus verniciflua* Stokes (RVS) extract exclusively[3]. RVS, commonly known as the lacquer tree, is used for treating tumor in East Asia, including Korea[4,5]. Recent experimental studies proved that the RVS extract has antiangiogenic and antitumor activities in Lewis lung carcinoma, as well as synergetic activities with cisplatin in human cancer cell lines[6,7]. Here, we report on the outcomes of the standardized RVS extract combined with conventional therapy regimens in patients with advanced NSCLC after first or more line therapy failure.

Patients and Methods

1. Patients

All patients were identified as having advanced NSCLC and were treated with the standardized RVS extract at East-West Neo Medical Center (Seoul, Korea) between June 1, 2006 and June 30, 2007. The patients who fulfilled the following eligibility criteria selected for this study had:

1) historically confirmed advanced NSCLC,
2) at least one prior palliative chemotherapy regimen,
3) one or more cycles of second or more line regimens such as pemetrexed (Alimta®), erlotinib (Tarceva®), and gefitinib (Iressa®) with RVS treatment. All patients signed a written informed consent form. Records were retrospectively reviewed with particular attention to the initial history and physical examination, histopathologic findings, operative and postoperative treatments including chemotherapy, and follow-up.

2. Standardized extract of RVS and treatment course

A standardized extract of RVS was manufactured according to the method disclosed in Korean patent (No. 0504160). 10-year-old RVS stalks including bark, grown in Wonju, Korea, were processed to sawdust, which was dried and extracted with 10-fold volume of water at 90-95℃ for 6 hours. After the filtration and concentration process, the final product was a dark brown powder. The RVS extract included flavonoids such as fustin, fisetin, sulfuretin, and butein, confirmed by a high performance liquid chromatography. The quality of the RVS extract was tested and controlled according to the hospital's standards (fustin > 13.0%, fisetin > 7.0%, urushiol not detected). Daily therapy with 1350 mg of orally-administered RVS extract was prescribed.

3. Treatment evaluation

The primary end-point in this analysis was time to progression (TTP). Progression of radiological findings during or after chemotherapy was determined according to Response Evaluation Criteria in Solid Tumors (RECIST). TTP was defined as duration from the starting day of treatment with the chemotherapy such as pemetrexed (Alimta®), erlotinib (Tarceva®), and gefitinib (Iressa®) to the day on which a judgment of disease progression was made. Safety was assessed in terms of toxicity and evaluated as grades 1 to 4 based on the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Results

A total of 13 patients met our eligibility criteria. According to the concurrent conventional therapy agents, they were classified into three groups; pemetrexed, erlotinib, and gefitinib. The main characteristics and tumor responses of the patients are summarized in Table 1.

The median age was 50 years (range 36-64 years). Two patients had undergone prior surgical resection

of their primary tumor; metastatic regions were not found. Before RVS treatment, two patients received radiotherapy for metastasis to the brain or spine. The average number of chemotherapy regimens were 1.6 with six patients (46.1%) receiving two or more regimens before RVS treatment. Patients received RVS treatment for a median period 296 (range, 84-810) days. The median TTP was 182 (range, 36-738) days, and three patients (No. 5, 8, 10) had TTP values of 15 more months. There was no significant adverse effect from RVS treatment.

Discussion

Erlotinib, pemetrexed, and gefitinib were recently approved by the U.S. Food and Drug Administration as second or third line treatments for advanced NSCLC. Erlotinib and gefitinib are tyrosine kinase

Table 1. Demographic, clinical characteristics and tumor response of all patients (n=13).

Patient number	Gender	Age	Stage*	Metastasis region	Diagnosis day	Previous chemotherapy	Previous operation or radiotherapy	Initial day of RVS treatment†	RVS treatment (day)	Concomitant chemotherapy with RVS‡	Line	Time to progression (day)
1	Female	55	IIIB	Pleura	2006-0222	Gemcitabine/ Cisplatin	-	2006-06-13	748	Gefitinib Pemetrexed	Second Third	409 126
2	Male	39	IV	Bone	2005-06-28	Gemcitabine/ Cisplatin Gefitinib	-	2006-07-12	208	Erlotinib	Third	54
3	Male	47	IIIB	Pleura	2006-01-17	Heptaplatin /Paclitaxel	-	2006-07-21	698	Gefitinib	Second	336
4	Female	37	IIIB	Pleura	2005-11-30	Paclitaxel/ Cisplatin	-	2006-09-14	187	Gefitinib	Second	207
5	Male	63	IV	Lung	2006-10-02	Gemcitabine/ Carboplatin	-	2006-11-06	614	Pemetrexed	Second	471
6	Male	56	IV	Brain	2005-09-22	Paclitaxel/ Carboplatin Cisplatin/ Docetaxel	Lobectomy Radiotherapy	2006-10-10	296	Erlotinib	Second	292
7	Male	48	IV	Lung	2006-01-13	Gemcitabine /Cisplatin Docetaxel	-	2006-10-24	84	Gefitinib	Third	59
8	Female	64	IIIB	Pleura	2006-06-08	Cisplatin/ Vinorelbine Docetaxel	-	2006-12-01	821	Erlotinib	Third	573
9	Female	36	IV	Lung	2006-04-15	Gemcitabine /Irinotecan	-	2006-12-22	122	Gefitinib	Second	124
10	Female	56	IV	Lung	2005-10-20	Gemcitabine/ Cisplatin	Lobectomy	2006-12-26	810	Gefitinib	Second	738+
11	Female	50	IV	Bone	2006-05-08	Gemcitabine/ Carboplatin Gefitinib Docetaxel	Radiotherapy	2007-04-19	245	Pemetrexed	Forth	157
12	Female	52	IIIB	Pleura	2005-07-01	Gemcitabine/ Paclitaxel Gefitinib Vandetanib	-	2007-05-21	119	Pemetrexed	Forth	36
13	Male	44	IV	Brain	2006-10-16	Irinotecan/ Cisplatin	-	2007-06-28	305	Pemetrexed	Second	234

*Staging is based on the sixth edition of the TNM Classification of Malignant Tumors.
†The standardized Rhus verniciflua Stokes (RVS) extract 1350 mg was orally-administered daily.
‡The chemotherapy that the patient was receiving when given the standardized RVS extract.

inhibitors of the human EGFR, which has a pivotal role in progression of NSCLC[8]. By blocking EGFR activity by interfering with the adenosine triphosphate-binding site on the intracellular region of the receptor, it leads to inhibition of cell cycle progression, promotion of apoptosis, and antiangiogenesis[9]. By inhibiting the EGFR, apoptosis, cell-cycle arrest, and tumor growth inhibition are induced. Pemetrexed is a multi-targeted antifolate agent which disrupts folate-dependent metabolic processes essential for cell replication[10].

In this study, we evaluated the clinical feasibility of the standardized RVS extract as complementary medicine for patients with advanced NSCLC showing refractory to conventional chemotherapy. A total of 13 patients were selected according to our eligibility criteria. Three of these patients (No. 5, 8, 10) showed outstanding TTP outcomes. Patient 5, with an adenocarcinoma of the both lungs, stage IV (T4, N2, M1) was treated by a total of 21 cycles of pemetrexed (Alimta®) as the second line therapy, after failure of gemcitabine (Gemzar®) plus carboplatin (Paraplatin®) as the first line. The TTP of his tumor was 471 days, while the median TTP was 3.4 months in the study of pemetrexed versus docetaxel in patients with advanced NSCLC previously treated with chemotherapy[11]. After progression of his tumor, he was lost to follow-up. Patient 8, with an adenocarcinoma accompanying malignant pleural effusion, stage IIIB (T4, N3, M0), was treated by erlotinib (Tarceva®) as the third line therapy, after failure of the first line, vinorelbine (Navelbine®) plus cisplatin (CDDP), and the second line, docetaxel (Taxotere®). The TTP of her tumor was 573 days, while the median progression free survival (PFS) was only 2.2 months in the study of erlotinib in NSCLC patients previously treated with one or two chemotherapy regimens[12]. The PFS means the time from the beginning of treatment until progression or death from any cause. Thus, a person who dies of another cause before progression of disease would be counted in PFS, but not in TTP[13]. After progression of her tumor, she received 3 cycles of pemetrexed (Alimta®) and radiotherapy for brain metastases. Patient 10, with lung to lung metastasis, stage IV (T2, N0, M1) was treated by gefitinib (Iressa®) as the second line therapy, after failure of Gemcitabine (Gemzar®) in combination with cisplatin (CDDP) as the first line. The TTP of her tumor was 738 days up to the present (March 2009), while the median TTP was 3.0 months in a placebo-controlled study of gefitinib as the second- or third-line treatment for patients with advanced NSCLC[14]. The use of gefitinib is currently restricted to patients who were already receiving and benefiting from it, based on negative results of that study. European Cooperative Oncology Group (ECOG) performance statuses of patient 8 and 10 were 1, meaning that they were restricted from physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. In these three patients described, cytostatic and good performance statuses in advanced NSCLC were achieved by the standard therapy combined with oral administration of the standardized RVS extract. Though these outcomes may not be generalizable to all lung cancers, they obviously show that the standardized RVS extract has a synergetic effect with conventional therapy agents in NSCLC refractory to chemotherapy.

The clinical application of RVS has been limited because an allergenic component, urushiol, causes severe contact dermatitis in sensitive individuals[15]. Urushiol is a mixture of several derivatives of catechol, and should be removed from RVS for pharmaceutical uses. The aqueous extract of the standardized RVS extract was *in vivo* shown to suppress tumor volume in a xenograft mouse model system using A549 non-small cell lung cancer and Lewis lung cancer cells via inhibiting the proliferation and migratory activity of vascular endothelial growth factor[6]. It could also be a chemopreventive agent because it prevents cisplatin-induced cytotoxic damage

by inhibiting reactive oxygen species product with modest antitumor activity[7]. The mechanisms of RVS on cancer cells were recently proposed as follows: flavonoids from RVS induce p53-mediated mitochondrial stress resulting in apoptosis via a decrease in Bcl-2 level, the activation of Bax, and the release of cytochrome c from the cytoplasm[16]. An RVS ethanol extract also induces apoptosis through caspase activation followed by the inhibition of a serine/threonine kinase[17] Therefore, it is possible that the standardized RVS extract has a synergetic effect with molecularly targeted or antimetabolite agents, because it has both chemopreventive activity and different pathways to induce apoptosis.

In conclusion, we suggest that the standardized RVS extract has synergetic effects by assisting apoptosis in NSCLC with concurrent therapy agents. Based on this report, further preclinical studies on the mechanism of action and more clinical trials with long-term follow-up will assist in determining the efficacy and safety of the standardized RVS extract in treating advanced NSCLC in combination with the standard therapy.

Acknowledgement

This work was supported by the Kyunghee University Research Fund in 2007 (KHU-20080602).

References

1. Socinski MA, Morris DE, Masters GA, Lilenbaum R; American College of Chest Physicians. Chemotherapeutic management of stage IV non-small cell lung cancer. Chest. 2003; 123 (Suppl 1):226-43.
2. Johnson DH. Targeted therapies in combination with chemotherapy in non-small cell lung cancer. Clin Cancer Res. 2006; 12:S4451-7.
3. Jeong JS, Park JW, Yoon SW, Choi WC. Carcinostatic effect of allergen removed *Rhus verniciflua* Stokes-based traditional Korean medicine on a patient with lung adenocarcinoma; single case report. OPEM. 2008; 5:573-8.
4. Jang HS, Kook SH, Son YO, Kim JG, Jeon YM, Jang YS, *et al*. Flavonoids purified from *Rhus verniciflua* Stokes actively inhibit cell growth and induce apoptosis in human osteosarcoma cells. Biochem. Biophys Acta. 2005; 1726(3): 309-16.
5. Son YO, Lee KY, Lee JC, Jang HS, Kim JG, Jeon YM, *et al*. Selective antiproliferative and apoptotic effects of flavonoids purified from *Rhus verniciflua* Stokes on normal versus transformed hepatic cell lines. Toxicol Let. 2005; 155(1):115-25.
6. Choi WC, Lee JH, Lee EO. Study on antiangiogenic and antitumor activities of processed *Rhus verniciflua* Stokes extract. Korean J Oriental Physiology & Pathology. 2006; 20:825-9.
7. Lee JH, Lee HJ, Lee HJ, Choi WC, Yoon SW, Ko SG, *et al*. *Rhus verniciflua* Stokes prevents cisplatin-induced cytotoxicity and reactive oxygen species production in MDCK-I renal cells and intact mice. Phytomedicine. 2009; 16(2-3):188-97.
8. Silvestri GA, Rivera MP. Targeted therapy for the treatment of advanced non-small cell lung cancer: a review of the epidermal growth factor receptor antagonists. Chest. 2005; 128(6):3975-84.
9. Mendelsohn, J. The epidermal growth factor receptor as a target for cancer therapy. Endocr Relat Cancer. 2001; 8:3-9.
10. Adjei AA. Pemetrexed (ALIMTA), a novel multitargeted antineoplastic agent. Clin Cancer Res. 2004; 10:S4276-80.
11. Cohen MH, Johnson JR, Wang YC, Sridhara R, Pazdur R. FDA drug approval summary: pemetrexed for injection (Alimta) for the treatment of non-small cell lung cancer. Oncologist. 2005; 10(6):363-8.

12. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, *et al*.; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005; 353(2):123-32.
13. Pazdur R. Endpoints for assessing drug activity in clinical trials. Oncologist. 2008; 13(Suppl 2): 19-21.
14. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, *et al*. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet. 2005; 366(9496):1527-37.
15. Lovell CR. Poison oak. In: Plants and the Skin. Blackwell Scientific Publications: Oxford; 1993 :106-10.
16. Kook SH, Son YO, Chung SW, Lee SA, Kim JG, Jeon YM, et al. Caspase-independent death of human osteosarcoma cells by flavonoids is driven by p53-mediated mitochondrial stress and nuclear translocation of AIF and endonuclease G. Apoptosis. 2007; 12(7):1289-98.
17. Kim JH, Go HY, Jin DH, Kim HP, Hong MH, Chung WY, *et al*. Inhibition of the PI3K-Akt /PKB survival pathway enhanced an ethanol extract of *Rhus verniciflua* Stokes-induced apoptosis via a mitochondrial pathway in AGS gastric cancer cell lines. Cancer Let. 2008; 265(2):197-205.