Full-dose Gemcitabine is a More Effective Chemotherapeutic Agent than 5-fluorouracil for Concurrent Chemoradiotherapy as First-line Treatment of Locally Advanced Pancreatic Cancer

Huapyong Kang

Department of Medicine

The Graduate School, Yonsei University

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Directed by Professor Seungmin Bang

The Master's Thesis submitted to the Department of Medicine, the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Master of Medical Science

Huapyong Kang

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This certifies that the Master's Thesis of
Huapyong Kang is approved.

Thesis Supervisor: Seungmin Bang

Thesis Committee Member #1: Woo Jung Lee

Thesis Committee Member #2: Chang Geol Lee

The Graduate School
Yonsei University

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<ABSTRACT>

Full-dose Gemcitabine is More Effective Chemotherapeutic Agent than 5-fluorouracil for Concurrent Chemoradiotherapy (CCRT) as First-line Treatment in Locally Advanced Pancreatic Cancer

Huapyong Kang

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Seungmin Bang)

Objectives: To compare the therapeutic efficacy and tolerability of full-dose gemcitabine-based CCRT (FG-CCRT) and conventional 5-FU-based CCRT (5FU-CCRT) for locally advanced pancreatic cancer (LAPC).

Methods: From January 2006 to March 2013, 109 patient cases of LAPC treated with FG-CCRT (n=89) or 5FU-CCRT (n=20) were reviewed retrospectively. The FG-CCRT group was composed of a full-dose weekly gemcitabine monotherapy (1000mg/m^2) arm and a full-dose gemcitabine and cisplatin (70mg/m^2) combination arm. The 5FU-CCRT group was treated with a radiosensitizing bolus dose of 5-FU (500mg/m^2, weekly) plus leucovorin (20mg/m^2, weekly). In both groups, concurrent radiotherapy was targeted at the primary tumor with a 5 mm margin without lymph node irradiation.

Results: Objective response rate (ORR) and disease control rate (DCR) was significantly higher in the FG-CCRT group (ORR – 32.6% vs. 5%; P = 0.013; DCR – 79.8% vs. 50.0%; P = 0.006). Additionally, FG-CCRT showed remarkable

superiority to 5FU-CCRT for the control of distant metastasis (18.0% vs. 45.0%; *P* = 0.017). Both groups showed similar loco-regional control rates (93.3% vs. 85.0%; *P* = 0.362). With regards to toxicity, grade 3 or higher neutropenia (34.8% vs. 10%; *P* = 0.032) and thrombocytopenia (21.3% vs. 0.0%; *P* = 0.021) were more frequent in the FG-CCRT group as originally expected. In a subgroup analysis, toxicities of the full-dose gemcitabine monotherapy-based CCRT group were not different than those of the 5FU-CCRT group.

Conclusion: FG-CCRT, especially full-dose gemcitabine monotherapy-based CCRT, was more effective for the initial control of LAPC than 5FU-CCRT and can be used without concerns of increasing toxicity.

Key words: Locally advanced pancreatic cancer, Chemoradiotherapy, CCRT, Gemcitabine, 5-FU

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I. INTRODUCTION

Pancreatic cancer is one of the major causes of cancer-related deaths in United States.[1] It is also still one of the most disastrous malignancies in the world. In spite of the introduction of several newer drugs, the 5-year survival rate remains less than 5% and has a median survival of only 9 – 10 months.[2] These disappointing statistics can be attributed to the fact that only 20% of newly diagnosed pancreatic cancer is surgically resectable, distant metastasis is seen in 50% percent of cases, and the remaining 30% is locally advanced pancreatic cancer (LAPC).[3]

LAPC is defined as surgically unresectable pancreatic cancer without distant metastasis that usually invades or infiltrates major arteries including the celiac axis or superior mesenteric artery. Concurrent chemoradiotherapy (CCRT) has been suggested as a standard first line treatment option in LAPC even though there are still debates on this modality. After the Gastrointestinal Tumor Study Group reported that CCRT with 5-fluorouracil (5-FU) was more beneficial for survival

than radiotherapy (RT) alone in LAPC,[4] 5-FU-based CCRT became more widely used. Gemcitabine, a nucleoside analog,[5] has been used as the front line chemotherapeutic agent for managing advanced pancreatic cancer,[6] since gemcitabine was reported to be superior to 5-FU in patients with advanced symptomatic pancreatic cancer.[7] Furthermore, with its potent radiosensitizing effect,[8] gemcitabine-based CCRT has been suggested as an ideal treatment for LAPC because of efficient loco-regional control and substantial systemic control effects. Interestingly, results of numerous trials have all reported discrepant data. Recently, Loehrer et al.[9] showed an improved survival benefit of gemcitabine CCRT compared to gemcitabine chemotherapy alone.

CCRT with full-dose gemcitabine (1000mg/m^2, weekly) is expected to have a maximal cytotoxic effect in addition to local control effects with concurrent radiation. However, there is not currently a universally accepted consensus on the optimal dosage of gemcitabine or radiation. Because of apprehension in regards to increasing the rate of treatment-related toxicity, most studies adopted diminished gemcitabine doses or reduced the total dose of concurrent radiotherapy.[10-13] On the other hand, some trials insisted that full-dose gemcitabine-based CCRT is relatively safe.[14]

This study aimed to retrospectively compare the therapeutic efficacy and tolerability of FG-CCRT and 5FU-CCRT for the first line treatment of LAPC.

II. MATERIALS AND METHODS

1. Patients selection

Patients greater than 18 years of age diagnosed with LAPC who received definitive FG-CCRT or 5FU-CCRT as first line treatment between the dates of January 2006 to March 2013 were evaluated retrospectively. According to the definition of LAPC, all patients had unresectable pancreatic cancer without distant metastasis. All patients underwent pre-treatment assessment. In accordance with National Comprehensive Cancer Network (NCCN) guidelines for pancreatic cancer[6], staging work-up included high-resolution computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and endoscopic ultrasound (EUS). Histological confirmation of malignancy was done by EUS-guided fine needle aspiration, percutaneous biopsy, or exploratory laparotomy as indicated. Endoscopic retrograde cholangiopancreatography (ERCP) and biliary drainage were performed if necessary. Exclusion criteria were as follows: 1) under 18 years of age, 2) diagnosed with borderline resectable status and underwent neoadjuvant CCRT, 3) preexisting distant metastasis before CCRT, 4) treatment other than CCRT as the first line treatment for LAPC, 5) past history or coexistence of other malignancy, and 6) absence of histological diagnosis. Those initially diagnosed with unresectable cancer that regressed to a resectable status after CCRT and then underwent surgical resection were included. Additionally, patients with an initially resectable status but had received CCRT due to medical inoperability were included in the analyses.

2. Full-dose gemcitabine based chemoradiotherapy (FG-CCRT)

Full-dose weekly gemcitabine monotherapy and combination therapy with cisplatin were included in this group. For gemcitabine monotherapy, intravenous infusion of full-dose gemcitabine (1000mg/m^2) was delivered for 30 minutes weekly from day 1 with concurrent RT, and treatment was continued until the conclusion of RT. For combination therapy with cisplatin, chemotherapy began on day 1 of RT. Full-dose gemcitabine was administrated intravenously for 30 minutes on day 1, 8, 15, 29, and 36 and intravenous cisplatin (70mg/m^2) was infused for 2 hours on day 1 and 29. Patients who received less than full-dose gemcitabine (1000mg/m^2) were excluded from the analysis

3. Conventional dose 5-fluorouracil based chemoradiotherapy (5FU-CCRT)

Intravenous bolus injection of low-dose 5-FU (500mg/m^2) with leucovorin (20mg/m^2) was started with RT on day 1 and continued until day 29. CCRT with other dosages or schedules of 5-FU or combination therapy with other chemotherapeutic agents were excluded from the analysis.

4. Concurrent radiotherapy

All patients underwent simulation CT scans in a supine position for RT planning. Dual contrast agents, including diluted oral Gastrografin and intravenous contrast, were used to better define the duodenum. Median RT dose of FG-CCRT and 5FU-CCRT groups were 50.4 Gy (range, 42.8 - 59.9 Gy) given in 25 fractions and 47.7 Gy (range, 41.4 - 58.4 Gy) given in 26 fractions, respectively. For both groups, radiotherapy was conducted without routine use of elective nodal irradiation (ENI).

The dose coverage of planning target volume (PTV), defined as the gross tumor volume plus a 5-mm margin, was covered by the 90% isodose surface. The maximal irradiated dose to 2 cc of the duodenum was limited to 50 Gy. For patients who received a high RT dose, helical tomotherapy was generally used with higher fractionated doses (range, 2.2 to 3.0 Gy). Details of helical tomotherapy regarding simulation, RT planning, dose prescription, and image-guidance have been described in a previous paper.[15]

5. Assessment of treatment-related toxicity

Treatment-related toxicities during CCRT were evaluated and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Severe (grade 3 or higher) toxicities that required suspension or modification of treatment were analyzed separately.

6. Response evaluation

Four weeks after completion of CCRT, a helical CT scan was performed. On the basis of World Health Organization (WHO) criteria, treatment response was evaluated by comparison of both pre- and post-treatment CT scans. If the response evaluation indicated treatment failure, each site of disease progression (primary tumor, regional lymph node, or distant metastasis) was recorded.

7. Data analyses and statistical methods

The primary therapeutic parameter of this study was objective response rate

(ORR: complete response (CR) + partial response (PR)). The secondary parameters were disease control rate (DCR: CR + PR + stable disease (SD)), pattern of treatment failure and treatment related toxicities. The Mann-Whitney test was used to analyze continuous variables and Fisher's exact test or Pearson`s chi-square test were used to analyze categorical variables. A *P*-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out with SPSS (version 20.0, SPSS Inc., Chicago, IL, USA).

III. RESULTS

1. Patient and treatment characteristics

Medical records from a total of 138 patients were reviewed. For the FG-CCRT group, 28 of the 117 total patients were excluded because of no histological confirmation (11 patients), past histories of other malignant disease (14 patients), and prior treatment for LAPC (3 patients). After exclusions, 89 patients in the FG-CCRT group and 20 patients in the 5FU-CCRT group were included in the final analysis.

There were no significant differences in patient characteristics between either group except weight loss and T-stage (Table 1). Patients in the FG-CCRT group had more advanced T-stage ($P = 0.010$) and experienced more frequent weight loss (70.8% vs. 40.0%; $P = 0.009$) before treatment.

Table 2 shows treatment related characteristics. In the FG-CCRT group, 55 patients (61.8%) received full-dose gemcitabine monotherapy (GEM) as the

chemotherapeutic agent, and the remaining 34 patients (38.2%) were given full-dose gemcitabine plus cisplatin combination therapy (GP). Total radiation doses were higher in the FG-CCRT group (50.4 Gy vs. 47.7 Gy; P = 0.037). Other RT related characteristics including RT modality, daily RT dose, fraction, and rate of treatment completion were not significantly different between the two groups.

Table 1. Patient characteristics

	FG-CCRT (n=89)	5FU-CCRT (n=20)	*P*
Sex, n (%)			0.779†
Male	52 (58.4)	11 (55.0)	
Female	37 (41.6)	9 (45.0)	
Age, median (range)	65 (35 - 78)	63 (37 - 80)	0.950‡
ECOG performance status, n (%)			0.495†
0	29 (32.6)	4 (20.0)	
1	50 (56.2)	14 (70.0)	
2	10 (11.2)	2 (10.0)	
Jaundice, n (%)	27 (30.3)	6 (30.0)	0.976†
Weight loss, n (%)	63 (70.8)	8 (40.0)	0.009†*
Laboratory tests before CCRT, median (range)			
Creatinine, mg/dL	0.8 (0.36 - 4.23)	0.73 (0.28 - 1.17)	0.065‡
Albumin, g/dL	4.3 (2.7 - 5.2)	4.0 (3.0 - 5.0)	0.085‡
Total bilirubin, mg/dL	0.7 (0.3 - 17.1)	0.7 (0.2 - 17.9)	0.621‡
CA 19-9, U/mL	273.0 (0.1 – 20,000)	339 (6.10 – 14,000)	0.695‡
CEA, ng/mL	3.1 (0.62 - 2510)	2.95 (0.62 - 67.52)	0.602‡
Pretreatment biliary drainage, n (%)			0.673†
None	60 (67.4)	13 (65.0)	
PTBD	1 (1.1)	1 (5.0)	
ERBD	12 (13.5)	2 (10.0)	
Metal stent	16 (18.0)	4 (20.0)	
Tumor location in pancreas, n (%)			0.627†
Head	40 (44.9)	11 (55.0)	
Body	37 (41.6)	6 (30.0)	
Tail	12 (13.5)	3 (15.0)	
Tumor size, cm, median (range)	3.7 (1.4 - 9.0)	3.3 (1.2 - 6.8)	0.091‡

Histology, n (%)			0.561†
Adenocarcinoma	86 (96.6)	19 (95.0)	
Carcinoma NOS	3 (3.4)	1 (5.0)	
Differentiation, n (%)			0.595†
Well	5 (5.6)	0 (0.0)	
Moderate	17 (19.1)	3 (15.0)	
Poor	8 (9.0)	3 (15.0)	
Unidentified	59 (66.3)	14 (70.0)	
T-Stage, n (%)			0.010†*
T3	12 (13.5)	8 (40.0)	
T4	77 (86.5)	12 (60.0)	
N-stage, n (%)			0.206†
N0	58 (65.2)	10 (50.0)	
N1	31 (34.8)	10 (50.0)	

ECOG: Eastern Cooperative Oncology Group, CA: Carbohydrate antigen, CEA: Carcinoembryonic antigen, PTBD: Percutaneous transhepatic biliary drainage, ERBD: Endoscopic retrograde biliary drainage, NOS: Not otherwise specified. †Calculated by Fisher`s exact test or Pearson`s chi-square test. ‡Calculated by Mann-Whitney test. *Statistically significant

Table 2. Treatment characteristics

	FG-CCRT (n=89)	5FU-CCRT (n=20)	*P*
Regimen, n (%)			
Gemcitabine	55 (61.8)	-	-
Gemcitabine + Cisplatin	34 (38.2)	-	-
5-FU/Leucovorin	-	20 (100.0)	-
RT modality, n (%)			0.230†
3DCRT	54 (60.7)	15 (75.0)	
IMRT	35 (39.3)	5 (25.0)	
Total RT dose, Gy, median (range)	50.4 (42.8 - 59.9)	47.7 (41.4 - 58.4)	0.037‡*
Daily RT dose, Gy, median (range)	1.8 (1.8 - 2.9)	1.8 (1.8 -2.5)	0.205‡
Fraction, median (range)	25 (15 - 30)	26 (20 - 28)	0.818‡
Completion of CCRT, n (%)	85 (95.5)	18 (90.0)	0.303†

3DCRT: 3-dimensional conformal radiation therapy, IMRT: Intensity modulated radiotherapy. †Calculated by Fisher`s exact test or Pearson`s chi-square test. ‡Calculated by Mann-Whitney test. *Statistically significant.

2. Treatment responses

Response evaluation was conducted four weeks after completion of CCRT by helical CT and results were compared between the two groups (Table 3). CR was not observed in either group and PR was more frequent in the FG-CCRT group (32.6% vs. 5.0%; $P = 0.013$). The rate of SD was similar, while progressive disease (PD) was more common in the 5FU-CCRT group (20.2% vs. 50.0%; $P = 0.006$). Because there were no cases of CR in either group, the result of ORR was the same as that of PR (32.6% vs. 5.0%; $P = 0.013$). DCR was also higher in the FG-CCRT group (79.8% vs. 50.0%; $P = 0.006$).

Both groups showed similar loco-regional control rates (93.3% vs. 85.0%; $P = 0.362$), whereas the rate of distant metastasis observed during response evaluations was significantly more frequent in the 5FU-CCRT group (18.0% vs. 45.0%; $P = 0.017$).

Table 3. Response evaluation

	FG-CCRT (n=89) (%)	5FU-CCRT (n=20) (%)	$P^{\int}$
Complete remission (CR)	0	0	-
Partial remission (PR)	29 (32.6)	1 (5.0)	0.013*
Stable disease (SD)	42 (47.2)	9 (45.0)	0.859
Progressive disease (PD)	18 (20.2)	10 (50.0)	0.006*
Objective response	29 (32.6)	1 (5.0)	0.013*
Disease control (CR+PR+SD)	71 (79.8)	10 (50.0)	0.006*
Loco-regional control†	83 (93.3)	17 (85.0)	0.362
Distant metastasis‡	16 (18.0)	9 (45.0)	0.017*

†Without progression of primary tumor or regional lymph node metastasis. ‡Newly developed distant metastasis after CCRT. ∫Calculated by Fisher`s exact test or Pearson`s chi-square test.
*Statistically significant.

3. Failure pattern

Among patients with confirmed PD, the pattern of treatment failure was evaluated. Both groups showed similar patterns of treatment failure. A total of 25 patients who were analyzed (89.3%) developed distant metastasis, which was the most common cause of treatment failure in CCRT for LAPC. On the other hand, progression of regional lymph node metastasis was the least common cause of treatment failure (n = 4; 14.3%).

Table 4. Failure pattern

	FG-CCRT (n=18) (%)	5FU-CCRT (n=10) (%)	Total (n=28) (%)	$P^{\int}$
Primary tumor	7 (38.9)	3 (30.0)	10 (35.7)	0.703
Regional lymph node	3 (16.7)	1 (10.0)	4 (14.3)	1
Distant Metastasis	16[†] (88.9)	9[‡] (90.0)	25 (89.3)	1

[†] Liver (10), Carcinomatosis (5), Liver + Carcinomatosis (1). [‡]Liver (5), Carcinomoatosis (2), Lung (2). [∫]Calculated by Fisher`s exact test or Pearson`s chi-square test.

4. Treatment related toxicities

Grade 3 or higher treatment-related toxicities for each group are listed and compared in Table 5. In the FG-CCRT group, hematologic toxicity, especially neutropenia, was the most frequent treatment related complication (n = 31; 34.8%) followed by thrombocytopenia (n = 19; 21.3%). Late gastrointestinal (GI) bleeding defined as GI bleeding that occurred four weeks after completion of CCRT was seen in 12 patients (13.5%). In comparison with the 5FU-CCRT group, neutropenia (34.8% vs. 10.0%; $P = 0.032$) and thrombocytopenia (21.3% vs. 0.0%; $P = 0.021$)

were the more common statistically significant differences in the FG-CCRT group. As previously mentioned, the FG-CCRT group was divided into two subgroups, GEM and GP, according to the chemotherapeutic regimen used in CCRT. Between the GEM subgroup and 5FU-CCRT group, there were no significant differences in toxicities, but the GP subgroup showed a significantly higher incidence of neutropenia, thrombocytopenia, and late GI bleeding than the 5FU-CCRT group (50.0% vs. 10.0%; $P = 0.003$, 47.1% vs. 0.0%; $P < 0.001$, 23.5% vs. 0.0%; $P = 0.020$, respectively). Among all patients, only 1 patient who received GP died because of treatment-related GI bleeding.

Table 5. Toxicities (≥ Grade 3)

	A FG-CCRT (n=89) (%)	**B** GEM (n=55) (%)	**C** GP (n=34) (%)	**D** 5FU-CCRT (n=20) (%)	**A vs. D** *(P)*	**B vs. D** *(P)*	**C vs. D** *(P)*
Fatigue	5 (5.6)	2 (3.6)	3 (8.8)	0 (0.0)	0.582	1.000	0.287
Hematologic							
Neutropenia	31 (34.8)	14 (25.5)	17 (50.0)	2 (10.0)	0.032*	0.208	0.003*
Anemia	5 (5.6)	1 (1.8)	4 (11.8)	1 (5.0)	1.000	0.465	0.640
Thrombocytopenia	19 (21.3)	3 (5.5)	16 (47.1)	0 (0.0)	0.021*	0.560	<0.001*
Gastrointestinal							
Anorexia	5 (5.6)	1 (1.8)	4 (11.8)	0 (0.0)	0.582	1.000	0.285
Nausea / Vomiting	5 (5.6)	1 (1.8)	4 (11.8)	1 (5.0)	1.000	0.465	0.640
Dyspepsia	1 (1.1)	1 (1.8)	0 (0.0)	1 (5.0)	0.335	0.465	0.370
Diarrhea	1 (1.1)	1 (1.8)	0 (0.0)	0 (0.0)	1.000	1.000	-
Neutropenic fever	3 (3.4)	0 (0.0)	3 (8.8)	0 (0.0)	1.000	-	0.287
GI bleeding†							
Early	1 (1.1)	0 (0.0)	1 (2.9)	1 (5.0)	0.335	0.267	1.000
Late	12 (13.5)	4 (7.3)	8 (23.5)	0 (0.0)	0.118	0.568	0.020*
AST/ALT elevation	1 (1.1)	0 (0.0)	1 (2.9)	0 (0.0)	1.000	-	1.000

GI : Gastrointestinal, AST : Aspartate aminotransferase, ALT : Alanine aminotransferase, GEM : CCRT with full-dose gemcitabine monotherapy, GP ; CCRT with full-dose gemcitabine and cisplatin combination therapy. †GI bleeding that occurred 4 weeks after completion of CCRT was categorized as late GI bleeding. *Statistically significant. All *P* values were calculated by Fisher`s exact test or Pearson`s chi-square test

IV. DISCUSSION

The objective of this study was to compare the therapeutic efficacy and tolerability of FG-CCRT to 5FU-CCRT for the first line treatment of LAPC. Our results indicate that the primary parameters of therapeutic efficacy are superior in patients treated with FG-CCRT compared to 5FU-CCRT. Although there were no patients that showed CR after CCRT in either group, the ORR and DCR of the FG-CCRT was significantly higher than the 5FU-CCRT group. Previous phase II trials with full-dose gemcitabine-based CCRT in patients with LAPC showed similar results. Small et al. reported an ORR and DCR of 5.1% and 84.6%, respectively.[12] Additionally, Murphy et al. reported a 15% ORR and 88% DCR.[13] Meanwhile, the ORR and DCR of the 5FU-CCRT group in this study were not inferior when compared to results of recent trials,[16] but were significantly lower than those of the FG-CCRT group.

As mentioned above, administrating full-dose gemcitabine with concurrent radiotherapy has two clinical advantages. The first is a maximum cytotoxic effect of gemcitabine as a single chemotherapeutic agent. The second is the potential radiosensitizing effect that can be achieved even at cytotoxic doses of gemcitabine.[8] To the best of our knowledge, there have only been a few studies that compared the efficacies of 5-FU-based CCRT to gemcitabine-based CCRT for treatment of LAPC. The results of previous randomized trials showed a discrepancy and included relatively small patient numbers.[16-18] Furthermore, those trials did not use full-dose gemcitabine. There was only one retrospective study that compared full-dose

gemcitabine-based CCRT to 5-FU based CCRT.[19] In that study, the authors did not report the tumor responses, but an improved overall survival was observed in the FG-CCRT group compared to the 5FU-CCRT group without differences in toxicities (median 12.5 months vs. 10.2 months; $P = 0.04$). The results of present study argue persuasively for the hypothesis that there is superior efficacy of FG-CCRT compared to standard 5FU-CCRT.

Interestingly, patients of the FG-CCRT group experienced more frequent weight loss before diagnosis and had more advanced baseline T-stages than the 5FU-CCRT group. These significant differences in patient characteristics might be explained by a poorer general pre-treatment condition and more advanced disease in the FG-CCRT group, although the ECOG performance status was not different. Despite these differences, the FG-CCRT group showed superior therapeutic efficacy.

Distant metastasis (DM) is known to be the major cause of treatment failure after CCRT for LAPC.[15,17] This event was also observed when analyzing failure patterns. Among all patients of each group, locoregional control rates were found to be similar but the rate of distant metastasis was significantly higher in the 5FU-CCRT group. According to these results, the increased efficacy of FG-CCRT may be explained. This suggests that an optimized systemic control effect should be considered primarily when choosing the chemotherapeutic agent to be used in CCRT for LAPC.

Toxicities of FG-CCRT have been controversial in spite of former trials. In our study, more frequent hematologic toxicities were seen in the FG-CCRT group than

the 5FU-CCRT group. However, they were generally within an acceptable range, which allowed for side effects to be managed medically, and there were no hematologic toxicity-related mortalities. A noteworthy result was found in the subgroup analyses of the FG-CCRT group. The GEM subgroup showed no differences in toxicity compared to 5FU-CCRT, while the GP subgroup showed a higher rate of hematologic toxicity and late GI bleeding, which resulted in the death of one patient.

Since gemcitabine has a relatively narrow therapeutic range, concerns regarding toxicities grow when using full-dose gemcitabine.[20] Previous studies suggested that the exclusion of prophylactic lymph node irradiation could diminish the toxicity and was not associated with marginal failures.[13,21] Similar to those studies, we limited the RT field to the gross tumor volume with a 5-mm margin and omitted prophylactic lymph node irradiation. Favorable locoregional response rates and tolerable toxicities were obtained and may provide supporting evidence for limiting the RT field when using full-dose gemcitabine-based CCRT. Thus, FG-CCRT can be tolerated with use of a limited RT field and cautious monitoring of hematologic toxicities. Moreover, using gemcitabine as the sole chemotherapeutic agent is safer than combined therapy with cisplatin.

The retrospective nature of this study may be an important limitation. However, patients were selected by strict inclusion and exclusion criteria, all patients received CCRT with standardized therapeutic protocols, and characteristics of both groups were similar. While there are inherent limitations of a retrospective study, we

believe these features help to minimize those limitations and increase the significance of our findings.

Regardless of the significant differences of therapeutic efficacy shown in this study, more scientific evidence is required to prove the superiority of FG-CCRT compared to 5FU-CCRT for LAPC. Our results should be considered part of the emerging evidence in favor of recommending FG-CCRT as the first-line approach to patients with LAPC. It also highlights the need of well-designed, phase III, randomized, controlled trials with larger number of participants..

V. CONCLUSION

Full-dose gemcitabine-based CCRT is more effective for initial disease control for LAPC than bolus 5-FU based CCRT. With cautious monitoring of hematologic toxicities, GEM-CCRT can be tolerably conducted. Considering that distant metastasis is the major cause of treatment failure in CCRT, full-dose gemcitabine-based CCRT should be regarded as the first option for LAPC treatment.

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ABSTRACT (IN KOREAN)

국소 진행 췌장암의 초 치료로 동시 항암화학방사선요법 시 5-fluorouracil 과 비교한 Full-dose gemcitabine의 임상적 우수성

<지도교수 방 승 민>

연세대학교 대학원 의학과

강 화 평

연구목적: 국소 진행성 췌장암 치료에서 Full-dose gemcitabine을 사용한 동시 항암화학방사선요법과 기존 용량의 5-fluorouracil을 사용한 동시 항암화학요법의 치료 효과 및 안정성을 비교하기 위해 연구를 진행하였다.

연구방법: 2006년 1월부터 2013년 3월까지 총 109명의 국소 진행성 췌장암으로 진단된 환자의 의무기록을 후향적으로 분석하였다. Full-dose gemcitabine군 (FG-CCRT) 은 총 89명으로 gemcitabine (매주 1000mg/m^2) 단독 투여군과 cisplatin (4주마다 70mg/m^2) 복합 투여군을 포함하였다. 5-flurouracil군 (5FU-CCRT) 은 총 20명으로 매주 500mg/m^2을 leucovorin (매주 20mg/m^2) 과 함께 정주한 환자를 포함하였다. 두 군에서 동시 방사선 요법은 예방적 임파선 방사선 조사 없이 주 종양 및 5mm 주변부를 대상으로 시행하였다.

결과: 객관적 반응률 (Objective response rate, ORR) 과 질병 통제율

(Disease control rate, DCR) 모두 FG-CCRT 군이 5FU-CCRT군 보다 유의하게 높았다. (ORR – 32.6% vs. 5%; P = 0.013; DCR – 79.8% vs. 50.0%; P = 0.006). 특별히, FG-CCRT군에서 치료 후 반응평가시 원격전이를 보인 비율이 월등히 낮았다. (18.0% vs. 45.0%; P = 0.017). 두 군에서 국소 질병 조절율 (loco-regional control rate) 은 비슷한 수준을 보였다. (93.3% vs. 85.0%; P = 0.362). 치료 독성에 있어서는 FG-CCRT군에서 Grade 3 이상의 백혈구 감소증 (34.8% vs. 10%; P = 0.032) 과 혈소판 감소증 (21.3% vs. 0.0%; P = 0.021) 의 발생이 유의하게 높았다. 그러나 하위 집단 분석에서 gemcitabine 단독요법을 받은 환자군만을 비교해 보았을때는 5FU-CCRT 군과 치료 독성 발생의 차이를 보이지 않았다.

결론: Full-dose gemcitabine, 특히 gemcitabine을 단독으로 사용한 동시 항암화학방사선요법은 5FU를 사용할 때에 비해 국소 진행성 췌장암의 초기 치료로서 임상적인 효과가 더 높을것으로 기대되며 치료 관련 독성의 증가에 대한 걱정 없이 비교적 안전히 사용할 수 있을것으로 생각된다.

핵심되는 말: 국소 진행성 췌장암, 동시 항암화학방사선요법, CCRT, Gemcitabine, 5-FU