

Can nigella sativa and pure honey improved chemoradiotherapy effects in advanced pancreatic cancer

Abstract

The cancer treatments cause many side effects in patients. This is more important in pancreatic cancer (PCa) than other types of cancer because the PCa patients already suffer from abdominal pain, nausea, and loss of appetite. Therefore, it is necessary to focus on new treatment ways that decrease the toxicity and increase the survival time in PCa patients. A retrospective study was performed with 20 PCa patients who had non-metastatic locally advanced inoperable PCa. Patients were divided into 2 groups. Group 1 (n=9) included patients who received chemoradiotherapy and, taken Nigella sativa(NS) and pure honey (H) (NS+H+CRT group). Group 2 (n=11) consisted of patients who treated with concurrent chemoradiotherapy (CRT or control group). The median survival time was 15months, and %11.11 of patients (n=1) had a survival time of 36months in group 1. In control group (Group 2), the median survival time was 10months. Results revealed that chemoradiotherapy supported by NS and pure honey consumption increased the survival time when used before and during treatment of PCa patients.

Keywords: gemcitabine, nigella sativa, pure honey, advanced pancreatic cancer

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Abbreviations: NS, nigella sativa; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy; TQ, thymoquinone; DIM, dithymoquinone; COX-2, cyclo-oxygenase-2; H, honey; MLC, multi leaf collimator; CTV, clinical tumor volume; PTV, planning tumor volume; OS, overall survival; MRI, magnetic resonance imaging

Introduction

Cancer is the formation of different cells the ability to overgrow. Sometimes its formation becomes easier with some factors. The carcinogens, which is one of the causing factors of cancer, and mutations of some genes that suppress cancer formation are known the most important contributing factors for cancer.^{1,2} The risk of cancer can be diminished an average of 30-40% with an adequate diet and exercise. Approximately 5million people in the world would be protected by appropriate diet from cancer each year.³⁻⁷

Cancer may develop very easily in the pancreas gland due to insulin or Circulating Insulin-Like Growth Factor Binding Proteins related over-enlargement, degeneration. For this reason, the most negatively affected type of cancer from the diet is PCa.^{3,5-7}

PCa incidences were 2.3% in all cancer of the World According to

the National Cancer Information Center of Korea. For gender, 53,070 estimated cases and 41,780 (%7) expected death for PCa in U.S.A. Generally, PCa incidences are 3% in all cancer of the World.⁸

More than 80% of PCa are diagnosed in advanced stages because of fast spread and non-clear early symptoms such as abdominal pain, nausea, and loss of appetite.⁹ Smoking, high-fat diet, chronic pancreatitis, primary sclerosing cholangitis, hereditary pancreatitis, family history of pancreatic cancer and diabetes mellitus are the most common cause of PCa.¹⁰

Median survival was 6 to 10months for advanced PCa.^{11,12} Treatment options for these patients are CT, RT, CRT, and/or palliative surgery. The median survival of advanced PCa increases to 10months using concurrent CRT, compared to RT alone.^{13,14} 5-fluorouracil (5-FU) and gemcitabine are most using CT agents in PCa treatment regimes.^{15,16} Gemcitabine has been the most prominent CT for advanced PCa.^{12,17} However, the survival benefit of gemcitabine is very low and the median survival time was 5.7months for gemcitabine and 4.4months for 5-FU treatment respectively. Therefore more effective therapy is urgently needed in advanced PCa. Many studies have been made to improve the overall survival of patients with using gemcitabine and other agents.¹⁸ Gemcitabine alone or gemcitabine combination therapies were made which contain capecitabine, 5- FU, irinotecan, pemetrexed

and oxaliplatin. The response rates were increased by these treatments but significant survival advantage was not shown for the gemcitabine combination therapies over the gemcitabine monotherapy because gemcitabine resistance and increased toxicity.^{19,20} Therefore, a new approach is warranted. It is very important to make a balance between efficacy and quality of life in treatments of PCa, because PCa patients already suffer from cancer-related symptoms that loss of appetite, fatigue, nausea, vomiting and abdominal pain.

Intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT) or tomotherapy methods must be using as RT, because pancreatic location and possible side effects that diarrhea, vomiting, hepatic, renal functional anomalies because of surrounded organs in PCa.^{12,21,22} However, treatment outcomes not enough to change in locally advanced pancreatic cancer even these treatments.

Thymoquinone (TQ) shown to some health benefit effects in studies.²³⁻²⁵ TQ which often referred to as *black cumin* seeds is extracted from the seed of *NS*. These seeds had been used since a long time for toxicity or primary treatment of diseases. The antioxidant, antiproliferative, cytotoxic, organ safing, antimicrobial effects of 2 to 5g of *NS* demonstrated in multiple studies.²³⁻²⁶ Cancer Research group reported that the purified extract TQ and dithymoquinone (*DIM*) both were effective in killing the multiple cancer cell lines. TQ and *DIM* also reduces multi-drug resistance to doxorubicin and etoposide.²⁷

TQ alone inhibited cancer cell viability up to 70% because inhibites anti-apoptotic Bcl-2 and Bcl-xL, Mcl-1, survivin, XIAP, cyclo-oxygenase-2 (COX-2), PGE-2 accumulation, nuclear factor-kappaB (*NF-kappa B*) and induces pro-apoptotic molecule Bax in a dose dependent manner. *NF-kappa B* also may be causes resistance to gemcitabine. The COX-2 enzyme increased metastases that inhibites to apoptosis, also potentiates cell growth, angiogenesis and over expressed in PCa. The PCa cells were may sensitized to CT agents by using TQ. A 15-50% reduction of PCa cells were showed by treatment with TQ or other CT agents. The tumor reduction was obtained 66% and 58% by using gemcitabine or oxaliplatin while increase with combination to TQ which 85% for gemcitabine and 76% for oxaliplatin respectively.²⁸

However combining pre-treatment TQ and CT resulted in a 65–85% loss of viable cancer cells through increased apoptosis in PCa ($P < 0.001$). CT can decrease viable cancer cells while increases *NF-kappa B* which cause progression and chemoresistance.²⁹ TQ can decreases to *NF-kappa B* and improves treatment results.³⁰

Honey has been used as a food source, and current research shown that it may be a beneficial aid to cancer therapy. The antioxidant, immunomodulative and anti-inflammatory action of honey and related to its phenolic constituents was showed in many studies.³¹⁻³⁶ Ellagic acid, gallic acid, caffeic acid, chlorogenic acid, kaempferol, catechin, quercetin, luteolin, are some phenolic compounds of honey.³⁶ Biswa Mohan and colleagues made a preliminary study about pure honey for decreasing oral mucosal toxicity. The studies shown that topical pure honey reduces oral mucositis as dramatical.^{37,38} The antioxidant, antiproliferative, antimicrobial effects of 3 to 20g of honey demonstrated in multiple studies.³⁸⁻⁴³ In Islamic medicine and Iran, the combination of *NS* with honey is used for alleviating gastrointestinal symptoms like abdominal pain, bloating and diarrhea.⁴⁴⁻⁴⁶ We obtained a study increasing CRT effectiveness with *NS* and Honey (H) for decreasing oral and gastrointestinal toxicity.

Methods

A retro-spective study was performed on 20 patients with PCa who had advanced PCa and came to our clinic between 2012-2014. Their ages ranged from 39 to 70 and Eastern Cooperative Oncology Group (ECOG) performances ranged from 1-4 (Table 1) (Table 2). Patients were divided into 2 groups. 9 patients in the 1st group who were applied *NS*, H, RT and concurrent RT and CT (*NS+H+CRT* group) diagnosed as inoperable advanced PCa. CT and concurrent RT were applied to 11 patients in the 2nd group (CRT group) who diagnosed as inoperable advanced PCa.

- NS* dust was given 3gr with 12hours interval for 7days and daily 5g H using concurrent with *NS* orally. After this interval, CRT and concurrent *NS* dust and H was given with same doses and 12hours interval were used throughout the RT. Gemcitabine used intravenous only 600mg/m² weekly in *NS+H+CRT* group throughout the RT. RT was performed in 28 fractions with 180cGy fraction and a total of 5040 cGy.
- 600mg/m² of intravenous gemcitabine given per week and simultaneous RT was performed in 28 fractions with 180cGy fraction and 5040cGy total dose in the 2nd group (CRT group). Staging was determined according to the American Joint Committee of Cancer 7th edition with FDG-positron emitting tomography scans to evaluate distant metastasis.²⁰ Eastern Cooperative Oncology Group (ECOG) performance status, pre and post-treatment contrast enhanced Computed Tomography (CT)

imaging and CA19-9 (Carbohydrate Antigen 19-9) levels were performed for response evaluation.

Table 1 Pre-treatment patient characteristics of group I (*NS+H+CRT*)

Characters	Number	%
Gender		
Male	5	55.55
Female	4	44.44
Age		
35-49	2	22.22
50-59	4	44.44
60-70	3	33.33
CA19-9		
400-1000	3	33.33
1000-4000	6	66.66
Tumor Location		
Head of P	7	77.77
Tail of P	2	22.22
ECOG Scoring		
0-1	0	0
2	5	55.55
3	4	44.44
Toplam	9	100

NS, nigella sativa; H, pure honey; CRT, chemoradiotherapy; P, pancreas

Table 2 Pre-treatment patient characteristics of group 2 (CRT)

Patient characters	Number	%
Gender		
Male	6	54.54
Female	5	45.45
Age		
35-49	3	27.27
50-59	5	45.45
60-70	3	27.27
CA19-9		
400-1000	8	72.72
1000-4000	3	27.27
Tumor location		
Head	8	72.72
Tail	3	27.27
ECOG scoring		
0-1	2	18.18
2	6	54.54
3	3	25
Toplam	12	100

Radiotherapy

RT was performed in group 1 and 2 with a Varian Linear Accelerator (MNT, Health Care and Trade Corporation, Turkey, Bozlu Holding) device. In the 1st and 2nd group, the pancreatic tumors were treated with Three Dimensional (3-D) conformal or dynamic IMRT (Intensive Modulated Radiation Therapy) method with MLC (Multi Leaf Collimator) blocked fields, with 6 and 18MeV X-rays, including Gross Tumor Volume (GTV), pancreatic and regional lymphatics that Clinical Target Volume(CTV) and Planning Tumour Volume (PTV). Total dose of 5040cGy was applied to 28 fractions with 180cGy 5 times per week.

Clinical tumor volume (CTV) was created by giving margin to GTV and lymphatic zone only 0.5mm to avoid toxicity. The planning tumor volume (PTV) was established by giving a 1-mm margin to CTV. 85-95% of the targeted radiation dose received 95% of the tumor in the radiation field (Figure 1). Conformity index and homogeneity index were median 0.97 and 0.35respectively for PTV (Table 3).

Statistical analyses

Statistical Analyses were performed with Mann Witney U test. The differences of between the two groups $p \leq 0.05$ values accepted as significant according to Mann Witney U test. Kaplan Meier method was used for obtained survival curve and calculated survival rates in two groups of PCa patients.

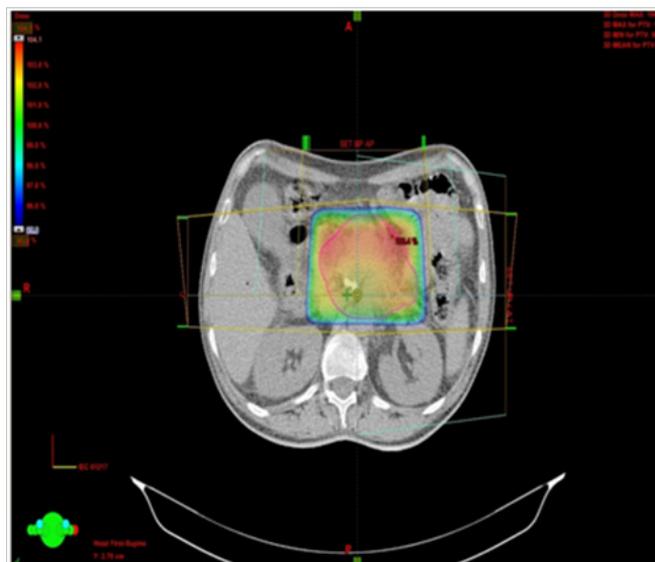


Figure 1 Isodose distribution of radiation planning on PCa patients.

Table 3 Radiotherapy characteristics of group 1 and 2 of PCa patients

RT characters	Dose median(Gy)	HI median	CI median	Rena dose (Gy)I	RT volume median (ml)
PTV tm+LN	50.4	0,35	0,97	6.3	972

HI, homogeneity index; CI, conformity index; TM, pancreatic tumor; LN, regional lymph nodes; PTV, planning target volume

Primary endpoint of this study was Overall survival (OS) rates. Secondary endpoint was treatment toxicities. OS time was defined as from beginning of RT or CT since to death or the last follow-up date in survivors. Progression free survival time defined from beginning of RT or CT to relapsing or times of metastases. Treatment response was assessed by Response Evaluation Criteria in Solid Tumors ver. 1.1.²¹ Treatment results determined to comparing dynamic abdomen CT/ MRI (Magnetic Resonance Imaging) or PET CT images and CA19-9 levels of patients which taken before and after treatments.

Results

Characteristics of patients were shown in Table 1 & 2. Complete response was achieved on 3 of 9 patients (33.33%) and partial response on 3 of 9 patients (33.33%). 2 of 9 patients (22.22%) remained stable in NS+H+CRT group. Complete response obtained 2 of 11patients (18.18%) and partial on 4 of 11patients (36.36%) in CRT group according to RECIST ver. 1.1 (14.12) (Table 4).

Median survival was 15months, threeyears survival 11.11% in NS+H+CRT group. The median survival was 10months and threeyears survival 0% in the group of CRT. Recurrence sites and median recurrence months according to groups shown on Table 5. The patients whose pre-treatment levels of CA19-9 >1000 U/mL demonstrated to 6 and 10months median survival time for CRT and NS+H+CRT groups respectively But the patients whose pre treatment levels of CA19-9 <1000 U/mL has been to 14 and 20months median survival time in CRT and NS+H+CRT groups respectively ($p < 0.05$) (Figure 2).

Table 4 Response rates for group 1 and 2 of PC a patient

Groups and responses	Patient number	%	Median life (Month)
NS+H+CRT	9	100	15
CR	3	33.33	20
PR	3	33.33	18
S	2	22.22	8
P	1	11.11	5
CRT	11	100	10
CR	2	18.18	15
PR	4	36.36	12
S	2	18.18	6
P	3	27.27	3

NS, nigella sativa; H, pure honey; RCT, chemoradiotherapy; P, progression; S, stationar; PR, partiel response; CR, complete response

Table 5 Recurrence sites and median recurrence times for group 1 and 2 of PC a patients

CRT	Patient number	%	Median recurrence (Month)
NS+H+CRT	9	100	12
Dist. met	3	33.33	12
CP	2	22.22	13
Local P	5	55.55	14
CRT	11	100	8
Dist. met	9	81.81	8
CP	8	72.72	8
Local P	7	63.63	9

NS, nigella sativa; H, pure honey; RCT, chemoradiotherapy; CP, peritoneal carcinomatosis; P, progression; Dist.met, distance metastases; Met, metastases; R+CT, radiotherapy and chemotherapy

5 of 9 patients (55.55%) of NS+H+CRT had local, 3 of 9 patients (33.33%) had distant progression and 2 of 9 (22.22%) had peritoneal carcinomatosis. 7 of 11 patients of CRT (63.63%) had local, 9 of 11 patients (81.81%) had distant progression and 8 of 11 (72.72%) had peritoneal carcinomatosis after treatments.

7 of 9 patients experienced grade 2 haematologic (77.77%), 1 of 9 patins (11.11%) grade 3, 6 of 9 patients grade 2 gastrointestinal toxicity (66.66%) in NS+H+CRT. 11 of 11 patients experienced grade 1-2 haematologic (100%), 3 of 11 patient grade 3 gastrointestinal and haematologic toxicity (33.33) in CRT according to RTOG/EORTC.²²

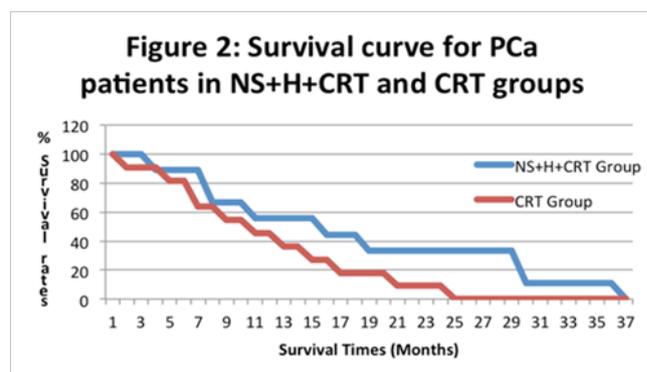


Figure 2 Survival curve for PC a patients in two groups.

Discussions

Median survival was 6 to 11.4months in combined CT regimes with high toxicity rates, and 4.4 to 7.4months in single CT regimes for advanced PCa.^{11,12,19,20,47} The median survival of advanced PCa increases to 10months using concurrent CRT including gemcitabine or 5-FU with acceptable toxicity.^{13,14} Studies have shown anti-cancer and chemosensitivity effects of TQ, a predominant bioactive product of NS in PCa.⁴⁶ Apoptotic activity could be increased by regulating anti-apoptotic *Bcl-2, Bcl-xL, XIAP, Caspase-3, Caspase-9, Bax* molecules from pro-apoptotic molecules using pre-gemcitabine TQ in PCa. As well as the antiproliferative effect of TQanalogues and a successful chemosensitising agent with gemcitabine.⁴⁷ In the one *in vitro* trial, 60-80% anti-proliferative effect was observed with gemcitabine and oxaliplatin by giving TQbefore CT and only 15-25% effect was obtained with gemcitabine and oxaliplatin application.²⁷

The achieved 66.66% complete and partial response and 15months survival rates of NS+H+CRT group in this study were better than many other studies in literature although has been high pre-treatment levels of CA19-9>1000U/mL than literature, also with acceptable toxicity.¹¹⁻²⁰ The median OS was 15 and 10months in this study for NS+H+RCT and RCT groups respectively. Pre-treatment value of CA19-9 demonstrated one of the most prominent prognostic factors for PCa. Two large studies shown to the cut-off value of pre-treatment CA19-9 were evaluated 420U/mL and 400U/mL respectively as unfavourable predictor of OS in PCa patients who underwent CRT.^{48,49} Also, pre treatment levels of CA19-9>1000U/mL indicated to dismal OS for PCa.⁵⁰ In our study the patients whose pre-treatment levels of CA19-9>1000U/mL demonstrated to 6 and 10months median survival time for CRT and NS+H+CRT groups respectively. But the patients whose pre treatment levels of CA19-9 <1000U/mL has been to 14 and 20months median survival time in CRT and NS+H+CRT groups respectively. Other studies shown to similar results that median OS being 12-14months in patients with <1000 U/mL, and 4-6months, in ≥1000U/mL with used CRT in PCa patients.⁴⁸⁻⁵¹

In this study demonstrated to low toxicity rates than other studies in literature. We observed 77.77% and 11.11% Grade 1-2 and grade 3 haematologic toxicity respectively. The study also showed that grade 2 and grade 3 gastrointestinal toxicity 66.66% and 11.11% in NS+H+CRT. But grade 1-2 haematologic toxicity was experienced 100%, grade 3 gastrointestinal and haematologic toxicity were 33.33% in CRT arm. Common Grade 3-4 gastrointestinal toxicities were achieved 20-43%, infections were 13-30%, 60-75% grade 1-2, 10-15% 3-4 haematologic toxicity in CRT arm on other studies.^{11-20,51,52}

High dose RT applicated in some studies for increasing survival rates but severe acute and late toxicities occurred although improved OS.⁵³ The general advanced pancreatic cancer treatments were much toxic because pancreas with tumor and lymph node areas must be included in RT fields.⁵⁴ Recent studies shown that RT of only gross tumour areas was sufficient for prevent marginal failures with low toxicity and increasing OS even high doses.^{46,55,56} It may be possible to identify more accurately to target delineations with increasing RT dose also improvements in both local control and OS rates using such as IMRT, SBRT, or proton therapy methods. Recently, SBRT can be applicated in only several days with achieving equivalent to or better tumor control rates than standard CRT regimes although without CT with limited toxicity especially elderly and low ECOG performance patients with pancreatic cancer.⁵⁷ NS and H can also improved to treatment outcomes with using low total dose of radiation with standard IMRT or SBRT methods with or without CT by reducing toxicities and increasing cytotoxic effects.⁵⁸⁻⁶²

Conclusion

In this study, NS and H improved results with low toxicity in NS+H+CRT group.

Recommendation

The limitations in this study are a retrospective study and sample size is relatively small. But this study may be useful for literature because favorable OS and toxicity outcomes.

Authorship

Formulating the research questions: H.S.K., A.G.B. Designing the study: H.S.K., A.G.B., M.K.T. Carrying out: H.S.K., M.İ. Analyzing the data: H.S.K., AGB, MI, NO, ANA. Writing the article: H.S.K., AGB.

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Conflict of interest

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