



Palliative Treatment of Advanced Lung Cancer with Radiotherapy and Thai Herbal Medicine as Supportive Remedy, Analysis of Survival

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Abstract

Objective: To evaluate the outcome of Thai herbal medicine, Vilac Plus (G716/45) on standard palliative radiotherapy for advanced non small cell lung cancer, stage IIIB-IV compared with historic control from the literature reports.

Patients and Methods: Between March 2003-June 2006, thirteen patients of advanced non small cell lung cancer, stage IIIB -IV with poor performance status were treated by palliative radiotherapy in adjuvant with the Thai herbal tonic solution (Vilac Plus G716/45) as supportive remedy. This study was performed at Radiotherapy Division, Department of Radiology, Faculty of Medicine, KhonKaen University, KhonKaen 40002, Thailand. The results were analysed in the aspect of clinical benefit rate of survived patients more than 15 months, median survival time and overall survival rates. The survival curve was estimated by the Kaplan-Meier method.

Results: Thirteen patients (8 male, 5 female) of advanced non small cell lung cancer with poor performance status (Eastern Co-operative Oncology Group 2-3), stage IIIB 11 cases, stage IV 2 cases were treated by palliative radiotherapy in adjuvant with the Thai herbal tonic solution (Vilac Plus G716/45) as supportive remedy. Median age was 66 years (range 44.4 -83 years). The pathological reports were classified to be squamous cell carcinoma (5 cases), adenocarcinoma (2 cases), bronchioalveolar carcinoma (1 case), mixed squamous and adenocarcinoma (1 case). There were 30.77% (4/13 cases) of clinically advanced lung cancer by evidenced of computed tomography chest scan / chest X-ray. The clinical benefit rate of survived patients more than 15 months was 84.62%. The median survival time was 28 months (range 14-74 months). The overall 1, 2, 3, 4 and 5 survival year rates were 100%, 53.85%, 30.77%, 23.08% and 15.38% respectively.

Conclusion: This pilot study was limitation in the aspect of a small number of patients, but all cases were in advanced stages of diseases with poor performance status. The results of this study were promising in the aspect of improving overall survival rates and cost effectiveness. The treatment of cancer patients has many interrelated and confounding factors that have to be sorted out so further research will be necessary.

Key words: advanced lung cancer, palliative radiotherapy, Thai herbal medicine

Introduction

In advanced lung cancer, palliative radiotherapy alone or in combination with the appropriated combination of chemotherapeutic agents are the available methods of treatment with not fully satisfactory results.¹⁻²¹ The disadvantage side effects are not only poor quality of life but also very expensive chemotherapeutic agents. The other modality may be using oral epidermal growth factor receptor (EGFR) inhibitors which have demonstrated anti-tumor activity in advanced non small cell lung cancer (NSCLC) without serious side effects.¹⁷ Both of these agents are very expensive, therefore can not be accessible by the low socioeconomic group of patients.

The reports of antioxidants combined with therapeutic modalities reveal enhancing the therapeutic effects of chemotherapy and/or radiotherapy, decrease side effects, protect normal tissues and also increase survival.²² Most of the studies demonstrate the evidences of synergistic effect of antioxidants and radiotherapy and decrease adverse effect of the therapy.²³

Based on this rationale, the Thai herbal medicine was used as another choice for supportive to the standard palliative radiotherapy in this study. The Thai herbal medicine (Vilac Plus G716/45) was proven to have no acute oral toxicity in animal study.²⁴ No traces of prednisolone and dexametasone were detected.²⁵ An In Vitro study, the Vilac Plus (G716/45) presented an important antioxidant capacity.²⁶ The recipe of the ingredients of the Thai herbal tonic solution consisting of three edible herbs, the whole part of mushroom namely *Ganoderma Lucidum*, *Houttuynia Cordata Thunb* (leaves) and the roots of *Boesenbergia Pandurata Holtt* (Kra chai), all of them have found to be an effective anti-tumor promoting agents.^{27,28}

We therefore conducted a follow-up study to determine whether the survival rates of palliative treatment in advanced NSCLC by using palliative radiotherapy and the Thai herbal medicine as supportive remedy.^{29,30}

Objective

To evaluate the outcome of Thai herbal medicine, Vilac Plus (G716/45) on standard palliative radiotherapy for advanced NSCLC, stage IIIB-IV compared with historic control from the literature reports.

Patients and methods

This study was performed at radiotherapy division, department of radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand. Between March 2003 to June 2005, thirteen patients of advanced NSCLC stage IIIB-IV according to TNM staging³¹ with poor performance status were treated by palliative radiotherapy (tumor doses range 20-60Gy/2-6 weeks) in adjuvant with the Thai herbal tonic solution (Vilac Plus G716/45) daily dose 15-30 cc, orally three time after meal as a supportive remedy.³⁰ Staging procedures were performed by chest oncologist/expert opinions using history, physical examination, routine laboratory evaluations, chest X-ray, bronchoscopic examination included cytology/ biopsy, chest computed tomography scan and bone scan. Inclusion criteria were: (1) advanced stage lung cancer; (2) superior vena cava obstruction; (3) metastatic lung cancer; (4) poor performance status; (5) minimal response of the tumor to standard radiotherapy 30-40 Gy/3-4 weeks; (6) the informed consent has been signed by the patients. Exclusion criteria was the patients to be refuse on this treatment modality.

The results were analyzed in the aspect of clinical benefit rate of survived patients more than 15 months, median survival time and overall 1, 2, 3, 4, and 5 year survival rates. The survival curve was estimated by the Kaplan-Meier method. The procedure of this project has been approved by the Committee of Khon Kaen University Human Ethics (HE 480745).

Radiotherapy Technique³⁰

Results

Thirteen patients (8 male, 5 female) of advanced NSCLC, stage IIIB 11 cases, stage IV 2 cases with poor performance status (ECOG2-3) were treated by palliative radiotherapy in adjuvant with

the Thai herbal tonic solution (Vilac Plus G716/45). The median age was 66 years (range 44.4 -83 years). The pathological reports were classified to be squamous cell carcinoma (5 cases), adenocarcinoma (2 cases), bronchioalveolar carcinoma (1 case), mixed squamous and adenocarcinoma (1 case). There were 30.77% (4/13 cases) of clinically advanced lung cancer by evidenced of computed tomography chest scan /chest X-ray according to poor performance of the patients. (Table 1).

The clinical benefit rate of the survived patients more than 15 months was 84.62%. The survival analysis (Kaplan-Meier survival estimate) revealed median survival time of 28 months (range 14-74 months). It was noted that improving survival

Table 1 Patient characteristics³⁰

Patient characteristics	Cases (%)
Gender	
Female	5 (38.46%)
Male 8 (61.54%)	
Age in years	
Median (range)	66 (44.4-83)
Stage of disease	
Stage III B	11 (84.62%)
Stage IV, 1 case, T4N3M1 (bone metastasis), 1 case, T3N3M1 (contralateral lung metastasis)	2 (15.38%)
Median survival time (range) in months	28 (14-74)
Pathology	
SCC	5 (38.46%)
Adenocarcinoma	2 (15.38%)
Mixed Adeno CA. + SCC.	1 (7.69%)
Bronchoalveolar CA	1 (7.69%)
Clinically advanced lung cancer stage IIIB	4 (30.77%)
- superior vena cava obstruction (1 case)	
- patients refused to perform biopsy (2 cases)	
- bronchoscopy revealed brochogenic mass obstruction but biopsy showed negative of malignancy (1 case).	

time of 59 months in 1 case of metastatic squamous cell carcinoma with superior vena cava syndrome was detected while a case of NSCLC stage III B, poor performance status (ECOG2-3), adenocarcinoma poorly differentiated are still alive of 74 months after diagnosis.

The overall 1, 2, 3, 4, and 5 year survival rates were 100%, 53.85%, 30.77%, 23.08% and 15.38% respectively (Table 2 and Fig 1). There were 2/13 cases of stage IIIB NSCLC survived more than

5 years (1 case of stage IIIB, T3 N2-3 M0, ECOG2-3, adenocarcinoma poorly differentiated while 1 case of clinically stage IIIB lung cancer by expert opinions).

Discussion

Advanced NSCLC patients with poor performance status should generally not be recommended chemotherapy because these patients tend to experience increase toxicity, decrease survival without clinical benefit.¹ The treatment with chemotherapy reveals median survival times approximately 4.2-15 months.¹⁻²¹ The most common site of relapses is in the brain. The median survival times of superior vena cava (SVC) syndrome is approximately 1.2 months -15 months.¹⁹ Treatments of advanced NSCLC by using 3D conformal radiotherapy revealed median survival time of 15.8 months, 1, 2, 3, 4 and 5 year survival rates are 61%, 35%, 23%, 19% and

Table 2 The overall 1, 2, 3, 4 and 5 year survival rates (Kaplan-Meier survival estimate)

Follow up time (year)	Overall survival rates (%)	95% Cont. Int.
1	100	0.2-0.8
2	53.85	0.2-0.4
3	30.77	0.1-0.6
4	23.08	0.1-0.5
5	15.38	0.02-0.4

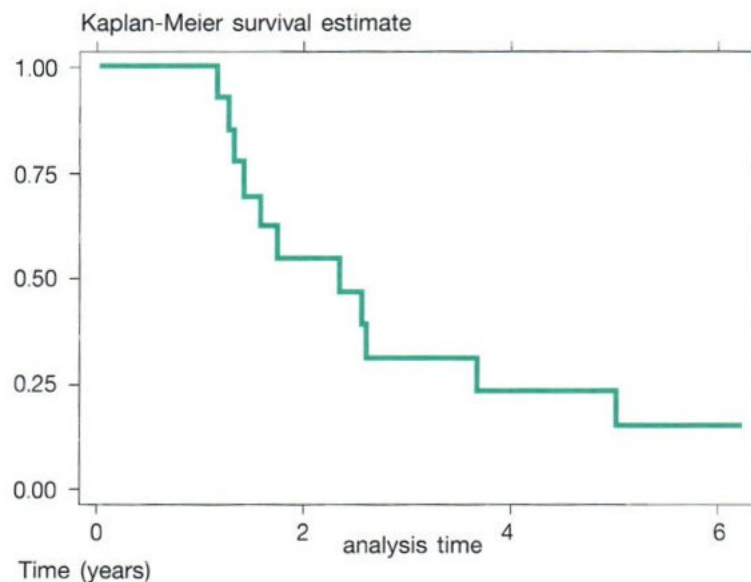


Fig.1 The overall survival curve of advanced NSCLC treated with palliative radiotherapy and Thai herbal medicine as supportive remedy.

17% respectively.¹⁸ The median survival times of palliative radiotherapy for NSCLC are approximately 7-9 months. The 1, 2 year survival rates are 9-28%, 6-18% respectively.¹⁻²¹ There are evidences of radiation esophagitis and radiation myelitis of 17Gy in 2 fractions and 39 Gy in 13 fractions.¹ There is no significant survival difference between brachytherapy combined with external irradiation versus external radiation alone.¹

The enhancing effect of Thai herbal medicine (Vilac Plus G716/45) on radiotherapy to prolong the survival of these patients was very impressive. Our study revealed 84.62% of the clinical benefit rate of the survived patients more than 15 months. The median survival time was 28 months (range 14-74 months) compared with 7 months (range 10-15 months) from historic control.¹⁻²¹ The overall 1, 2, 3, 4 and 5 year survival rates were 100%, 53.85%, 30.77%, 23.08%, and 15.38% respectively compared with 1, 2, and 3 year survival rates of 9-40%, 4.1-18% and 3.3% respectively from historic control.¹⁻²¹ It was noted that improving survival time of 59 months in 1 case of metastatic squamous cell carcinoma with superior vena cava syndrome was detected while a case of stage III B, adenocarcinoma poorly differentiated, ECOG2-3 are still alive of 74 months after diagnosis. The clinical outcomes were shown higher survival rates than historic control suggested to be synergistic results of Thai herbal medicine (Vilac Plus G716/45) on radiotherapy.

The enhancing effect of Vilac Plus[®] on radiotherapy to prolong the survival of these patients can be explained under the principle of antioxidants by anti-tumor effect and normal tissue protection. The Vilac Plus[®] tonic revealed antioxidant potency²⁶ which being concurrently bioavailable in the subcellular level. The hypothesis of radical-

scavenging activity of the tonic against excess free radicals of the radiotherapy may be explained by specific protection on DNA damage of normal cells. This is the key and crucial evidence for scientific explanation upon the mechanism and pharmacological action of our clinical studies, therefore further research deep in detail will be needed.

The ingredients of the Vilac Plus[®] tonic consisting of anti-tumor mushroom, LingZhi (*Ganoderma lucidum*), *Houttuynia cordata*, *Thunb* and *Boesenbergia pandurata* Holtt (Krachai) were demonstrated. The tonic preparation accomplished by fermentation by using *Lactobacillus casei* spp. (Genebank Reg. No. AF 320255) and *Lactobacillus plantarum* spp. (Genebank Reg. No. AF 320256). The promising supportive adjuvants actions contributed from each composition of the 4 ingredients in Vilac Plus[®] including the microorganism used in the fermentation proceedings that should be recognized as the "probiotics" which is one key component in the biotechnology procedure of production. The herbal ingredients are world recognition mushroom, Ling Zhi (*Ganoderma lucidum*) or Reishi, where it has been mentioned as sacred mushroom which has been found the 119 different terpenoids, about 80 of which biologically active.³²⁻³³ The role to be the supportive action in cancer treatment is immunomodulation anticancer by protection DNA damage of normal cell through its powerful antioxidant mechanism and inhibition of tumor necrosis factor (TNF). There are a number of reports that have mentioned the benefit on various cancers.^{34,35}

The other herbs are the edible plants, *Houttuynia cordata* Thunb³⁷⁻³⁸ and the root of *Boesenbergia Pandurata* Holtt (Krachai).³⁵ The role to contribute as supportive remedy of phytosterols in addition to their characteristic is one of the essen-

tial antiproliferative of cancer cells such as flavonoids and volatile oil which the strongest one that present this action is linolool.³⁶ The co-operative actions of these herbs are reported to be the “interferon-inducing herb” that may contribute some important role to play on antitumor-antiviral activity through the “interferon” molecule.³⁷⁻³⁸

The probiotics/ antioxidants action on role of cancer therapy could be summarized as follows.

1. The antioxidants combined with therapeutic modalities reveal enhancing the therapeutic effects of chemotherapy and/or radiotherapy, decrease side effects, protect normal tissues and also increase survival.²²⁻²³

2. The antioxidants mechanism by inhibiting the activation of mitogen activated protein kinase pathway, cell proliferation and phosphorylation of p53 have been reported.³⁹

3. Antitumor and antimetastatic effects by induction or stimulation the synthesis of several cytokines have been known to be the immunomodulating factor. The small molecular weight cytokines such as IFN-gamma, IL-1 beta and TNF alpha being one of the enhancement transfer factor to work effectively has been reported.⁴¹

4. Immunomodulation enhancement through probiotics that resulting in the delayed or inhibit the process of distance metastases in various cell type of cancers and delayed process of cancer recurrences have been reported.^{40,42}

5. The clinical reports of probiotics in adjuvant with radiotherapy demonstrate an enhancing tumor regression, prolonged survival and relapse-free survival compared with radiotherapy alone.⁴²

The clinical trails of Vilac Plus[®] in the study as an supportive adjuvant to radiation therapy on lung cancers shown this potentiative and synergistic

effect due to powerful antioxidant and probiotics properties with improving survival times and survival rates were noted. The cost effectiveness is another considerable issue compared with chemotherapeutic agents and oral epidermal growth factor receptor (EGFR) inhibitors of lung cancer treatments.

Potential advantages of integrating complementary therapies into cancer care, future areas of research will be included improving access for patients, improving symptom control for patients, improving patient well-being, enhancing patient satisfaction, and cost effectiveness.⁴³

Conclusion

This pilot study was limitation in the aspect of a small number of patients, but all cases were in advanced stages of NSCLC with poor performance status. The results of this study was promising in the aspect of improving survival rates and cost effectiveness. The treatment of cancer patients has many interrelated and confounding factors that have to be sorted out so further research will be necessary. This modality is being investigated as part of the cost effectiveness complementary therapies in advanced NSCLC care for developing countries.

The value could be expressed as follows:

1. Improving the 1, 2, and 3 year survival rates of 100%, 53.85%, and 30.77% respectively compared with 1, 2, and 3 year survival rates of 9-40%, 4.1-18% and 3.3% respectively from historic control.¹⁻²¹

2. Improving the median survival time of 28 months (range 14-74 months) compared with 7 months (range 10-15 months) from historic control.¹⁻²¹

3. Improving the clinical benefit rate of 84.62%

for survived patients more than 15 months was detected.

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