Combination 5-Fluoruracil/Cisplatinum Versus 5-Fluoruracil/Leucovorin Adjuvant Chemotherapy Efficacy for R0 Gastric Resection in Locally Invasive Gastric Cancer

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Background: *The efficacy of adjuvant chemotherapy for advance resectable gastric cancer is controversial. Recently, less than 20% of the patients that received surgery can survive locally advance gastric cancer for 5 years. The purpose of the present study was to compare the therapeutic efficacy of the combination 5-fluoruracil (5-FU) with cisplatinum based and single 5-FU based regimen for the treatment of gastric cancer after post-operative gastric resection.*

Material and Method: *Patients were recruited if they underwent curative R0 gastric resection surgery with standard D1 or D2 lymph node dissection. Between 2002 and 2007, we conducted a cohort study, and collected prospective data of 88 patients with advanced gastric cancer. They were analyzed for median survival time and rate, recurrence rate, and chemotherapy toxicity prevalence. The median survival time was the primary study end point. The median survival time was compared between groups by a log-rank test.*

Results: *In the present study, combined 5-FU based regimen did not show a significantly superior survival time to single 5-FU regimen, both poor stage groups had better median survival in both combined 5-FU and single 5-FU regimen when compared to surgery. There was more than 50 months median survival in the first group, and 52 months in the latter. However, in cisplatinum with 5-FU group, there are only a small number of signet ring cells. In addition, those have poorer clinical profile before treatment ($p = 0.003$). No difference on mortality rate related to toxicity.*

Conclusion: *Both regimens are useful regimens with efficient benefit for gastric cancer patients as well as a cheaper regimen than other new combination drug regimens. However, second line drug or other combined second generation based chemotherapy regimen that has similar action to cisplatinum such as oxaliplatin may be safer for toxicity, and may get better out outcome. 5-FU regimen is still the reference group in future clinical trial for advanced gastric cancer treatment. The value of any new adjuvant treatment approach could be proven by a randomized study comparing it with cisplatinum based regimen plus 5-FU or single 5-FU regimen.*

Keywords: *Adjuvant chemotherapy, Cisplatinum, 5-fluouracil, Gastric cancer*

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Gastric cancer is a common gastrointestinal cancer and a major health problem worldwide, despite its incidence declining over the past 60 years[1]. In Asian countries, gastric cancer remains a major cause of cancer-related death. Nowadays, in our northern regional hospital, Maharaj Chiang Mai Hospital, the prevalence of new gastric cancer is increasing to more than hundred cases per year. It is the second most common gastrointestinal tract cancer diseases that presented in our hospital.

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Surgery is still the treatment of choice[2] but most patients are not curable by surgery alone because of late detection. At diagnosis, approximately 50% of patients have gastric carcinoma that extends beyond the locoregional confines. In that group, 50% of the patients cannot undergo a curative resection (R0)[3].

The 5-year survival rate of gastric carcinoma is less than 20% and has not changed significantly in the last 30 to 40 years in western world[4]. Some randomized trials demonstrated that chemotherapy regimens for adjuvant treatment provided superior survival when compared with the best supportive care alone in patients with advanced gastric cancer[5-7]. Almost all patients with advanced disease required several regimens of chemotherapy such as a

cisplatin-based, 5-FU based, taxane-based, or irinotecan-based treatment[8-10]. However, no regimen has been proven to improve survival rate and quality of life. Systemic chemotherapy administration is frequently associated with related toxicity, which particularly serves patients presenting in poor general condition.

The 5-fluorouracil (5-FU) is the most widely used adjuvant treatment. It is a single chemotherapy agent for gastric cancer. Another regimen is the 5-FU in combination with cytotoxic drugs. The use of continuous 5-FU infusion is promising and may lead to the development of even more effective treatment by combination with other chemotherapy. This method could eventually alter the belief that gastric cancer is not a chemosensitive neoplasm.

Recently, the combined chemotherapy regimen achieved only a 25 to 60% response rate, but it has significantly affected the survival because of its toxicity[11]. Unfortunately, no definite conclusion has been drawn from recent randomized clinical control trials for various regimens. The study cannot conclude which could be a better regimen to improve survival, have lower side effects, and provide patients a good quality of life. In this study, the authors aimed to study the efficacy of the 5-FU based chemotherapy regimen for treatment of gastric cancer in Northern-Thai patients. The goal was to assess the 5-FU leucovorin regimen by comparing it with the combination 5-fluoruracil cisplatinum regimen on patients that underwent R0 curative gastrectomy. In addition, we evaluated the safety of these regimens by analyzing the adverse side effects and the toxicity rate.

Material and Method

The medical records of all patients who underwent gastric resection of a pathologically confirmed gastric adenocarcinoma in the Department of General Surgery, Maharaj Chiang Mai Hospital, Thailand between January 2002 and December 2007 were prospective studied and followed-up until end of 2009. Some data were collected by direct interview. Additionally, questionnaires were sent to the patient's home after review of the basic data. The authors also collected data on recurrence, survival rate, and toxicity as a prospective trial on an intention to treat basis. The present study was approved by the Ethical Committee of the Faculty of Medicine, Chiang Mai University. The expected sample size was more than 30 patients for each group.

Inclusion criteria

Patients aged 18 to 75 years, who underwent complete D1or D2 gastric resection by three experienced and qualified gastrointestinal tract surgeons. The pathological documents were reviewed by oncosurgical pathologist to confirm gastric adenocarcinoma. The type of operation was staged. The authors included only R0 resection for locally invasion that are in stage III by AJCC TNM seventh edition staging. Patients needed an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or better and life expectancy of 12 weeks or longer with the following criteria, adequate marrow (WBC count $\geq$ 4,000/μL, hemoglobin $\geq$ 9.5 g/dL, platelets $\geq$ 100,000/μL), liver (AST and ALT within three times the upper limit, bilirubin $\leq$ 2.0 mg/dL), renal (creatinine clearance $\geq$ 50 mL/min), and cardiac function (normal EKG).

Exclusion criteria

Patients with serious tumor complications, advance distant metastasis with less than three months length of survival expectancy, active carcinoma at other sites, large amounts of ascites, and those who received radiation therapy or other chemotherapy before this treatment. After surgery, patients were randomly assigned to receive either 5-FU leucovorin or combination or 5-FU cisplatinum regimen. Chemotherapy was started within 28 days after surgery and administered according to the following schedule. For the 5-FU Leucovorin regimen, the 5-fluorouracil at 500 mg/m^2/day and leucovorin at 20 mg/m^2/day were administrated for day 1 to 5[7]. For the combination cisplatinum plus 5-FU regimen, the cisplatinum at 20 mg/m^2/day, 5-fluorouracil at 500 mg/m^2/day, and leucovorine at 20 mg/m^2/day were administrated for day 1 to 5. The cycle was repeated every 28 days in the single FU and 21 days in cisplatinum based regimen. Those were done for six cycles.

Baseline evaluation included the patient's characteristics [mean age (year), sex (male/female), location of tumor, type of gastrectomy, lymph node involvement, and staging], and the toxic side effect was evaluated using the WHO toxicity criteria. Survival and recurrence were measured from the date of the first admission, comparison of patient characteristics, toxicity, and response rates between groups were calculated by the α two tailed test. All patients registered were included in the survival analysis on an intention-to-treat basis. Overall survival was calculated from the date of surgery to the date of death or to the last contact date, using the

Kaplan-Meier method. Survival and progression-free survival were calculated by the Kaplan-Meier method and compared by the log-rank test. p-value of less than 0.05 was considered statistically significant. Student t-test or Mann-Whitney U-test was used for quantitative data. Chi-square test or Fishers' exact test was used for qualitative data according to data distribution.

Results

Between 2002 and 2007, eighty-eight patients who underwent both complete gastric resection with one of selected post-operative chemotherapy regimens in Maharaj Nakorn Chiang Mai Hospital were recruited into the present study. The patients included in this study consisted of 46 male and 42 female. Forty-nine patients had been treated with single 5-fluouracil regimen and 39 had been treated with cisplatinum plus 5-fluouracil regimen. Clinical features and characteristics were similar among the groups (Table 1).

All 88 patients who received chemotherapy were assessed for toxicity. The toxicity grade for all patients was mild grade and well-tolerated. There was no death related toxicity in eight groups in our center.

Table 1. Demographic data

Variable	5-FU + Cisplatin, n = 39 (%)	5-FU, n = 49 (%)	p-value
Sex (%)			
Male	20 (51.28)	26 (53.06)	0.868
Female	19 (48.72)	23 (46.94)	
Age (year)			
Mean (SD)	51.43 (13.05)	55.53 (13.04)	0.147
ECOG (%)			
Grade 0	33 (84.62)	35 (71.43)	0.387
Grade 1	5 (12.82)	11 (22.45)	
Grade 2	1 (2.56)	0	
Grade 3	0	1 (2.04)	
Grade 4	0	1 (2.04)	
Grade 5	0	1 (2.04)	
Positive pathological lymph node (%)			
Yes	27 (69.23)	22 (44.90)	0.022
No	12 (30.77)	27 (54.17)	
Pathological stage III			
Poor prognosis (%)	29 (74.36)	22 (45.83)	0.052
Good prognosis (%)	10 (25.64)	27 (54.17)	
Location (%)			
Distal third	30 (76.92)	41 (83.67)	0.219
Middle third	1 (2.57)	4 (8.16)	
Upper third	7 (17.94)	2 (4.08)	
More than two-thrid	1 (2.57)	2 (4.08)	
Histologic grade (%)			
Poorly differentiated	11 (28.21)	23 (46.94)	0.003
Moderately differentiated	8 (20.51)	11 (22.45)	
Well differentiated	0	5 (10.20)	
Signet ring cell	17 (43.59)	5 (10.20)	
Undifferentiated	3 (7.69)	5 (10.20)	
Surgical treatment (%)			
Total gastrectomy with jejunostomy	20 (51.28)	32 (65.13)	0.336
Total gastrectomy without jejunostomy	1 (2.56)	0	
Subtotal gastrectomy	14 (35.89)	14 (28.57)	
Antrectomy	4 (10.27)	3 (6.30)	

There was no treatment-related serious complication or death in 30 days after surgery in the present study. Common hematological toxic side-effects were seen significantly more often in the combination cisplatinum with 5-FU group than in the single 5-FU regimen (Table 2). In the first or second cycle, some patients suffered from prolonged and delayed nausea and vomiting, which affected their quality of daily life. However, almost all patients with these symptoms responded well to intravenously or orally administered ondansterone. In those, the rate of nausea/vomiting decreased in subsequent days. Feeding jejunostomy for early enteral feeding gave benefit to patients. Those were earlier recovery post-operatively, and tolerability of chemotherapy caused anorexia.

For survival analysis (Fig. 1, 2 and Table 3), the overall survival was 52 months. The median survival times were 52 months and 53 months in the combination cisplatinum with 5-FU group and single 5-FU group, respectively. There were no significant differences between the groups in regard to overall median survival, p = 0.325 (95% CI = 0.18-1.74). However, the patients with signet ring cell had significantly higher number in the combination regimen group than in those in the single 5-FU regimen. The prognosis in the combination regimen was worse than in the single 5-FU regimen. However, the relative superior benefit of the combination regimen was seen, although no significant difference by statistic was found. The clinically significant benefit in poorer cell type group such as signet ring cell was seen. For both genders, we found that woman had a significant better survival rate in the 5-FU group than in the combination regimen. Female has better overall prognosis than in male by p-value = 0.084 (95% CI = 0.37-30.52).

The 3-year survival rate was 75.04% in the combination cisplatinum and 5-FU regimen group, and 84.46% for single 5-FU regimen group.

Recurrence occurred in the group of combination cisplatinum with 5-FU faster than in

Table 2. Baseline characteristic

Variable	Cisplatin + 5-FU (n = 39)	5-FU (n = 49)	p-value
Side effect (%)			
Leukopenia	6 (15.79)	6 (12.24)	0.634
Anemia	9 (27.27)	5 (10.42)	0.049
Vomiting	1 (2.94)	2 (2.48)	0.784
Diarrhea	0	0	
Alopecia	0	12 (25.00)	0.002
Stomatitis	4 (11.76)	4 (8.16)	0.585
Cardiac	2 (6.06)	1 (2.27)	0.395
Renal	1 (3.03)	0	0.225
Thrombocytopenia	10 (26.32)	3 (6.12)	0.009
Status (%)			
Alive	35 (89.74)	48 (97.96)	0.098
Death	4 (10.26)	1 (2.04)	
Recurrence (%)			
Yes	6 (15.38)	8 (16.33)	0.904
No	33 (84.62)	41 (83.67)	

Table 3. Median survival time by sex and recurrence

	Cisplatin, survival time (months)			5-FU, survival time (months)		
	25%	50%	p-value (95% CI)	25%	50%	p-value (95% CI)
Sex						
Male	52	52	0.278 (0.7-30.52)	38	53	0.122 (0.00-1.56)
Female	23	-		61	61	
Recurrence						
No	-	-	1.000	-	-	1.000
Yes	12	20		18	27	

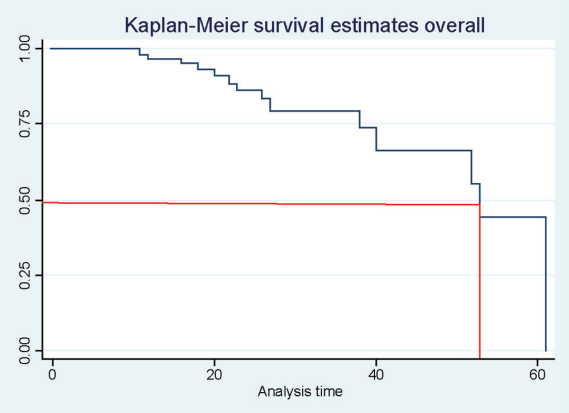

Fig. 1 Survival curve of gastric cancer
Median survival time 52 months

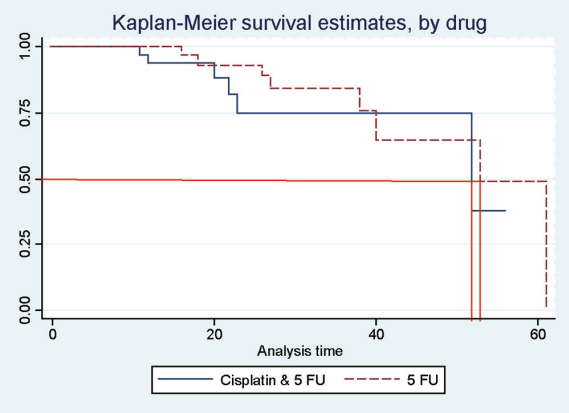

Fig. 2 Survival curve of gastric cancer by adjuvant chemotherapy
Median survival time (cisplatin) = 52 months
Median survival time (5 FU) = 53 months
p-value = 0.325, 95% CI = 0.18-1.74

5-FU group. This could be explained by the difference of histologic demographic. Eighty percent of the patients in both group that suffered from recurrence, occurred at 32 and 34 months. This was not significantly different.

Discussion

The 5-FU infusion is promising and may lead to the development of even more effective treatment. Those could eventually alter the belief that gastric cancer is not a chemosensitive neoplasm, created by the modest results of the 1970s. It is worth mentioning that two recent randomized trials showed a significant survival benefit for chemotherapy compared to best supportive care[5,12].

Many studies have demonstrated that the combination regimen produced a more modest response rate than single 5-FU based regimen, but the combination regimen did not influence significant overall survival more than single 5-FU[13-15]. They proved that the value of any new treatment approach could be a randomized comparison to single 5-FU regimen[14]. However, these studies did not describe in detail of prognosis by hisologic grading in comparative group.

Some studies showed that single agents with proven activity in the first line setting are 5-FU, cisplatin, etoposide, doxorubicin, mitomicin C, paclitaxel, and irinotecan. With these agents, the response rates have been reported[16] to range from 14 to 44%. The 5-FU, cisplatin, paclitaxel, and irinotecan have also been used as single agents and second line treatment. The achieved response rate were about 12 to 26%[16]. However, the benefit of the combination regimen over single agent chemotherapy for patients has not been clearly verified in any randomized controlled study. The MAGIC trial is biggest phase III trial nowadays for combination therapy. However, shifting stage effect resulted on less than 30% of the patients can be cured by surgery alone. Therefore, new strategies need to be found.

Some studies showed that the therapeutic effectiveness of FAMe (5-FU, doxorubicin, and methyl lomustine), FAP (5-FU, doxorubicin and cisplatin), and FAMe alternating with triazinate (TZT), when compared with a standard therapy of 5-FU alone in patients with advanced gastric cancer did not showed a significant advantage over 5-FU alone in improving performance score, weight gain, and patient survival. Each of the three combinations has more toxicity than single 5-FU based regimen[13,17,18].

Recently, FAM did not show a significantly superior survival rate over the FL group in our center interim analysis. Therefore, we selected to use combination cisplatinum and 5-FU in the present study. The median progression-free survival in the FL alone group was slightly longer than that in the combination group. The limitations of the present study were bias of surgeon on histologic grading. Therefore, the chance selection to use cisplatinum on poorer prognosis histologic grade patients was there. Furthermore, there was a small sample size. This study relied on medical records and the oncology chart for information regarding comorbid illnesses. However, this study result could be the basic comparative data for further study, or for further comparative study on other

chemotherapy regimen arm. The authors propose to use median survival as the most reliable and reasonable end point with future studies to select the chemotherapy regimen for gastric cancer patient. The single or combined 5-FU based regimen will also remain reference groups in our future trial for advanced gastric cancer for adjuvant or neo-adjuvant treatment. However, the second line drug or other combined second generation based chemotherapy regimen that has similarly action to cisplatinum such as oxaliplatin might be safer for toxicity. Randomized controlled trial should be conducted.

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Potential conflicts of interest

None.

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การศึกษาเปรียบเทียบประสิทธิภาพการให้ยาเคมีบำบัดแบบเสริมระหว่าง 5-fluoruracil/cisplatinum และ 5-fluoruracil/leucovorin หลังการผ่าตัดชนิด R0 ในโรคมะเร็งกระเพาะอาหารระยะลุกลามเฉพาะที่

สิริกาญจน์ ยามาดะ, ปาริชาติ ฤทธิ์ฉิ้ม, ธีรภัทร์ จักรพันธุ์, วิไลวรรณ จงรักษ์สัตย์

วัตถุประสงค์: *ประสิทธิภาพการใช้ยาเคมีบำบัดในผู้ป่วยกลุ่มมะเร็งกระเพาะอาหาร เพื่อการรักษาเสริมหลังการผ่าตัดมะเร็งนั้นยังไม่เป็นที่เข้าใจดีนัก ในสมัยก่อนอัตราการรอดชีวิตหลังการผ่าตัดในผู้ป่วยระยะมะเร็งกระเพาะอาหารลุกลามเฉพาะที่มีเพียงร้อยละ 20 การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาเปรียบเทียบประสิทธิภาพในการให้ยาเคมีบำบัดในผู้ป่วย 2 กลุ่ม โดยกลุ่มแรกให้ยาเคมีบำบัด 5-FU ร่วมกับ cisplatinum และกลุ่มที่ 2 ให้ยาเคมีบำบัด 5-FU เท่านั้น หลังการผ่าตัดรักษามะเร็งกระเพาะอาหารที่ทำการตัดมะเร็งได้สำเร็จ*

วัสดุและวิธีการ: *ผู้ป่วยที่รวมในการศึกษานี้ได้รับการผ่าตัดโดยวิธีการผ่าตัดต่อมน้ำเหลืองมาตรฐาน D1 หรือ D2 ได้ทำการศึกษาติดตามไปข้างหน้าในผู้ป่วยที่รับการรักษาในช่วงปี พ.ศ. 2545-2550 และเก็บรวบรวมข้อมูลในผู้ป่วย 88 ราย โดยวิเคราะห์อัตราการตายและระยะเวลาการอยู่รอด อัตราการกลับซ้ำ และอัตราการเกิดผลข้างเคียงจากการใช้ยา โดยมีเป้าประสงค์เพื่อทราบระยะเวลาการอยู่รอดเป็นหลักโดยการศึกษาเปรียบเทียบระยะเวลาการอยู่รอดระหว่างกลุ่มการรักษา 2 แบบ โดยวิธี log-rank test*

ผลการศึกษา: *ผลจากการศึกษานี้พบว่าระยะเวลาการอยู่รอดของผู้ป่วยจากการให้ยา cisplatinum ร่วมกับ 5-FU ไม่มีความแตกต่างอย่างมีนัยสำคัญ ในกลุ่มแรกมีระยะเวลาการอยู่รอดเท่ากับ 52 เดือน และในกลุ่มที่ 2 เท่ากับ 53 เดือน ตามลำดับ อย่างไรก็ตามผู้ป่วยในกลุ่มที่ให้ยาเคมีบำบัด cisplatinum ร่วมกับ 5-FU มีอาการและพยากรณ์แย่กว่าโดยรวม เนื่องจากเป็นกลุ่มที่มีผู้ป่วยที่เป็นชนิด signet ring cells เป็นจำนวนมากกว่ากลุ่มที่ให้ 5-FU เท่านั้นอย่างมีนัยสำคัญ ($p = 0.003$) และไม่มีความแตกต่างสำหรับอัตราการเสียชีวิตที่เกิดจากพิษของเคมีบำบัด*

สรุป: *ในการศึกษานี้พบว่าการให้ยาทั้งสองแบบมีประสิทธิภาพดี และสามารถเพิ่มอัตราการรอดชีวิตในผู้ป่วยมะเร็งกระเพาะอาหารระยะลุกลามให้มีระยะเวลาการอยู่รอดโดยเฉลี่ยนานขึ้นกว่าการผ่าตัดเท่านั้น และมีราคาไม่แพง อย่างไรก็ตามอาจลดอัตราการเกิดผลข้างเคียงจากเคมีบำบัดกลุ่ม cisplatinum ได้ และอาจให้ผลที่ดีขึ้น ถ้ามีการศึกษาเพิ่มเติมเปรียบเทียบยาในกลุ่มใกล้เคียง เช่น oxaliplatin เป็นต้น ยาเคมีบำบัดกลุ่ม 5-FU ยังเป็นยาพื้นฐานที่ใช้ได้ผลดี รวมทั้งเป็นกลุ่มอ้างอิงในการศึกษาในอนาคตต่อไป สำหรับการรักษามะเร็งกระเพาะอาหารระยะลุกลาม การศึกษายาเคมีบำบัดกลุ่มอื่นน่าจะมีความเป็นไปได้สำหรับการทำการศึกษาไปข้างหน้าแบบสุ่มเปรียบเทียบกับยา cisplatinum หรือ กลุ่ม cytotoxic drug อื่นร่วมกับ 5-FU ต่อไป*