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Therapeutic Effects of SB Natural Anticancer Drug in 50 Patients with Stage IV Pancreatic Cancer

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Abstract: Purpose: Pancreatic cancers are still difficult in early dection and progression is rapid that can be hardly cured. Surgical therapy is limited by its hypervascularity, poor responses of radiational therapy and anticancer drugs. Root extract of Pulsatilla Koreana, SB365 has shown apoptotic effect by Pulsatilla saponin D component, and inhibition of angiogenesis by deoxypodophyllotoxin element as well as c-Met signal pathway inhibition in the pancreatic cancer. We present its therapeutic effect in 50 patients with stage IV pancreatic cancer for the first time in Korea. Materials and Methods From March 2013 to May 2014, there were 50 patients with stage IV pancreatic cancers admitted to Sahmyook Seoul Hospital for SB anticancer treatments with 24 control patient who did not get SB anticancer treatments in the same time interval.SB anticancer drug were administrated directly intratumoral injections using radiofrequent ablation techniques by interventional radiologist and intravenously by physician. Results Total 50 patients received SB anticancer therapy, male 25, female 25, and age ranged from 27 to 86 years with median age of 57 years with liver, lung, peritoneum and/or bone metastases, Control 24 patients, male 10, female 14, age ranged from 36 to 90 years with median age of 69 years. There was no significant side effect clinically as well as by laboratory measurement after every SB injections. Number of survived patients in SB study group was 27cases (54.0%), but only 2 cases(8.3%) in SB not treated control group ($p<0.01$ with statistical significance). The total survival duration after diagnosis in SB treated group was 7 months, but 4 months in SB not treated control group. The interval from initial diagnosis to SB treatment in survived group was 2 month, less than 1 month in 12(44.4%) patients while in death group 5 months, and less than 1 month in only 3(14.3%) cases ($p< 0.01$ with statistical significance).The follow up duration and progression free estimate after SB treatment in survived group was median 5 months each, while in control group, median 2 months. Conclusion: SB natural anticancer drug administration is safe and increases survival rate and duration compared with control group, especially when treated within 1 month after diagnosis of stage IV pancreatic cancer. Long term follow up study with more numbers of patients are needed for accurate efficacy of SB treatment for advanced pancreatic cancer.

Keywords: Pancreatic Cancer Stage IV, SB, Natural Anticancer Drug

1. Introduction

Pancreatic cancer still continues to be difficult in early detection, and progression is rapid that can be hardly cured and remains one of the leading causes of cancer related death all over the world(1).

Surgical therapy is limited by its hypervascularity and delayed diagnosis, and the radiational therapy is also poorly responded. Anticancer chemotherapy is not so effective though gemcitabine has been introduced for advanced pancreatic cancers based upon a 1977 trial comparing gemcitabine versus fluorouracil showed a slight improvement in patient survival (2).

However, once patients have progressed on gemcitabine-based chemotherapy, there is a limited evidence that further systemic therapy provides a meaningful benefit (3).

The gemcitabine plus other anticancer drugs like cisplatin, S-1 did not show significant survival benefits(4,5).

Most phase II studies of target cell therapy using erlotinib have noted median progression free survival in the range of 2 to 4 months, and only few responses (6).

Wang et al. found that gemcitabine resistance is highly associated with epithelial-mesenchymal transition (EMT) phenotype of pancreatic cancer cells with high expression of HIF-1α,and inhibition of HIF-1α in gemcitabine resistant cells caused partial reversal of EMT phenotype, suggesting that HIF-1 α was critically involved in gemcitabine-resistant-mediated EMT(7). Novel and efficacious strategies including low toxic agents that can overcome the effect of gemcitabine are urgently needed for the treatment of pancreatic cancer.

SB is a root extract of Pulsatilla koreana and has been used traditionally as an antitumor agent in South Korea for more than 30 years.

There are many preclinical evidences for the antitumor effect of SB drug in various kinds of malignancies without significant toxicities(8,9).

We wanted to analyse the therapeutic effects of Pulsatilla Koreana root extract, SB 365,by discovering apoptotic Pulsatilla saponin D fraction(10) and antiangiogenic deoxypodophyllotoxin component(11) in 50 patients with stage IV advanced pancreatic cancers for the first time in Korea.

2. Materials and Methods

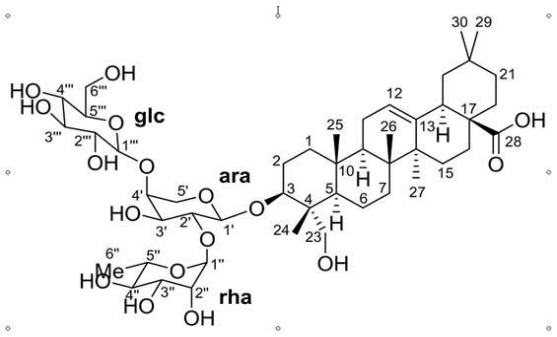
2.1. Patient Selection

From March 2013 to May 2014, there were 50 consecutive patients diagnosed radiologically and histologically as stage IV advanced pancreatic cancers, and they were admitted to Sahmyook Seoul Hospital for SB anticancer treatments. There were 24 control patients who did not received SB anticancer treatments during the same time interval.

Performance status was 3-4, an absolute granulocyte count>1.5x10 9/L, hemoglobin level 10g/L, platelet count, 50x10 9/L and adequate renal and hepatic function, serum creatinine and bilirubin<1.5x upper limit of normal(ULN), AST and ALT <2.0x ULN

Exclusion criteria included concurrent other malignancies and serious medical conditions that would impair the ability of the patient to receive protocol treatment.

2.2. Structure and Functions of Two Active Compounds from Pulsatilla Koreana



Molecular structure is C30 H46 O4 as shown above

Pic 1. *pulsatilla saponin D(SB 365).*

It is the most effective saponin that induces cancer cell apoptosis.

In animal model 6.4mg/kg/day, 82% of inhibitory activity of cancer cells was demonstrated which was better than adriamycin, 0.5mg/kg/day that showed 60% of inhibition of mouse cancer cells(10).

No cytotoxicity was revealed at concentration of 5ug/ml, so that SB 365 content in SB injection should be 0.8 -1.0mg/vial and more(12). Fifty to eighty percents of the growth of pancreatic cancer cells were inhibited at concentrations of 2-10uM(14).

Recent study also showed a suppression of c-Met signaling in proliferation and angiogenesis of various cancers and exerts antitumor and antiangiogenic activities(16).

Molecular structure is C22H22O7 as shown above.

Pic 2. *Deoxypodophyllotoxin.*

Inhibition of new blood vessel formation at 20mg/kg/day and 60% of cancer cells were inhibited(10).

2.3. Treatment Plan

SB anticancer drug were administrated using radiofrequent ablation techinique, directly percutaneous intratumoral injection, 2-15 vials (each contained Pusatilla saponin D 0.85mg) depending on size of tumor(0.3 vial/ Cm) and 1-3 times according to the severity of disease, by interventional radiologist and intravenously, 7-10vials daily depending on

surface area (4.3vial/m 2) of patient for 5-10 days by condition of the patient. Radiological assessment for tumor measurement were conducted every 2 months after each treatment.

2.4. Statistical Analysis

The statistical analysis program SPSS software (version 12 Chicago, IL) was used and a p-value below 0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

Total 50 patients received SB anticancer chemotherapy from March 2013 to May 2014, male 25, female 25 cases and age ranged from 27 to 86 years with median age of 57 years with liver, peritonium, lung and/or bone metastasis. Control group 24 patients, male 10, female 14, age ranged from 36 to 90 years with median age of 69 years (Table 1).

Table 1. *Characteristics of enrolled pancreatic cancer patients.*

variables	SB study group	Control group
No of cases	50	24
Age(years)		
Range	27~86	36~90
Median	57	69
Gender		
Male	25	10
Female	26	14
Clinical pictures		
Liver metastasis	33	13
Peritoneum	22	7
Lung	7	3
Bones	5	0
Performance scale	3~4	3~4

3.2. Toxicities

There were no significant side effects clinically and by laboratory tests after every SB injections. Side effects more than grade 2 are shown in Table 2.The most common treatment related side effects included fever, chills and injection site pain. But, there were no grade 4 to 5 toxicities(Table 2).

Table 2. *Toxicity profile(WHO Toxicities Grade III-IV).*

Grade	2	3	4
Hematologic toxicity			
Anemia	0	0	0
Leucopenia	0	0	0
Thrombocytopenia	0	0	0
Nonhematologic toxicity			
Fever/chill	9/9	1/1	0/0
Nausea/Vomiting	0/1	2/2	0/0
Skin rash, urticaria	1	0	0
Injection site pain	14	2	0
Mucositis	0	0	0
Diarrhea	1	0	0
Abdominal pain	1	0	0
Abnormal liver function	0	0	0
Abnormal kidney function	0	0	0

3.3. Objective Response

Fifty patients were accrued over 15 months and 49 received treatment.Two patients were lost after their first SB anticancer chemotherapy.Six patients died while on study.Fifteen patients came off due to progressive disease.

Number of survived patients in SB treated group was 27 patients with 54.0% survival rate, but only 2patients with 8.3% survival rate in SB not treated control group ($p<0.01$ with statistical significance),(Table 3)

3.4. Survival Analysis

The total survival duration after diagnoses in SB treated group was 7 months but 4 months in SB not treated control group ($p<0.01$ significance), (Fig 1).

The interval from initial diagnosis to SB treatment in survived group was 2 month, less than 1 month in 12 (44.4%) cases , but in death group was 5 months and less than 1 month in only 3(14.3%) cases ($p< 0.01$ with statistical significance) (Table 3).

The follow up duration after SB treatment in survived group, median survival was 5 months while in death group median 2 months (Fig 2).

The progression free estimate in SB treated group was more than 5 months, but less than 2 months in control group($p<0.01$ with statistical significance),(Fig 3).

Table 3. *Survival analysis.*

Variable	SB study group	Control group
No(%) of cases(survived/death/lost)	50(27(54.0%)/21/2	24(3(8.3%)/19/2
Time to SB treatment(months)	Less than 1month	
Survived group	2(12, 44.4%)	
Death group	5(3, 14.3%)	
Follow up duration after SB treatment(months)		
Survived group	5	
Death group	2	
Total survival duration(months)		
Survived group	7	
Death group		4

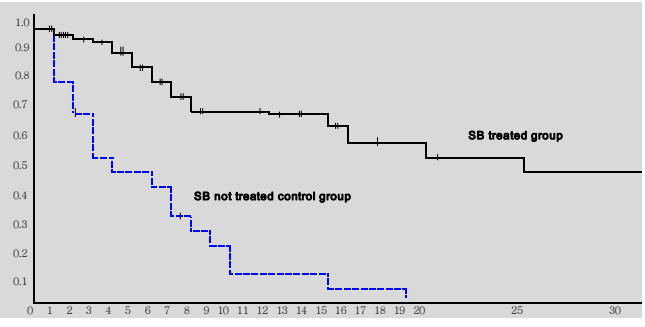
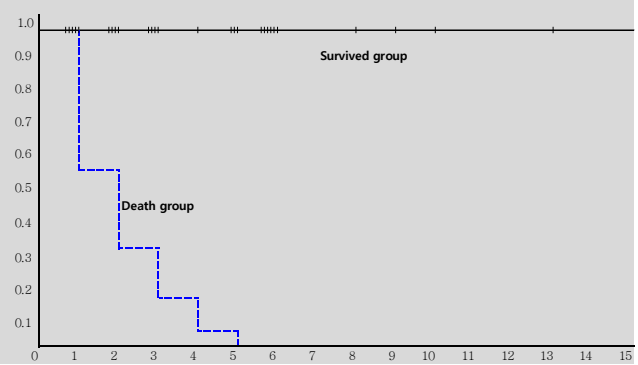
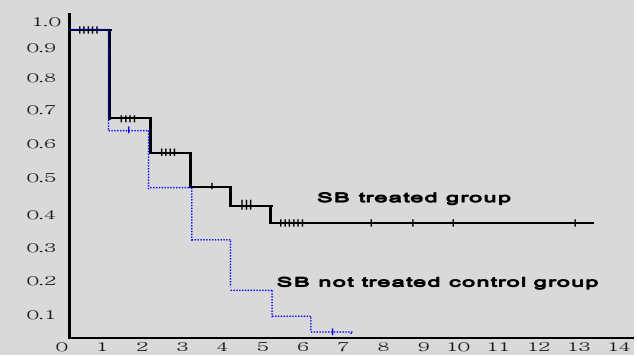


Fig. 1. *Survival curve of all patients.*



Follow up duration after SB treatment (months)

Fig. 2. *Survival curves of SB treated patients.*



Progression free survival estimate(months)

Fig. 3. *Survival curves of progression free estimate.*

4. Discussion

Pancreatic cancer still remains one of the most incurable human cancers. Most of available anticancer drugs for pancreatic cancers are not so effective, and agents for target cell therapies are not yet in desirable efficacy. Recently, bioactive components from plants have obtained considerable attention and promising options for the prevention or treatment of cancers.

The discovery of active medicinal compounds from herbal, natural sources has provided alternative treatment choice(13). Son et al. isolated SB 365, saponin D from the root of Pulsatilla koreana and conducted a comprehensive analysis of the effect of SB 365 on pancreatic cancer cells using both in vivo and in vitro model that significantly reduced cell growth and proliferation, inducing apoptosis in pancreatic cancer cells. In that study, SB365 inhibited 50-80% of the growth of pancreatic cancer cells at concentrations of 2-10 uM(14).

Angiogenesis is an important process in the growth and metastasis of solid tumor(15). VEGF is a potent inducer of angiogenesis and HIF-1α is the major regulator of VEGF transcriptional activation(16). SB 365 obviously decreased the expression of HIF-1α and VEGF under hypoxia, and inhibited hypoxia-induced angiogenesis, and demonstrated potent antiangiogenic effects along with the potential for inhibition of metastasis(14).

SB365 also targets c-Met signal pathway by increasing the cleaved caspase 3 activity and exert apoptotic and antiangiogenic activities in many cancers(17,18).

And also in pancreatic cancer c-Met pathway is frequently deregulated as in other cancer cells and by SB 365 targeting c-Met is anticipated effective therapeutic strategy like as Hong S W et all. confirmed in other cancers previously (16).

Our data revealed 54.0% of survival rate in 50 advanced pancreatic cancer patients who received the SB anticancer treatment. This is much higher when compared with that of SB not treated 24 control group (8.3%) during the same time interval Because of lower toxicities of SB drug systemically and also locally to contacted normal tissue, we could perform directly percutaneous intratumoral injection using radio frequent ablation technique produces a moderate degree of temperature for the good drug spreading into the softened tumors.

Previously anticancer chemotherapy including gemcitabine were done in 18 cases (56%) in SB treated group and 9 cases (36%) in SB not treated control group without survival benefits. The interval to SB treatment from the initial diagnosis is closely related with better survival rate in SB treated group. Especially treatment within 1 month after initial diagnosis has become a very important parameter for good survival duration after SB treatment, because of their good performance status and lesser late toxicities of other antecedent anticancer drugs.

Follow up duration after SB treatment and progression free estimate in survived group was 5 months, while in control group 2 months and anticipated more prolonged with time progressing.

The total survival duration after diagnosis in SB treated group was 7 months, but in SB not treated control group was 4 months, and overall longer survival duration after randomization is anticipated in the future time.

Though we had study with stage IV advanced pancreatic cancer patients, we hope that our study candidates could be locally advanced, restricted pancreatic cancer patients with stage II and III disease after their surgical resection and using this SB anticancer drug as adjuvant chemotherapeutic agent expecting good outcomes

5. Conclusion

SB natural anticancer drug administration is safe without significant toxicities and increased survival rate and duration, especially treated within 1 month after diagnosis of stage IV advanced pancreatic cancer.

Long term follow up study with more numbers of patients is needed for more accurate efficacy of SB treatment.

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