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위암환자에서 근치적 위절제술후 시행한 보조적 PMF 항암 화학요법에 대한 무작위 전향적 연구

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Randomized Clinical Trial of Adjuvant Chemotherapy with Mitomycin, Cisplatin and 5-FU in Patients with Curative Resected Gastric Cancer

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국문초록

연구 목적: 위암 수술 후 보조 항암 치료의 효과에 대하여서는 아직 논란이 있다. 전향적으로 무작위표본 추출법으로 근치 절제 수술한 위암 환자에서 수술 후 cisplatin, mitomycin C 그리고 5-FU(PMF)의 주사가 5년 생존율이나 무병 생존율을 증가할 수 있는지를 연구하였다.

연구 방법: 1995년 5월부터 2002년 5월까지 147명의 근치 수술된 위암 환자들 중에 병기 IB, II, IIIA, IIIB 및 IV를 대상으로 하였으나 65세 미만을 대상으로 하여 무작위적으로 2군으로 나누어, 경구 5-FU제를 투여하는 군(대조군)과, PMF 항암 주사 치료군(치료군)으로 나누어 치료하였다. 경구 5-FU항암제는 수술 후 퇴원할 시기부터 투여하였다. PMF 주사치료는 수술 후 8주 이내에 시작하며 2코스 이상 완료한 사람들을 치료군에 포함하였다. 항암 주사는 다음과 같이 진행하였다; cisplatin 30mg 정맥 주사를 제 1-5일에, mitomycin C 4mg과 5-FU 250mg정맥 주사를 주 2회 4 주간 주사하였다. 이런 주사치료를 매 4주마다 시행하였다. 이 후 5년 생존율과 무병 생존율을 Kaplan-Meier 분석과 log-rank 검정으로 구하였다.

결과: 중앙 추적기간은 36개월이었다. 전체 5년 생존율은 치료군과 대조군에서 각각 68.8%와 65.2%(p=0.26), 무병 생존율은 각각 72%와 64%(p=0.24)로 치료군에서 다소 나았으나 유의성은 없었다. 치료에 동의한 환자의 수가 적어 각 병기별 생존율보다 비교적 조기인 병기 IB와 병기 II를 A군으로, 병기 IIIA을 B군, 그리고 진행된 병기인 병기 IIIB와 병기 IV를 C군으로 나누어 생존율 비교하여 보았다. A군과 C군은 5년 생존률이나 무병생존율의 차이가 없었으나, B군에서는 5년 생존율이 치료군에서 100%, 대조군은 40.8%(P=0.0019)로 유의한 차이가 있었고, 무병 생존율도 치료군 100%, 대조군 52.94%(p=0.005)으로 의미 있게 차이가 있었다. 항암 주사치료에 의한 부작용은 심하지 않았으며, 사망자는 없었다.

결론: 위암 수술 후 PMF에 의한 항암 보조치료는 경구 5-FU에 비하여 병기 IB, II, IIIB와 IV에서는 5년 생존율이나 무병 생존율에 차이가 없었으나 병기 IIIA에서는 5년 및 무병 생존율에 의미있게 좋았다. 앞으로 C군에 대한 수술 후 보조 항암치료법의 연구가 요망된다.

중심단어: 위암 수술, PMF, 보조항암 치료

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서 론

Gastric cancer is a very aggressive disease, with a tumor doubling time of 40 to 80 days. Surgery is the treatment choice, with less than 30% of 5-year survival for patients with complete tumor resection.[1-3] Although the incidence

of gastric cancer has decreased progressively in recent decades, the prognosis of the disease has not changed in the last 30 years. Global survival to 5 years remains between 7% and 15%.4-7)

The efficacy of adjuvant chemotherapy in the disease is controversial. The results of trials performed to study its effects did not recommend its use.[8-9] On the other hand, in Japan, the administration of mitomycin and fluoropyrimidines has been considered standard adjuvant chemotherapy since the late 1970s.[10,11] However, the Japanese results have been criticized the lack of randomized studies to confirm efficacy.[12,13]

In 1988, there was a report of cure of gastric cancer by combined chemotherapy with cisplatin, mitomycin C, and 5-fluorouracil(Tanemura et al, 1988)[16] . We found it was active both in advanced gastric cancers and preliminary adjuvant settings (data not shown).

PATIENTS AND METHODS

Patients;

Include in this study, 216 patients entered into a prospective, randomized controlled trial of cisplatin, mitomycin C, and 5-FU (PMF) based adjuvant chemotherapy after curative gastrectomy at Kosin University Gospel Hospital in Pusan, Korea, between May 1995 and May 2002. We included patients with stage IB, II, IIIa, IIIb and IV. and age below 65 year old. We lost follow up 2 patients(their stages were II, and IIIa) from control arm(follow up rate was 98.6%). Patients who have an even number of his ID were classified to study group, and patients who have an odd number of his ID were classified to control group. Informed consent was required for inclusion and 67 patients from study group were refused to have chemotherapy. Thus 48 patients were enrolled in study group and 99 patients in control arm. All patients had a post surgical pathologic stage ranging from IB to IV without evidence of distent metastasis according to the American Joint Committee on Cancer Staging Manual(American Joint Committee on Cancer, 1997). Curative resection was defined by the General Rules for the Gastric Cancer Study in Surgery and Pathology of the Japanese Research Society for Gastric Cancer as : no involvement of surgical stumps; sufficient lymphatic dissection (D number ≥N number); no distant metastasis; removal of involved adjacent organs and structures by combined en-bloc resection; and no gross residual disease (Japanese Research Society for Gastric Cancer, 1981). None of these patients received chemotherapy prior to surgery.

Chemotherapy

After surgery, patients were randomly assigned, with equal probability. Patients in study group were received PMF chemotherapy followed by oral 5-FU administration, in control group were received oral 5-FU administration only. PMF chemotherapy was started within 28 days after surgery and was administered according to the following schedule; cisplatin 30 mg intravenously on day 1 through 5; mitomycin C 4 mg and 5-FU 250 mg intravenously on day 1 and day 5(bis weekly) for 4 weeks. The treatment were repeated every 4 weeks. More than 2 courses were repeated and toxic effects were evaluated using the World Health Organization criteria.

Statistical analysis

5-year survival, disease free survival and overall survival were calculated using the Kaplan-Meier method (Kaplan and Meier, 1958). Disease-free survival was defined as the time from the day of operation to a documented recurrence, or second primary cancer, or death from gastric cancer. Overall survival was defined as the time from the day of operation to death; data on survivors were censored at the last follow-up. P value under 0.05 is considered as significant. The differences between the survival curves were tested by using the log-rank test.

RESULTS

Of the 147 eligible patients, the control group included 99, and the treatment group included 48. 98 were male and 49 were female, and their median age was 51.66 and the median follow-up period was 36 month. Stages were IB in 26, II in 40, IIIa in 33, IIIb in 30, and IV in 18 patients. We made patients in three groups which were stage Ib + II in group A, stage IIIa in group B, and stage IIIb + IV in group C. All patients received the treatment to which they were randomized.

At baseline, the three groups were similar in demographic characteristics, and there was larger number of patients with subtotal gastrectomy than total gastrectomy. According to the results, there was statistically difference of T and N stage distribution between treatment and control arm in group A. It is because there are larger percentage of T1 stage patients in treatment arm than control. Despite of statistically significant difference, the overall survival rate was better in control arm than treatment arm(68.8/65.2, P=0.26). However, there were no statistically significant difference of T and N stage distribution in group B and C(Table 1).

Table 1. Clinical characteristics of patients

Characteristic	Ⅰb + Ⅱ(66)		Ⅲa(32)		Ⅲb + Ⅳ(49)	
	Treatment	Control	Treatment	Control	Treatment	Control
Gender						
Male	10	32	13	11	10	22
Female	8	16	0	8	7	10
Age, years						
mean	51.44	51.48	51.46	50	50.82	53.56
Primary tumor depth						
T_1	5	5	0	0	0	0
T_2	10	19	2	1	0	1
T_3	3	24	11	18	14	26
T_4	0	0	0	0	3	5
p	0.31		0.552		0.756	
Regional lymph node metastases						
N_0	8	39	0	0	0	1
N_1	8	9	11	18	2	5
N_2	2	0	2	1	12	18
N_3	0	0	0	0	3	8
p	0.004		0.552		0.732	
Surgical technique						
Total	1	10	0	5	6	16
Subtotal	17	38	13	14	11	16

Toxicity

The treatment was tolerable. Side effects were generally mild or moderate. Especially gastrointestinal symptoms(nausea and vomiting) was mild. But thrombocytopenia 14 cases of grade 3(29.17%) and 9 cases of grade 4(18.75%) forced us to delay the administration of the therapeutic courses without having to use supportive measures. There were no fatal renal toxicity(Table 2).

Table 2. Number of side effects of the cisplatin, mitomycin C, and 5-fluorouracil chemotherapy.

	G0	G1	G2	G3	G4
Anemia	3	4	26	14	1
Neutropenia	6	7	26	7	2
Thrombocytopenia	7	8	10	14	9
Nausea	9	22	15	2	0
Vomiting	29	11	5	3	0
Cr. level	43	3	2*	0	0
Hematuria	47	1	0	0	0
Proteinuria	47	1	0	0	0

* Hemodialysis weekly

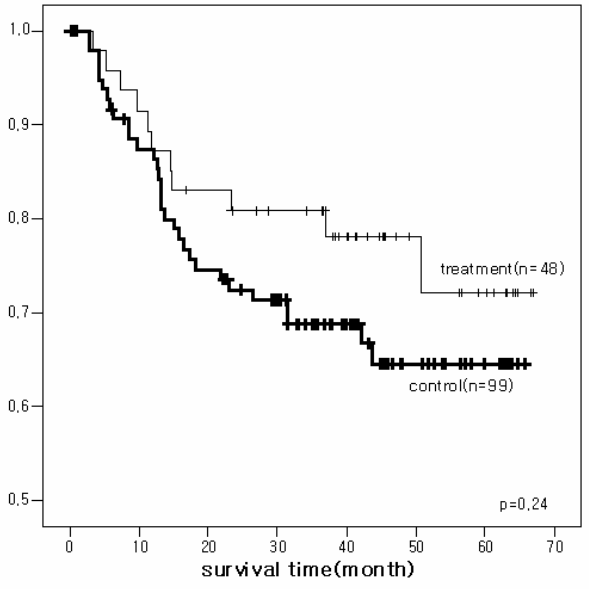
Survival and Disease-Free survival

Table 3 lists the overall results for the outcome variables. The overall 5-year survival rate and disease-free survival rate were not better in the group of patients treated with chemotherapy(P=0.26, and P=0.24). The overall survival rate of treatment group was 68.8%, and control group was 65.2%. The disease-free survival rate of treatment group was 72%, and control group was 64%, and the Kaplan-Meier curves were no statistically significant difference.(Fig 1, and Fig 2)

Table 3. Descriptive results of the outcome variables of the end of follow-up.

	Group A		Group B		Group C	
	Treatment	Control	Treatment	Control	Treatment	Control
mean Age	51.44	51.48	51.46	50	50.82	53.56
5-year survival rate(%)	90.91	95.56	100	40.8	18.7	32.91
Mean survival time(month)	62.15	63.47	-	38.8	33.41	30.78
P value	0.86		0.0019		0.51	
Disease free survival rate(%)	91.6	95.3	100	52.94	21.4	25.9
P value	0.83		0.005		0.88	

Figure 2. Disease-free survival rates of treatment and control group



Between treatment and control arm at group A (stage Ib+II) and group C (stage IIIb+IV), there also were no statistically significant difference. The 5-year survival rate of treatment and control arm at group A were 90.91% and 95.56% (P=0.86), and group C were 18.7% and 32.91% (P=0.66). The disease-free survival rate of treatment and control arm at group A were 91.6% and 95.3% (P=0.83), and group C were 21.4% and 25.9% (P=0.88) However, there was significantly better survival at the treatment arm of group B (stage IIIa). The 5-year survival rate of treatment arm were 100%, than its control arm, 40.8% (P=0.0019). The disease-free survival rate of treatment and control arm were 100% and 52.94% (P=0.005). Actuarial survival curves of each groups in treatment and control arm are displayed in Figure 3.

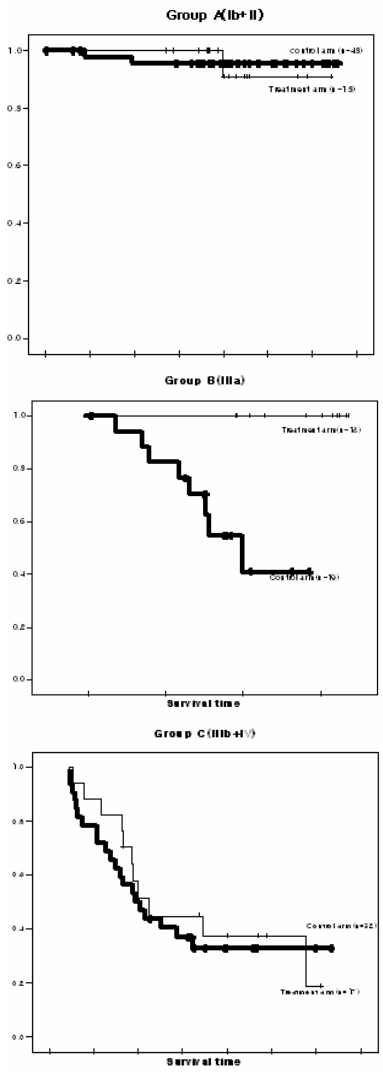


Figure 3. Actuarial 5-year survival rates of treatment and control arm at group A were 90.9% and 95.6%(p=0.86), group B 100% and 40.8%(p=0.005) and group C 21.4% and 25.9% (p=0.88), respectively.

DISCUSSION

The basic treatment of advanced gastric carcinoma is surgery. The stage and the number of affected lymph nodes were known as most important factors of recurrence or survivals after surgery. Despite radical surgery, however, there were locally or distent metastasis about 40% to 50% patients who had taken surgery. For the effort to decrease recurrence, there needed adjuvant chemotherapy or

radiation treatment after surgery.

In the study of adjuvant gastric carcinoma, Southwest Oncology Group (SWOG) 9008/Intergroup (INT) 0116 reported 603 patients who were resectable gastric cancer. In this study, they compared treatment group who had single course of 5- fluorouracil+leukovorin therapy, then radiation therapy, and then 2 courses of chemotherapy with same regimen to control group who had surgery only. The study reported statistically improved 3-year disease-free survival in treatment group(48%) than control group(31%) and also median survival time (36 month /27 month). But there were several problems in this study. The regimen of 5-FU, leukovorin were mainly used in colorectal carcinoma and did not effective in stomach cancer. And there had only 10% of D2 surgery, 36% of patients had D1, and 54% of patients had D0. In these reasons, there were 64% of patients with locally metastasis in the control group. However, it is significant that adjuvant chemotherapy and radiation therapy after surgery has improvement of survival and local recurrence rate than surgery only[17, 18].

In 1977, a Japanese group reported a statistically significant survival advantage in patients given postoperative intermittent mitomycin[19]. Nakajima[20] reported that mitomycin produced a significant survival advantage in patients with serosal and/or nodal involvement. In 1983, in a randomized Western trial, significant improvement in disease-free survival and overall survival were reported with the administration of four courses of high-dose mitomycin(20 mg/m^2) in resected stage II to III gastric cancer patients.[14]

In 1988, Tanemura et al was reported a complete response which was confirmed by roentgenography and endoscopy with cisplatin, mitomycin C, and 5-FU combined chemotherapy in advanced gastric cancer[16]. Evaluation of CDDP therapy for gastric cancer has not yet been established, but several previous studies were reported effectiveness of CDDP chemotherapy about 22.2% to 33.3% .[21,22] In this study, they performed CDDP therapy (intravenous administration at a dose of 30 mg/day for 5 consecutive days, and MMC at a dose of 4 mg/day and 5-FU at 250 mg/day were given intravenously twice a week within a month after surgery, amounting to 19 doses in total), single or in-combination with other chemo-therapeutics, in 12 case of unresectable or recurrent gastric cancer, and obtained complete response (CR) in 2 cases, minor response (MR) in 1 case, no change (NC) in 2 cases, and progressing disease (PD) in 7 cases - total effectiveness being 16.7%.[16]

We based the dose of CDDP, MMC, and 5-FU on a previous Tanemura et al's experience. In our study, we observed better survival for stage IIIa gastric cancer with adjuvant PMF chemotherapy. These data suggested that adjuvant PMF chemotherapy after curative resected surgery of stage IIIa gastric cancer is successful treatment and has better effect, but it is controversial to use in stage Ib, II, IIIb, and IV gastric cancer. There is a need for an updated, systemic review of adjuvant chemotherapy in gastric cancer to determine whether there is enough evidence to support its use or whether more clinical trials are needed.

CONCLUSION

There are little benefit from adjuvant PMF chemotherapy in stage Ib, II, IIIb, and IV. But we observed significant survival for stage IIIa gastric cancer with adjuvant PMF achemotherapy than oral 5-FU administration only. Despite no statistically significant difference, the overall 5-year survival rate and the overall disease-free survival rate were higher in the group of patients treated with this chemotherapy.

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