

Efficacy and Safety of Standardized Allergen-Removed *Rhus verniciflua* Stokes Extract in Patients with Advanced or Metastatic Pancreatic Cancer: A Korean Single-Center Experience

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Key Words

Pancreatic cancer • *Rhus verniciflua* Stokes

Abstract

Background: Pancreatic cancer has the worst prognosis because of poor response to conventional therapy. We investigated the clinical feasibility of the standardized allergen-removed *Rhus verniciflua* Stokes (aRVS) extract as a potential therapeutic agent for advanced or metastatic pancreatic cancer. **Patients and Methods:** From July 2006 to June 2010, patients with advanced or metastatic pancreatic adenocarcinoma were checked in our institution. After applying inclusion/exclusion criteria, 42 patients were eligible for the final analysis. Overall survival, clinical benefit and adverse events of these patients treated with aRVS in the aftercare period were determined. **Results:** In May 2011, 39 patients had died and the remaining 3 patients were alive with evidence of disease. The mean RVS administration period was 3.86 months (95% confidence interval 2.52–5.20). The median overall survival for the entire population was 7.87 months (95% confidence interval 5.14–10.59), and the 1-year survival rate was 26.2%, which is compatible with external controls. Using univariate and multivariate analyses, aRVS treatment including

performance status and prognostic index significantly affected overall survival. A clinical benefit response was also shown by aRVS treatment which was not dependent on concurrent chemotherapy. Adverse reactions to aRVS treatment were mostly mild and self-limiting. **Conclusions:** The standardized aRVS extract might be beneficial for patients with advanced or metastatic pancreatic cancer since it positively affected overall survival and clinical symptoms without significant adverse effects.

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Introduction

Pancreatic adenocarcinoma is generally a dismal disease, with 80–90% of patients diagnosed with metastatic or locally advanced disease which means the tumor is unresectable at initial presentation [1]. Due to recent advances in cancer therapy, many clinical studies of integrated treatments such as chemotherapy combined with cytotoxic or targeted therapy have been performed. However, survival outcomes of pancreatic cancer are still disappointing (e.g. a median life expectancy of 6 months for advanced or metastatic disease) [2, 3]. Besides, a consider-

ate number of patients cannot receive conventional therapy because of adverse effects or poor performance status. *Rhus verniciflua* Stokes (RVS) of the Anacardiaceae family, commonly known as the lacquer tree, was traditionally used for treating tumors in Korea and China in the 15th century [4, 5]. Experimental studies showed that flavonoids from RVS have apoptotic activities in several human cancer cell lines [4–7]. The standardized allergen-removed RVS (aRVS) extract was reported to stabilize cancer progression in clinical practice [8–10]. In addition, it was experimentally proven to have antiangiogenic activities by inhibiting the vascular endothelial growth factor and was recently shown to have an inhibitory effect on matrix metalloproteinase-2 (MMP-2) and MMP-9 activities in a human fibrosarcoma cell line [11, 12].

The standardized aRVS extract has been prescribed for advanced cancer patients since 2006. Here, we report on the outcomes of the standardized aRVS extract combined with or without conventional therapy regimens in patients with advanced or metastatic pancreatic adenocarcinoma.

Patients and Methods

Eligibility Criteria

From July 2006 to June 2010, patients who fulfilled the following eligibility criteria were enrolled in the study: (1) pathologically confirmed adenocarcinoma; (2) radiological findings showing nonresectability of the tumor that included evidence of distant metastasis, tumor involvement of the celiac trunk and/or superior mesenteric artery, and obstruction or bilateral invasion of the portal vein; (3) performance status of 0–3 according to the Eastern Cooperative Oncology Group (ECOG) scale; (4) normal hepatic function (total bilirubin level ≤ 1.5 mg/dl) and renal function (serum creatinine level ≤ 1.5 mg/dl). Exclusion criteria were neuroendocrine tumor of pancreas or ampullary carcinoma, prior history of taking herbal medicine including RVS, palliative gemcitabine or gemcitabine-based chemotherapy or palliative radiation therapy before aRVS treatment, and neurologic deficit such as dementia and epilepsy. This study was approved by the institutional review board of the Kyunghee University Hospital at Gangdong (Seoul, Republic of Korea).

Standardized Extract of aRVS and Treatment Course

The clinical application of RVS has been limited because an allergenic component, urushiol, causes severe contact dermatitis in sensitive individuals [13–15]. Therefore, urushiol, which is a mixture of several derivatives of catechol, should be removed from RVS for pharmaceutical use. A standardized extract of urushiol-removed RVS was manufactured as follows.

RVS stalk, which was 10 years old and grown in Wonju, Republic of Korea, was dried without exposure to direct sunlight and chopped up. The pieces were roasted in an iron pot at 240°C for 50 min to remove allergens and extracted two times with a 10-fold volume of water at 90–95°C for 6 h (Korean patent No. 0504160).

The extract was filtered with Whatman GF/B 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 material was 3.3 g. A component analysis method using high-performance liquid chromatography showed that the aRVS extract contained fustin, fisetin, sulfuretin and butein, among others. The quality of the aRVS extract was tested and controlled according to the quality standards of the Korea Food and Drug Administration and the standards of our hospital (fustin $>13.0\%$, fisetin $>2.0\%$, urushiol not detected). Daily oral administration of 1,350 mg (1 capsule containing 450 mg 3 times a day) of aRVS extract was prescribed. The dosage was based on historical consideration and preclinical safety tests; the NOAEL (no observed adverse effect level) in beagle dogs is 150 mg/kg/day and its human equivalent dose is 1,623 mg/day in the case of a 60-kg man [16].

Evaluation of Efficacy and Safety

A total of 42 consecutive patients passed our eligibility criteria among 122 advanced or metastatic pancreatic cancer patients who visited the Integrative Cancer Center, East-West Neo Medical Center (Seoul, Republic of Korea). The primary endpoint was overall survival in the intent-to-treat analysis. Overall survival was defined as the period from the date of the first visit or start of aRVS treatment until death from any cause. We verified the time of death using data officially recorded by the Korean National Health Insurance on May 2011. The secondary endpoints were clinical response and safety.

Clinical benefit was evaluated by three common signs and symptoms found in most patients with advanced pancreatic cancer: pain, functional status and weight loss [17, 18]. For pain, a positive score was a decreased dosage of analgesic consumption of $\geq 50\%$ from baseline that was sustained for ≥ 4 weeks, a negative score was any increase in analgesic dosage, and a stable score was anything else. Functional status was evaluated by ECOG, not the Karnofsky performance scoring system [19]. A positive score was an improvement in ECOG performance status of ≥ 1 from baseline sustained for ≥ 4 weeks, a negative score was any worsening of ≥ 1 , and a stable score was any other result. For weight loss, a positive score was weight gain (without fluid retention) of $\geq 7\%$ from baseline that was sustained for ≥ 4 weeks, and a non-positive weight score was any other result. Clinical benefit response required either an improvement in both pain and ECOG or an improvement in either factor and a stable situation in the other. A non-response was defined by a worsening in one or both factors. For patients with a stable situation in both factors, a clinical benefit response required a positive score in weight. A non-response was defined by any other result.

Toxicity was also evaluated as grades 1–4 based on the Common Terminology Criteria for Adverse Events, version 4.0, for patients treated with aRVS or concurrent chemotherapy.

Statistical Analysis

Survival curves were estimated using the Kaplan-Meier method and statistically compared by the log-rank test. A stepwise reward Cox proportional hazard model analysis of overall survival was used to assess potential predictors of survival. The χ^2 test or Fisher's exact test was used to compare categorical variables. A p value <0.05 was considered statistically significant, and all analyses were performed using SPSS 12.0 for Windows.

Table 1. Baseline demographic and clinical characteristics of patients (n = 42)

Patient characteristics	Patients
Gender	
Male	16 (38.1)
Female	26 (61.9)
Median age, years	63.0 [36–78]
Age ≥65 years	16 (38.1)
Performance status by ECOG	
0	1 (2.4)
1	23 (54.8)
2	15 (35.7)
3	3 (7.1)
Body mass index	
Median	21.8 [14.8–27.1]
<22	22 (52.3)
Tumor-related symptoms	
Abdominal discomfort	33 (78.6)
Weight loss ≥10%	24 (57.1)
Jaundice	7 (16.7)
Stage	
Locally advanced	8 (19.0)
Distant metastases	34 (81.0)
Primary tumor site	
Head	15 (35.7)
Body-tail	27 (64.3)
Distant metastatic sites	
0	8 (19.0)
1	23 (54.8)
≥2	11 (26.2)
Sites of metastasis	
Liver	21 (50.0)
Peritoneum	14 (33.3)
Lung	5 (11.9)
Lymph nodes	6 (14.3)
Other organ	2 (4.8)
Previous history	
Diabetes mellitus	11 (26.2)
Smoking	14 (33.3)
Alcohol	18 (42.9)
Previous treatment	
Whipple or pancreatectomy	6 (14.3)
Biliary prosthesis	9 (21.4)
Carbohydrate antigen 19-9	
Median	374.6 [0.6–23,264]
>1,000 U/ml	16 (38.1)
Carcinoembryonic antigen	
Median	3.55 [0.5–54.8]
>10 ng/ml	8 (19.0)
Prognostic index ¹	
Good	20 (47.6)
Fair	19 (45.2)
Poor	3 (7.1)

Figures in parentheses are percentages, figures in brackets are ranges.

¹ Prognostic index was as follows: score = 1 if PS is 0 or 1, 2 if PS is 2, and 5 if PS is 3 + 1 if primary site is body or tail, and 3 if primary site is head + 1 if C-reactive protein is <1 mg/dl, 3 if C-reactive protein is 1–3 mg/dl, and 6 if C-reactive protein is >3 mg/dl. Prognostic indices ranged from 3 to 14: good, prognostic index = 3 or 4; fair, prognostic index = 5–7, and poor, prognostic index = 8.

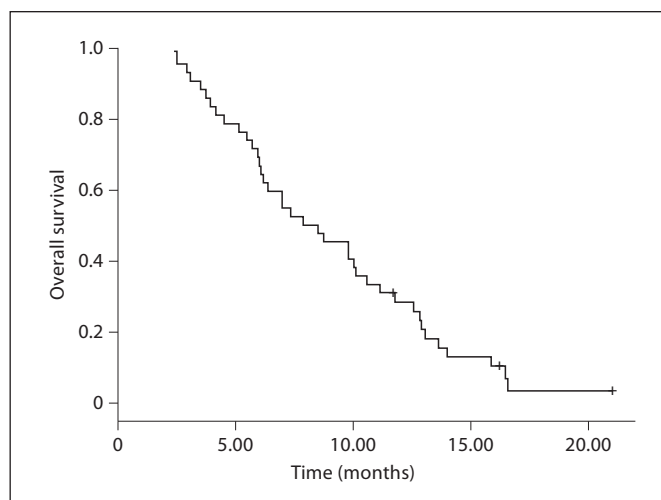


Fig. 1. Kaplan-Meier survival plots for overall survival including all participant (n = 42). The median overall survival was 7.87 months (95% CI 5.14–10.59), and the estimated 1-year survival rate was 26.2%.

Results

Patient Characteristics

The main characteristics of our patient population are summarized in table 1. Most of the patients were old (median age 63 years, range 36–78), with a low body mass index (median 21.8, range 14.8–27.1). Eighteen patients (42.9%) showed poor performance status (ECOG 2–3) at first presentation. Almost all patients initially presented with abdominal discomfort, weight loss and abrupt jaundice. Twenty-three patients (54.8%) chose aRVS treatment as a complementary therapy with chemotherapy or radiotherapy, while 19 patients (45.2%) wanted it as an alternative therapy because of advanced age, poor performance status, anxiety about the toxicity of chemotherapy, or preference for herbal medicine. They were classified by the developed prognostic index (ECOG, primary tumor location and C-reactive protein) of pancreatic cancer into three groups: good, fair and poor [20].

Treatment Outcomes and Safety of aRVS Extract

In May 2011, 39 patients had died and the remaining 3 patients were alive with evidence of disease within a median follow-up period of 8.18 months (range 2.37–21.03). The median overall survival for the entire population was 7.87 months [95% confidence interval (CI) 5.14–10.59], and the estimated 1-year survival rate was 26.2% (fig. 1). The mean aRVS administration period was 3.86 months (95% CI 2.52–5.20). Nineteen (45.2%) patients re-

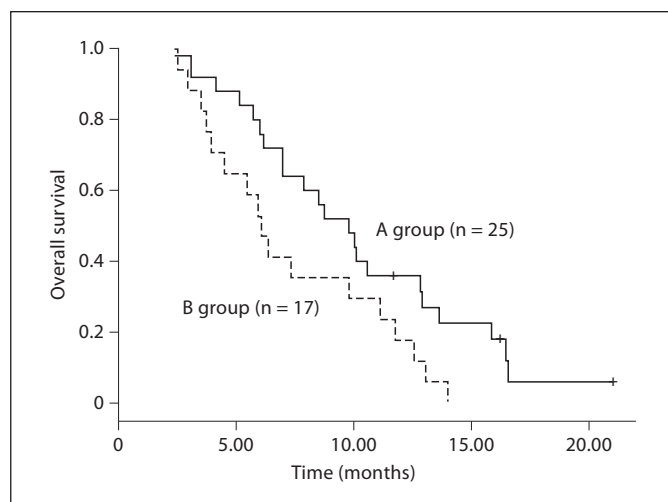


Fig. 2. Kaplan-Meier survival plots for overall survival according to aRVS treatment duration. The median overall survival of aRVS treatment ≥ 30 days (A group) and < 30 days (B group) was 9.80 months (95% CI 7.30–12.30) and 6.07 months (95% CI 4.86–7.28), respectively, which was significantly different by log-rank test ($p = 0.036$).

ceived concurrent palliative chemotherapy. By univariate and multivariate analyses, the performance status, prognostic index and the duration of aRVS treatment were significantly independent prognostic factors for overall survival (table 2). The median overall survival of the group with aRVS treatment ≥ 30 days and the other group was 9.80 months (95% CI 7.3–12.3) and 6.07 months (95% CI 4.86–7.28), respectively ($p = 0.036$; fig. 2). The reasons for receiving aRVS treatment for < 30 days were patient refusal ($n = 7$), preference for other complementary and alternative treatments ($n = 5$), and recommendation of the oncologist concerning drug interaction ($n = 5$). Palliative chemotherapy seemed to prolong overall survival, though this was not statistically proven (8.73 vs. 7.33 months; $p = 0.867$).

All patients in the group with aRVS treatment ≥ 30 days were evaluated for at least 8 weeks to determine clinical benefits, because any change should be maintained for at least 4 weeks. Nine (36.0%) of the 25 patients showed clinical benefit response, which was not dependent on concurrent chemotherapy (table 3). Five patients (38.5%) among the clinical responders were receiving only aRVS treatment and 4 patients (33.3%) received concurrent chemotherapy.

Although hematologic toxicity related to only aRVS treatment was not observed, nonhematologic adverse effects were reported. Mild dyspepsia and pruritus were

Table 2. Univariate and multivariate analyses of clinical factors potentially associated with survival outcome

Factors	Overall survival			
	univariate		multivariate	
	median months	p	HR	p
Age				
≥ 65 years ($n = 16$)	7.33	0.934	2.15 (0.86–5.41)	0.102
< 65 years ($n = 26$)	8.50			
Gender				
Female ($n = 26$)	6.17	0.250	4.68 (1.58–13.80)	0.005
Male ($n = 16$)	10.57			
ECOG				
2–3 ($n = 18$)	5.93	0.041	8.23 (2.54–26.64)	0.001
0–1 ($n = 24$)	9.80			
Body mass index				
≥ 22 ($n = 20$)	6.97	0.334	3.55 (1.31–9.62)	0.013
< 22 ($n = 22$)	9.80			
Weight loss				
$\geq 10\%$ ($n = 18$)	7.33	0.895	2.58 (1.04–6.44)	0.042
$< 10\%$ ($n = 24$)	7.87			
Primary tumor site				
Body-tail ($n = 27$)	6.97	0.492	1.46 (0.51–4.15)	0.476
Head ($n = 15$)	9.80			
Stage				
Metastatic ($n = 34$)	6.97	0.511	1.00 (0.38–2.63)	0.996
Locally advanced ($n = 8$)	10.57			
Prognostic index				
Poor ($n = 3$)	4.13	0.007	13.04 (1.73–98.44)	0.013
Fair ($n = 19$)	9.80			
Good ($n = 20$)	7.87			
Palliative chemotherapy				
No ($n = 21$)	7.33	0.867	2.64 (1.02–6.85)	0.046
Yes ($n = 21$)	8.73			
aRVS treatment, days				
< 30 ($n = 17$)	6.07	0.036	6.55 (2.65–16.23)	0.001
≥ 30 ($n = 25$)	9.80			

Figures in parentheses are 95% CIs. HR = Hazard ratio.

each observed in 1 patient with toxicity grade 1, and these symptoms spontaneously diminished without reducing the dosage of aRVS. Grade 2 pruritus was observed in 1 patient taking oral antihistamines. None of the patients discontinued treatment due to adverse events of aRVS extract alone. Specific drug interactions between aRVS and concurrent chemotherapy agents were not reported in any of the 21 patients (table 4). Among the patients treated with aRVS and concurrent chemotherapy, 4 patients (19.0%) with grade 3 or 4 toxicity required discontinua-

Table 3. Clinical response in the group with aRVS treatment ≥ 30 days (25 patients)

Score	aRVS treatment only (n = 13)	Concurrent chemotherapy (n = 12)	p
Pain			
Positive	3 (12.0)	3 (17.6)	0.804
Stable	7 (28.0)	5 (29.4)	
Negative	3 (12.0)	4 (23.5)	
Performance status			
Positive	1 (4.0)	0	0.618
Stable	9 (36.0)	9 (52.9)	
Negative	3 (12.0)	3 (17.6)	
Weight			
Positive	4 (16.0)	1 (5.9)	0.322
Non-positive	9 (36.0)	11 (64.7)	

Figures in parentheses are percentages.

Table 4. Concurrent chemotherapy regimens with aRVS treatments and treatment lines (21 patients)

	First-line regimen	Second-line regimen	Third-line regimen
Gemcitabine-based chemotherapy	21		
FOLFOX or oxaliplatin/S-1		4	
FOLFIRI		1	1
S-1			2
Paclitaxel		1	
Not available		5	

tion of gemcitabine. One patient had grade 4 neutropenia and then developed pneumonia after 1 cycle of gemcitabine. Two patients experienced grade 4 neutropenia after 1 cycle of gemcitabine or gemcitabine combined with capecitabine. One patient with grade 3 toxicity complained of nausea and vomiting after 1 cycle of gemcitabine combined with capecitabine. All other toxicities were mild (grade 1 or 2), expected and reversible.

Discussion

Gemcitabine has been regarded as the standard chemotherapy for advanced pancreatic cancer since 1997 [17]. Many clinical trials have been performed worldwide in an attempt to improve survival by comparing gem-

citabine with other cytotoxic or biological agents, either alone or in combination with gemcitabine. Although gemcitabine combined with capecitabine or erlotinib has been shown to be statistically effective, it is debatable whether this improvement is clinically significant [2, 3].

Standardized aRVS extract 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 [11]. 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 [12]. 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 [21]. These findings suggested that aRVS might be a potential candidate for the treatment of cancer metastasis. Recently, the median overall survival was reported to be 8.4 months, with a 1-year survival of 40% by aRVS treatment in 40 patients with previously treated advanced non-small-cell lung cancer [22].

In this study, we evaluated the clinical feasibility of the standardized aRVS extract as a potential therapeutic agent for patients with advanced or metastatic pancreatic adenocarcinoma. The median overall survival was 7.87 months (95% CI 5.14–10.59), which is consistent with the median survival of 5–7 months for gemcitabine in many clinical trials [3]. The median survival of 9.80 months (95% CI 7.30–12.30) in the group with aRVS treatment ≥ 30 days was superior to that of control groups, including other gemcitabine-based clinical trials. Thirteen of the patients (52.0%) could not receive conventional therapies because of advanced age and poor performance status. Nonetheless, their median survival of 7.87 months (95% CI 4.66–11.08) suggests that aRVS might be an alternative treatment, especially in patients who could not receive conventional therapy. Unfortunately, the efficacy could not be evaluated by a criterion other than overall survival and clinical benefit, such as progression-free survival, because most of our patients were inclined to refuse further radiological evaluation, and the duration of follow-up checks varied between cases.

As a new strategy, gemcitabine combined with naturally occurring nontoxic flavonoid compounds has been reported to overcome tumor cell resistance to apoptosis without increasing toxicity [23–27]. Chemoresistance of pancreatic carcinoma cell lines is associated with two an-

tiapoptotic signal transduction pathways, PI3K/Akt and nuclear factor- κ B (NF- κ B), which are believed to be attractive targets for cancer treatment [28]. RVS has been reported to induce apoptosis by inhibition of the PI3K-Akt/protein kinase B pathway in human gastric cancer cells but not in normal cells [29]. Fisetin was found to have apoptotic, antiproliferative and anti-invasive effects in chemoresistant human pancreatic cancer cells by modulating DR3 receptor-mediated downregulation of the NF- κ B signaling pathway [30]. Sulfuretin (3',4',6-trihydroxyaurone) from RVS and the phenolic-rich fraction from RVS also suppressed the NF- κ B transcriptional activity [31, 32]. A purified flavonoid fraction prepared from RVS was found to have effective antiproliferative and apoptotic activities on various tumor cell lines including human lymphoma, breast cancer, osteosarcoma and transformed hepatoma cells [4, 5, 33, 34]. Among these compounds, butein (3,4,2',4'-tetrahydroxychalcone) and sulfuretin are also suggested to have therapeutic value in suppressing cancer growth [35]. However, a synergistic effect of gemcitabine and aRVS extract was not observed in our study.

The aRVS treatment was very tolerable, showing only minor nonhematologic adverse effects of pruritus and dyspepsia in 3 patients. None of the patients discontinued aRVS treatment due to drug-related adverse events. Therefore, aRVS extract could be administered to the patients for whom chemotherapy is unavailable and it could

be combined with chemotherapy without increasing toxicity. Specific drug interaction with chemotherapeutic agents was not observed, though 21 cases are too few to determine the safety of aRVS with concurrent chemotherapy. In vitro studies showed that aRVS does not inhibit cytochrome (CYP) isoforms such as CYP3A4 and CYP2D6, the major human CYP enzymes responsible for metabolizing a large majority of currently known drugs [36]. However, further investigations are necessary regarding the interaction of aRVS with various chemotherapy regimens.

In conclusion, this study shows that aRVS treatment is well tolerated in advanced pancreatic cancer patients for whom conventional therapy is unavailable and might prolong overall survival either alone or in combination with chemotherapy. Our results also encourage the study on the chemosensitive effect of aRVS extract or its flavonoids due to low toxicity and a different mechanism of action from conventional chemotherapeutic agents. Additional randomized and well-controlled multicenter clinical trials involving large populations are necessary to evaluate its efficacy and safety in the treatment of pancreatic cancer.

Disclosure Statement

The authors declare that they have no competing interests.

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