Pilot Study of a Specific Dietary Supplement in Tumor-Bearing Mice and in Stage IIIB and IV Non-Small Cell Lung Cancer Patients

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Abstract: Previously, a specific dietary supplement, selected vegetables (SV), was found to be associated with prolonged survival of stage III and IV non-small cell lung cancer (NSCLC) patients. In this study, several anticancer components in SV were measured; the anticancer activity of SV was assessed using a lung tumor model, line 1 in BALB/c mice. SV was also used in conjunction with conventional therapies by stage IIIB and IV NSCLC patients whose survival and clinical responses were evaluated. A daily portion (283 g) of SV was found to contain 63 mg of inositol hexaphosphate, 4.4 mg of daidzein, 2.6 mg of genistein, and 16 mg of coumestrol. Mouse food containing 5% SV (wt/wt) was associated with a 53–74% inhibition of tumor growth rate. Fourteen of the 18 patients who ingested SV daily for 2–46 months were included in the analyses; none showed evidence of toxicity. The first lead case remained tumor free for >133 months; the second case showed complete regression of multiple brain lesions after using SV and radiotherapy. The median survival time of the remaining 12 patients was 33.5 months, and one-year survival was >70%. The median survival time of the 16 “intent-to-treat” patients (including ineligible patients) was 20 months, and one-year survival was 55%. The Karnofsky performance status of eligible patients was 55 ± 13 at entry but improved to 92 ± 9 after use of SV for five months or longer (p < 0.01). Five patients had stable lesions for 30, 30, 20, 12, and 2 months; two of them, whose primary tumor was resected, used SV alone and demonstrated an objective response of their metastatic tumors. In addition to the two lead cases, eight patients had no new metastases after using SV. Three patients had complete regression of brain metastases after using radiotherapy and SV. In this study, daily ingestion of SV was associated with objective responses, prolonged survival, and attenuation of the normal pattern of progression of stage IIIB and IV NSCLC. A large randomized phase III clinical trial is needed to confirm the results observed in this pilot study.

Introduction

Carcinoma of the lung is the leading cause of cancer-related deaths in North America (1). Stage IIIB and IV non-small cell lung cancer (NSCLC) is poorly responsive to systemic treatments (2–4). The generally accepted median survival time (MST) of stage IV patients is 3–5 months with supportive care and 8–15 months with recently introduced chemotherapy protocols, which have considerable toxicities (2–6).

Many edible plants contain components with anticancer activities (7–26). Some, such as inositol hexaphosphate (IP₆), daidzein, genistein, and coumestrol, have been purified and shown to have different modes of action, but their individual anticancer activities are modest (18–26). The potential benefit of using a mixture of vegetables known to contain anticancer components in multimodal cancer treatment has received little, if any, attention. This approach was initiated for a stage IV NSCLC patient whose primary tumor was previously resected. She remains alive and tumor free for 11 years after daily ingestion of selected vegetables (SV) for 3 months followed by an additional surgery and a 24-month regimen of adjuvant SV therapy. Subsequently, another NSCLC patient with three metastatic brain lesions achieved complete regression with radiotherapy and daily SV ingestion and survived 14 months. These cases led to the hypothesis that SV may contribute to prolonging the survival of stage IV NSCLC patients.

In a prior independent prospective controlled study, the anticancer efficacy and toxicity of SV were evaluated with stage III and IV NSCLC patients; the MST of the SV-treated
group was threefold longer than that of the control group without any detectable toxicities (27). In the present study, several anticancer components in SV were evaluated quantitatively and its antitumor activity was tested in a murine lung tumor model. The clinical responses and survival of 18 stage IIIB and IV NSCLC patients who used SV as an adjuvant therapy are also reported.

Methods

SV Preparation

SV was prepared by Sun Farm (Milford, CT) employing “the good manufacturing practices” to minimize contamination with heavy metals and bacteria (28). The ingredients of SV include soybeans, mushrooms, mung beans, red dates, scallion, garlic, lentils, leek, Hawthorn fruit, onion, ginsengs, angelica root, licorice, dandelion root, senegal root, ginger, olive, sesame seeds, and parsley. The mix was blended, boiled, and then stored frozen at 20°C and thawed at room temperature before use. This preparation of SV is essentially identical to that used in a previous study (27), except the latter was freeze-dried.

Nutritional Data and Toxicity

Random samples of SV were sent to Northeast Laboratory (Berlin, CT) for analysis of nutritional value, heavy metals, and bacteria as described previously (27).

 Phytoestrogens

The assay was modified from that described by Franke and co-workers (29). Freeze-dried SV (DSV, 1 g) was dispersed in 50 ml of HCl-ethanol-butylated hydroxytoluene (10:40:0.25, vol/vol/vol), refluxed, and filtered, and the filtrate (5 μl) was injected into a high-performance liquid chromatography column (Nova-Pak reverse-phase C18 column, Waters), eluted with a gradient (5–50%) of acetonitrile in water, and washed with 50% acetonitrile for 7.5 minutes. Molar extinction coefficients (20,893 at 250 nm for daidzein, 37,154 at 263 nm for genistein, 22,300 at 339 nm for coumestrol) were used for quantitative determination. The average and standard deviations of six batches of SV are reported.

 Inositol

IP6 was determined according to the method of Ellis and colleagues (30), designed to determine IP6 in the presence of high inorganic phosphate of dry samples of feed or grain. IP6 was extracted from DSV (5 g) by incubation with 10 ml of 0.333 N HCl containing 10% Na2SO4 for two hours, filtered, and diluted with deionized water (1:1, vol/vol). IP6 forms a stable complex specifically with ferric iron (0.4% FeCl3) in dilute acid solution (0.167 N HCl). The complex was sedimented by centrifugation at 10,000 g for 10 minutes, washed twice in the same buffer, and acid hydrolyzed to release phosphate, which was quantitatively determined (30). The average and standard deviation of six batches of SV are reported.

Mouse Lung Tumor Model

Four-week-old BALB/c male mice were divided into groups of five (Experiment I) or eight (Experiment II) mice. Mice in each group were fed one food preparation one week before tumor inoculation and during the entire study period. BALB/c line 1 lung tumor cells (10^4 cells, viability >90%) were injected subcutaneously in the right thigh (31). Tumor size was measured every two to four days. For Experiment I, Group 1 was fed Lab Chow powder mixed with water, made into pellets, and air-dried; Groups 2, 3, and 4 were fed pellets prepared in a similar fashion, except the Lab Chow powder was mixed with hot water extracts of mung beans or shiitake mushrooms (Lentinus erodes) or both. Thus these pellets contained 10% (by wt) mung bean extract—90% Lab Chow (Group 2), 10% shiitake extract—90% Lab Chow (Group 3), or 10% mung bean extract—10% shiitake extract—80% Lab Chow (Group 4). For Experiment II, Lab Chow powder was used alone (Group 5, control) or mixed with DSV powder (Group 6, 5% wt/wt). Food consumption per group was measured weekly.

Clinical Study Design

Sixteen patients with knowledge of the lead cases requested SV as a nutritional supplement and volunteered their participation. The study period was 60 months, from February 1992 to January 1997. Patients were treated with conventional therapies selected by their physicians and added SV to their daily diet. Their clinical status was monitored by their physicians and verified by the authors. Only 14 patients who ingested SV daily for two months or longer were included in the study group. Karnofsky performance status (KPS) was ascertained and recorded before the use of SV and five months later (32). The four patients who were unable to ingest SV at full dosage and also for less than two months were considered ineligible (Table 1). For conservative evaluation, two separate survival analyses, one including and one excluding these four patients, are presented and compared. Patients 1 and 2 provided retrospective data and were not included in the survival time analyses. Patient 3 had multiple recurrent lesions in both lungs, but these were not biopsied. Thus separate survival time analyses, including and excluding Patient 3, were made.

Diagnosis and Staging

All the patients were diagnosed in their local hospitals (see Appendix). The pathological slides were reviewed by the pathologist (TMF) and radiographs by the radiologists (YPH and H-CY). The International System for Staging Lung Cancer was used (3,4).
<table>
<thead>
<tr>
<th>Gender</th>
<th>Age, yr</th>
<th>Stage: T.N.M.</th>
<th>Cell Type</th>
<th>Metastatic Site</th>
<th>Treatments</th>
<th>Tumor Response</th>
<th>Other Complications</th>
<th>New Tumor After SV</th>
<th>KPS</th>
<th>Time, mo</th>
<th>Survival</th>
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<tr>
<td>Patient 1</td>
<td>F</td>
<td>69</td>
<td>IV:2.2.1</td>
<td>Lrg, large cell carcinoma</td>
<td>Adrenal</td>
<td>S</td>
<td>C, R, SV, SMANCS, S</td>
<td>No residual tumor</td>
<td>No</td>
<td>No</td>
<td>40</td>
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<tr>
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<td>F</td>
<td>75</td>
<td>IV:2.1.1</td>
<td>Adn, adenocarcinoma</td>
<td>Brain</td>
<td>S</td>
<td>SV, R, SMANCS</td>
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<td>57</td>
<td>IV:1.3.1</td>
<td>Adn, adenocarcinoma</td>
<td>Both lungs</td>
<td>S</td>
<td>SV</td>
<td>Partial</td>
<td>No</td>
<td>No</td>
<td>50</td>
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<td>F</td>
<td>73</td>
<td>IV:1.3.1</td>
<td>Adn, adenocarcinoma</td>
<td>Both lungs</td>
<td>S</td>
<td>SV</td>
<td>Partial</td>
<td>No</td>
<td>No</td>
<td>90</td>
</tr>
</tbody>
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**Objective response of metastatic tumors and no recurrent tumor after SV alone**

| Patient 5 | F | 80 | IV:4.2.1 | Adn, adenocarcinoma | Vert, pleural eff | R | R, SV | Stable/prog | No | No | 50 | 90 | >46 | 0 | >48 alive |
| Patient 6 | M | 67 | IIIB:4.2.0 | NSC, non-small cell carcinoma | Pleural eff | No | PD, SV, R, C | Partial | Nerve injury | Yes | 50 | 90 | 43 | 0 | 45 |
| Patient 7 | F | 34 | IIIB:2.3.0 | NSC, non-small cell carcinoma | Cont ral n | S | C, SV, R | No residual tumor | No | No | 50 | 100 | >32 | >30 | >33 alive |
| Patient 8 | F | 78 | IIIB:4.0.0 | NSC, non-small cell carcinoma | Pleural eff | S | R, C, SV | Stable | Pneumonia | No | 50 | 100 | >21 | >20 | >28 alive |
| Patient 9 | M | 69 | IV:2.0.1 | Adn, adenocarcinoma | Brain, bone | S | R, SV | Complete | No | Yes | 50 | 100 | 16 | NA | 22 |
| Patient 10 | F | 51 | IV:1.2.1 | Adn, adenocarcinoma | Brain | S, C, R, SV, R | No residual tumor | Depression | Yes | 50 | 90 | 14 | NA | 20 |
| Patient 11 | F | 59 | IV:1.1.1 | Adn, adenocarcinoma | Brain | No | SV, R | Stable/prog | Vein thromboses | No | 50 | 90 | 10 | 0 | 11 |
| Patient 12 | M | 58 | IV:2.3.1 | Adn, adenocarcinoma | Adrenal | S, C, SV, C | Stable/prog | Heart | Yes | 60 | 70 | 9 | 0 | 12 |
| Patient 13 | F | 76 | IIIB:4.3.0 | Adn, adenocarcinoma | Pleural eff | S | C, R, SV | Complete | No | No | 50 | 100 | 5 | 2 | >8 alive |

**Complete response, partial response, or stabilization of metastatic tumor after SV and other treatments**

| Patient 14 | F | 47 | IIIB:4.3.0 | Adn, adenocarcinoma | Pleural eff | C | C, SV | Complete | NA | NA | 50 | 50 | 5 | 0 | 6 |
| Patient 15 | M | 40 | IIIA:1.2.0 | Adn, adenocarcinoma | C, R, SV | SV | SV | 50 | 1.5 | 10 |
| Patient 16 | M | 56 | IV:4.0.1 | Squa m, squamous cell carcinoma | Vertebral c | R | R, SV | 40 | 1.4 | 5 |
| Patient 17 | M | 64 | IV:4.0.1 | Adn, adenocarcinoma | Brain, bone | S, C | SV | 40 | 0.2 | 6 |
| Patient 18 | M | 57 | IV:4.0.1 | Adn, adenocarcinoma | Spine, rib | C | R, SV | 40 | 0.5 | 3 |

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*a*: Lrg, large cell carcinoma; NSC, non-small cell carcinoma; Adn, adenocarcinoma; Sqm, squamous cell carcinoma.

*b*: Pleural eff, pleural effusion; Vert, vertebrae; V, vein; contral n, contralateral node.

*c*: S, surgery; C, chemotherapy; R, radiotherapy; PD, pleurodesis; SV, selected vegetables; SMANCS, neocarcinostatin conjugated with a polystyrene-maleic acid copolymer.

*d*: No residual tumor, patient had no detectable tumor subsequent to surgical resection; complete, complete regression; stable, tumor stopped growing; stable/prog, tumor was stable and then progressed; partial, partial regression.

*e*: Karnofsky performance status. Patients 1, 2, 3, and 14 were not included: Patients 1 and 2 were lead cases; multiple lesions in both lungs of Patient 3 were not biopsied. Patient 14 was adversely affected by concurrent chemotherapies. Average KPS of Patients 4–13 was 55 ± 13 at start of SV and 92 ± 9 at ≥5 mo of SV use.

*f*: Patient 2 had severe malnutrition due to loss of appetite during SMANCS therapy and died from aspiration pneumonia.

*g*: Patient 3 had a lobectomy and histologically documented adenocarcinoma. Her 42 recurrent lesions in both lungs were not biopsied. She was excluded from KPS analysis.

*h*: Patient 4 had 34 recurrent lesions in both lungs, of which 3 were resected and documented histologically as adenocarcinoma.

*i*: Patient 6 suffered severe pain due to thoracic nerve injury during a pleurodesis procedure. He was treated with Elavil, ibuprofen, atenolol, fentanyl, Decadron, and bupivacaine.

*j*: Patient 7 had severe malnutrition due to loss of appetite during SMANCS therapy and died from aspiration pneumonia.

*k*: Patient 11 suffered from deep vein thromboses and was treated with Decadron and phenobarbital after her tumor stabilized.

*l*: Patient 12 had coronary artery bypass surgery before his diagnosis of non-small cell lung cancer.

*m*: Patient 15 was at stage IIIA; Patients 15–18 ingested SV at less than full dosage and for <2 mo.

*n*: NA, data not available.
Statistical Analyses

Three populations of patients were analyzed: 1) study group or SV group (Patients 3–14, Group B; Table 1), 2) the same as Group B, except Patient 3 was excluded (Patients 4–14, Table 1), and 3) intent-to-treat patients, i.e., all participating patients, both the study group (Patients 3–14) and ineligible patients (Patients 15–18, Group C; Table 1). The survival time was calculated from the date of diagnosis of stage IIIB or IV NSCLC to the date of death or the cutoff date.

MST: The MST was calculated according to Kaplan and Meier (34). For comparison with historical controls, survival data for inoperable advanced NSCLC patients were obtained from a meta-analysis and are regraphed in Figure 3; the historical MSTs of the supportive care group and chemotherapy + supportive care group were 4 and 6.5 months, respectively (35).

Mean survival time: The nonparametric Wilcoxon signed-rank test can also be used to analyze the mean survival time of small sample sizes (36). The historical mean survival time of inoperable advanced NSCLC patients was assumed to be 7 months, which is longer than the 6.5-month MST of the patients treated with chemotherapy and supportive care (35) and the 4.8-month mean survival time of the control group in a previous study (27). For conservative evaluation, the time of SV use (Table 1) was assumed to be the censored time or the survival time. For example, Patient 3 ingested SV for >35 months; her censored time or survival time was assumed to be 35 months, even though she survived >39 months at the close of the study (Table 1). The mean survival times of Patients 4–14, 3–14, and 3–18 were calculated. The following hypotheses were tested: $H_0$: (mean survival time) = 7 months (historical value) = 0; $H_1$: (mean survival time) – 7 months > 0.

Ingestion of SV

SV is a dark brown paste with a slightly sweet taste. Patients ingested 10 ounces of SV (~283 g) daily as part of breakfast or lunch alone or mixed with other foods.

Materials

All chemicals were reagent grade. Genistein, daidzein, inositol, IP$_5$, butylated hydroxytoluene, and O-toluidine were obtained from Sigma Aldrich Chemical (St. Louis, MO); coumestrol, acetonitrile, acetic acid, trichloroacetic acid, and thiourea were obtained from Fisher Scientific (Pittsburgh, PA). Purina laboratory chow powder was acquired from Purina Mills (Richmond, IN). BALB/c mice were obtained from Charles River Laboratories (Wilmington, MA).

Informed Consent

All patients were informed of the ingredients in SV and that these ingredients have been used widely as foods or food flavors. They used SV daily as a food supplement and gave written permission to the authors to obtain and review their medical records and to include their clinical data in the study.

Results

Nutritional Value and Hazardous Contaminants of SV

The following components were measured in SV (mg/283 g SV daily dosage): IP$_5$ (63 ± 0.6), genistein (2.6 ± 0.1), daidzein (4.4 ± 0.1), and coumestrol (15.5 ± 0.4).

Anticancer Components in SV

In Experiment I, tumor size was measured on the 10th, 12th, 14th, 17th, and 22nd days after the inoculation of tumor cells (Figure 1A). The percent inhibition of tumor growth rate in Groups 2, 3, and 4 compared with the control (Group 1) were 16%, 49%, and 82% on the 14th day and 53%, 60%, and 82% on the 22nd day, respectively. Mung bean (Group 2) and mushroom extract (Group 3) showed clear inhibition of tumor growth, and these effects were additive when both extracts (Group 4) were used in combination. In Experiment II, tumor size was measured on the 14th, 16th, 19th, 21st, and 23rd days after tumor inoculation (Figure 1B). Laboratory chow containing 5% DSV produced 53–74% inhibition in tumor growth rate in the first 23 days. One of eight mice showed partial tumor regression after 26 days and complete regression after 32 days. The weekly food consumption per mouse in Groups 1–6 was 16.9 ± 1.4, 18.9 ± 0.8, and 16.0 ± 0.6 g in the first, second, and third week, respectively, after tumor inoculation. No appreciable difference between groups was found.

Patient Characteristics

The patients’ gender, age, stage, cell type, metastatic sites, conventional treatments for the primary tumor and subsequent treatments for metastatic lesions, tumor response, complications, and KPS are summarized in Table 1. Occurrence of metastatic disease after ingestion of SV, the time of SV use, the duration of tumor-free status, and survival are also summarized in Table 1.
Lead Cases

**Patient 1:** A stage IV patient whose tumor progressed while on chemotherapy and radiotherapy has been tumor free for >133 months after ingestion of SV, therapy with the anticancer protein neocarcinostatin conjugated with a polystyrene-maleic acid copolymer (SMANCS) (38), and resection of a metastatic lesion.

Patient 1 had a poorly differentiated large cell carcinoma in her right lower lobe (2.2 × 2 cm) with a positive subcarinal lymph node (Table 1). A lobectomy in January 1985 was followed with methotrexate, adriamycin, N-(2-chloroethyl)-N’-cyclohexyl-N-nitrosamine, and cyclophosphamide therapy. Her disease progressed with metastasis to the left adrenal gland (4 × 3 cm, August 1985), a right pleural effusion developed, and her KPS dropped to 40. Her adrenal tumor did not respond to radiotherapy and continued to grow (5 × 4 cm, November 1985). She began ingesting SV daily from September 1985. She was also treated with SMANCS and had an adrenalectomy in December 1985. The adrenal tumor was well encapsulated and contained mostly necrotic tissue. She continued SMANCS therapy for four months and ingested SV daily until December 1987. She remains tumor free.

**Patient 2:** Patient 2 experienced complete regression of three metastatic brain tumors.

Patient 2 had a well-differentiated adenocarcinoma in the right upper lobe and a lobectomy in March 1986. In October 1986, a computerized tomography scan showed three metastatic brain lesions (Figure 2). KPS was 40. She started SV, SMANCS, and a one-month course of radiotherapy. All three tumors disappeared completely in four months (Figure 2). She continued SV and SMANCS therapy until June 1987. During this time, she lost her appetite and developed severe malnutrition; she developed aspiration pneumonia and sepsis and died in December 1987 without clinical signs of tumor recurrence.

Study Group

**MST:** Patient 3 had a lobectomy and histologically documented adenocarcinoma of the lung. Her recurrent multiple lesions in both lungs were not biopsied. Thus the MST was determined with and without Patient 3 (Figure 3). The MST of Patients 4–14 was 45 months, according to Kaplan and Meier (34). The 95% confidence interval had a lower boundary of 12 months and no upper boundary. If Patient 3 is included, the MST was still 45 months, and the 95% confidence interval also had a lower boundary of 12 months and no upper boundary. With or without Patient 3, a conservative estimate of 33.5 months, which is the midpoint of the survival curve immediately above the median, i.e., between 22 and 45 months, was chosen as the MST (Figure 3). In either case,
one-year survival was >70%. In the intent-to-treat group (Patients 3–18), the MST was 20 months; the 95% confidence interval had a lower boundary of 10 months and no upper boundary (Figure 3). One-year survival was 55%.

**Mean survival time:** The mean survival times of Patients 4–14, 3–14, and 3–18 are 23.7, 25, and 20.25 months, respectively. The (mean survival time – 7 months) values of these groups of patients are 16.7, 18, and 13.3 months. The \( P \) values for the differences between \( H_0 \) and \( H_1 \) for these three groups of patients were <0.01, indicating that the mean survival times of these three groups are significantly different from the historical mean survival time.

**New tumors:** Ten (Patients 1–5, 7, 8, and 11–13; Table 1) of the 13 patients (Patients 1–13) had no new sites of metastasis after conventional treatments and SV therapy. Patient 14 suffered severe side effects from concurrent chemotherapy and was not evaluated for new tumors.

**SV therapy alone:** Patients 3 and 4 had objective regression of multiple lesions in both lungs after using SV alone.
for 5 and 15 months, and their remaining lesions have been stable 39 and 28 months after diagnosis. With SV alone, the pulmonary and vertebral body lesions of Patient 5 were stable for 40 months and subsequently progressed slowly; she was still alive at the conclusion of the study. The multiple intra-thoracic lesions of Patient 6 had been stable for 30 months while he used SV alone (Table 1).

**SV and radiotherapy:** Of the four patients who had brain metastases, three (Patients 2, 9, and 10) achieved complete regression after SV and radiotherapy. Lesions in brain and bone of Patient 9 regressed completely after radiotherapy (Figure 4). Patient 11 had radiotherapy to her left cerebellar brain lesions; her primary tumor and the multiple lesions in her brain stem remained stable without radiotherapy for 10 months while using SV alone.

**Toxicity and performance status:** Patients ingested SV daily for up to 46 months (Table 1). The condition of Patient 14 was adversely affected by concurrent chemotherapies; she was excluded from toxicity analysis. No patient in the cohort (Patients 3–13) showed any toxic complications attributable to SV. Their blood chemistry values revealed no compromise in hematologic, renal, hepatic, and metabolic function; all patients showed a significant improvement in KPS after ingesting SV for five months (Table 1). Since recurrent multiple lesions of Patient 3 were not biopsied, she was excluded from KPS analysis also. The average KPS of Patients 4–13 increased from 55 ± 13 to 92 ± 9 \( (p < 0.05) \).

**Discussion**

The present report describes the pursuit of unexpected clinical observations followed by evaluation with traditional methods. The benefits of fruits and vegetables for cancer prevention have been emphasized by the National Cancer Institute and the American Cancer Society (39); increased consumption of fruits and vegetables may contribute to the recent reductions in cancer rates and cancer-related deaths. The current study provides data suggesting that a mixture of edible plants, specifically selected for their anticancer attributes, may benefit patients who already have advanced cancer. In the initial characterization of the anticancer attributes of SV, only four anticancer components have been quantified to date. Whether the anticancer efficacy of SV is due to some other known or as yet unknown anticancer agents in SV or to synergistic interactions of these agents remains to be clarified.

The MST of stage IIIB and IV NSCLC has changed little in recent decades. Therefore, historical controls can be used to provide comparison for the results observed here (40). In a meta-analysis of clinical trials of chemotherapy vs. supportive care for advanced NSCLC, the MST was 4 months for the supportive care group and 6.5 months for the chemo-
Figure 4. Top: right cerebellar metastasis of Patient 9. A: postcontrast CT scan in superior orbitomeatal plane taken on 17 December 1992. An enhancing metastatic lesion (T, 1.5 × 1.2 cm) is located in quadrangular lobule of cerebellum on right side with considerable edema (low-density zone) of surrounding area, particularly anteromedially. Fourth ventricle (4) is displaced anteriorly and to left. Vermis (V) is also displaced to opposite side. Posterior fossa cisterns are narrow on right (unlabeled double arrow). B and C: post-gadolinium magnetic resonance (MR) section in exaggerated inferior orbitomeatal plane taken on 16 June 1994. Because of considerable difference from A in sectional angles, 2 consecutive MR sections (B and C) were selected to amply cover original site of cerebellar metastasis. Enhancing tumor attenuated and is no longer detectable in post-gadolinium axial MR T1-weighted image. Unlabeled single arrow in 2 consecutive MR images indicates presumptive location of original cerebellar metastatic lesion in A. Fourth ventricle and vermis have returned to their normal positions. Edema surrounding tumor seen before treatment is not observed. Bottom: radiograph of left scapula of Patient 9. A: mixed osteoblastic and osteolytic lesion (arrowheads) in inferior aspect of glenoid process due to metastatic cancer. B: much improvement in glenoid process lesion 12.5 mo later. [Note added in proof: The scapular lesion (bottom, A) is more clearly visualized in the original radiograph.]
therapy groups (35). The MSTs were reported to be 8–15 months using recently introduced chemotherapy protocols, which showed considerable toxicities (5,6). In this study, the MST for the patients who used SV for ≥2 months was 33.5 months without any detectable toxicities. The MST of the “intent-to-treat” group was 20 months. The sample size was small, but all patients had advanced disease; some patients showed objective responses to SV.

NSCLC patients with central nervous system (CNS) metastases have an MST of three to four months with radiotherapy, and complete regression is rare (41–43). Of four patients with CNS involvement, three (Patients 2, 9, and 10) had complete remission of CNS lesions and the fourth (Patient 11) had a partial response after radiotherapy and SV use. The complete regression of metastatic tumors in brain and bone (Patient 9) and multiple brain lesions (Patient 2) is unexpected. Recurrence of malignant pleural effusions and new metastases are common in stage III–IV patients (Refs. 2 and 3); 10 of 13 patients (Patients 1–13) developed new metastatic sites during this study period.

Patient selection bias is a major consideration in clinical trials. It is essential to consider sources of potential bias, especially when clinical outcomes differ markedly from historical controls. Attempts were made to minimize the potential bias in patient selection. Four patients (Patients 15–18) were unable to ingest an adequate dose of SV or vomited after they tried to eat SV. They were considered ineligible because they did not ingest sufficient amounts of SV; their survival times (3–10 mo) were within the expected historical range. They were, however, included in the intent-to-treat group for survival analyses. Furthermore, most patients reported here had already failed to respond to conventional treatments. Their KPS scores, except for Patient 4 at 90 and Patient 12 at 60, were 40 or 50 at entry. In most clinical trials, eligible patients must have a KPS ≥70 or an Eastern Oncology Cooperative Group score of ≤2 (5,6,41, 42,45,46,48,49). Therefore, the health status of these patients at entry was poorer than that of patients in most clinical trials. Other possible biases could result from the self-selection of highly motivated patients who sought new treatments after failing to benefit from conventional therapies and who were willing to make a commitment to daily SV use often with strong family support. Whereas patient compliance may be related to treatment efficacy, psychological factors alone are unlikely to result in a threefold increase in MST or in objective tumor regression and improved KPS in patients using only SV. This view is consistent with that of Cassileth and co-workers (44), who reported that clinical factors (e.g., stage, KPS, weight loss), but not psychosocial factors (e.g., “hopefulness”), could be considered predictors of survival. Thus the potential invalidation of the present findings by patient selection bias was minimized by the objective responses of tumor and KPS to SV, inclusion of ineligible patients in the survival analyses, attenuation of the normal pattern of progression of stage IIIB and IV NSCLC, and the low KPS (score of 40–60) at entry of most patients who already failed to respond to conventional treatments. The inhibition of tumor growth and objective response to SV observed in the mouse model (Figure 1) further support the hypothesis that some combination of ingredients in SV may have direct anticancer or immune-modulating activity.

Large clinical trials of advanced NSCLC often have a small number of long-surviving patients (2–6). It could be argued that, by chance or selection bias, such patients were overrepresented in this cohort. This is unlikely because of many instances of poor prognostic status and failed treatment history in this cohort when SV was initiated. Furthermore, tumor regression and improved KPS after use of SV alone are objective responses to SV. The causes of long survival in previous clinical trials have received relatively little attention, although studies of long-surviving patients may yield valuable clues for improved cancer treatment. Among all the possible causes, dietary supplements, which might have been used by some long-term survivors, are widely accessible and some are supported by scientific studies (7–26). The present study provides evidence for the long survival of advanced NSCLC patients who used a specific dietary supplement.

Well-known prognostic indicators for survival in NSCLC include stage of disease, KPS, and weight loss (44–47). KPS values increased from an average of 55 ± 13 to 92 ± 9 in five months after SV use (p < 0.01). In a prior study, the KPS of stage III and IV NSCLC patients in the SV-treated group also improved, but it decreased in the control group (27); similarly, in this study, the MST also improved significantly. Sequential body weight data were not available in the current study. In the prior study, however, the weight change was −2.1 ± 2.3% in the SV-treated group but −11.6 ± 5% in the control group (27). In both studies, blood chemistries revealed no evidence of toxicity in patients ingesting SV daily for 4–46 months. Significantly improved performance status and absence of toxicity are concordant with the prolonged survival times of these patients.

The immunostimulatory and anticancer effects of purified β-glucans (e.g., lentinan, pachymaran, zymosan, schizophyllan, KS-2) have been well documented (7–17). Other studies have identified anticancer actions of soybean components, e.g., protease inhibitors, IPα, coumestrol, daidzein, biochanin A, and genistein (18–26). Four of these components were quantitatively identified in SV; others are reported to be present in the vegetables included in SV. The most abundant ingredients in SV are soybeans, mushrooms, and mung beans. Because Purina laboratory chow already contains soy protein, the anticancer activities of mushrooms and mung beans were tested individually and in combination in tumor-bearing mice. Combining mushroom and mung bean extracts produced the greatest inhibition of tumor growth rate (82%) in the mouse model, indicating that the anticancer effect of these extracts may be additive.

The multiple instances of objective tumor response coupled with increased survival times, attenuation of disease progression, and consistent improvement in performance status indicate that SV therapy, as an adjuvant to surgery and
radiotherapy, should be evaluated further in a large, randomized study of NSCLC patients.

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References


Appendix

For Patient 1, diagnosis and treatment were conducted in Mount Sinai Hospital (New York, NY) and Kumamoto University Hospital (Kumamoto, Japan); for Patient 2 at Tri-Service General Hospital (Taipei, Taiwan), Kumamoto University Hospital, and Kumamoto Junkanki Hospital; for Patient 3 at Caylor-Nickel Medical Center (Bluffton, IN) and North Main Imaging and Diagnostic Center (Dayton, OH); for Patient 4 at North Shore University Hospital, Cornell University Medical College (New York, NY); for Patient 5 at New York Hospital (New York, NY); for Patient 6 at Alta Bates Medical Center (Berkeley, CA); for Patient 7 at University of Washington School of Medicine (Seattle, WA); for Patient 8 at Del E. Webb Memorial Hospital and Sun Health Corp. (Sun City West, AZ) and Robert Janker Klinik (Bonn, Germany); for Patient 9 at Stanford University Hospital and Palo Alto Medical Clinic (Palo Alto, CA); for Patient 10 at Brigham and Women’s Hospital (Boston, MA); for Patient 11 at Alexian Brothers Medical Center (Elk Grove Village, IL); for Patient 12 at North Shore University Hospital (Manhasset, NY) and Memorial Sloan-Kettering Cancer Center (New York, NY); for Patient 13 at Yale New Haven Hospital (New Haven, CT) and Mary A. Marietta Memorial Hospital (Marietta, OH); for Patients 14 and 15 at Massachusetts General Hospital (Boston, MA); for Patient 16 at New York Hospital and Mount Sinai Hospital (New York, NY); for Patient 17 at Memorial Sloan-Kettering Cancer Center (New York, NY); for Patient 18 at Arden Hill Hospital (Goshen, NY).