RESEARCH ARTICLE

# Can Capecitabine be used Instead of Concurrent Bolus 5-FU in Postoperative Chemoradiotherapy for Gastric Adenocarcinoma?

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## Abstract

**Background: 5-fluoro-uracil (FU) is a common agent in postoperative chemoradiation in gastric adenocarcinoma. However, FU is not well tolerated in a significant proportion of patients. Capecitabine (CA) is an orally administered fluoropyrimidine carbamate which is preferentially converted to active 5-FU and is one of the agents used instead of FU in such cases. We compared the toxicity, local and distant control and survival rates with FU or oral CA during the course of concurrent radiotherapy to assess the role of CA used instead of FU. Materials and Methods: We conducted an analysis of survival, disease control and toxicity data in 46 patients treated with postoperative chemoradiation following total or subtotal gastrectomy for gastric adenocarcinoma with either FU or CA between January 2008 and December 2012. Results: Median follow-up was 19 months (range: 3-59), median survival time was 23 (±6.08) months and 1-3 years overall survival (OS) rates were 64.9-39% for all patients. Compared with the CA regimen, the incidence of treatment interruption was higher with FU (p=0.023), but no significant differences were seen in local control (p=0.510), distant recurrences (p=0.721) and survival rates (p=0.866) among patients. Conclusions: Concurrent CA with radiotherapy seems to be a more tolerable and an equally effective regimen for the postoperative treatment of gastric adenocarcinoma when compared to FU.**

**Keywords:** Flurouracil - capecitabine - radiotherapy - postoperative chemoradiation - gastric adenocarcinoma

*Asian Pac J Cancer Prev,* **14 (9)**, 5127-5131

## Introduction

Radical surgery is the mainstay of curative therapy in gastric carcinoma. However, long-term survival is poor, especially in patients with T3-4 tumors and/or lymph node metastases with surgery alone (Wanebo et al., 1993; Hundahl et al., 2000). Local metastasis in the tumor bed and regional lymph nodes and distant metastasis via hematogeneneous or peritoneal spread are frequently seen and resulting with deteriorated survival (Gunderson et al., 1974). As a result of the phase III, INT 0116- SWOG0008 study in which better survival rates were achieved by adding chemotherapy (FU and leucovorin-FA) and concurrent 45 Gy radiotherapy to surgery, postoperative chemoradiotherapy has become a standard in gastric carcinoma, especially in USA (Macdonald et al., 2001).

In spite of its contribution to survival, the toxicity rates encountered in this therapy are considerably high. Non-completion rate reported in the same study is 34% (Macdonald et al., 2001). In order to decrease this high toxicity rate, there is an effort to modify this regime, and also, oral chemotherapeutic agents are in trial for use instead of the standard chemotherapeutic FU (Dahan et al., 2005; Lee et al., 2006).

Amongst the oral chemotherapeutic agents that have been used, CA has been tried primarily in advanced stage gastric cancer and locally advanced rectum cancer, as an alternative to FU and its efficacy has been ascertained (Van Cutsem et al., 2001; Lee et al., 2006). Following studies have shown that its efficacy in advanced disease as well as in postoperative therapy is similar to FU and is better tolerated (Jansen et al., 2007).

CA can not routinly be used in our country instead of FU in order to decrease the probable toxicity which has been caused by the use of FU. Barely, CA is chosen depending on patients economic status, since CA is not covered by the medical insurance system of our country. Generally, FU is once again the only agent which is being used.

In this study, the results regarding treatment compliance; toxicity; local and distant control after therapy and survival after replacement of the standard chemotherapeutic agent in postoperative chemoradiotherapy, FU have been compared with CA and the use of CA for this indication has been evaluated.

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## Materials and Methods

*Patient selection*

Patients with a histologically proven adenocarcinoma of the stomach or gastroesophageal junction as considered in the American Joint Committee on Cancer TNM 2002 system was used for staging and stage IB-IV (M0) were eligible for this study. Patients with previous malignancies or comorbidity which might have restricted the delivery of the planned treatment were excluded. Treatment had to be started within 75 days after surgery. All patients were invited to participate in this study succeeding a macroscopically radical gastric surgery. Patients had to be older than 18 years with a Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate function of major organs (including cardiac, hepatic, and renal functions); and adequate bone marrow function (hemoglobin _10g/dL; absolute neutrophil count [ANC]_1,500/_L; platelet count_100,000/_L). All patients underwent physical examination, chest X-ray, chest and abdominal computed tomographic scans.

All patients gave a written informed consent and all patients underwent (partial) gastrectomy with lymph node dissection. No routine splenectomy or pancreatic tail resection was done. The interval between surgery and the start of adjuvant therapy was 38 days (range, 17-70 days).

*Treatment*

Eligible patients in the order of admission to hospital were assigned to receive adjuvant CRT with FUFA or CRT with CA. In the FUFA arm, patients received one cycle of FU 425mg/m$^2$/day+leucovorin 20mg/m$^2$ for 5 days. The second course of chemotherapy was given for 4 days with the same doses, 28 days later in the 1$^{st}$ day of radiotherapy. The third course of chemotherapy was given during the last 3 days of radiotherapy again with same doses and with the same agents. After radiotherapy course, the first course chemotherapy scheme was repeted as adjuvant therapy for 3 months.

In the CA arm, patients received one cycle of CA 1,000 mg/m$^2$ twice daily on days 1 to 14 and then on the 22$^{nd}$. day CA was administered concomitantly with radiotherapy which consisted of 25 fractions of 1.8 Gy to a total dose of 45 Gy in 5 weeks (five fractions/week). At a dose of 825 mg/m$^2$ twice daily (bid) during the whole course of radiotherapy (days 1-33) without weekend breaks. CA doses were given 12 hours apart with one of the doses being taken 2 hours prior to irradiation. If radiotherapy was interrupted chemotherapy was not administered. Following radiotherapy three additional cycles of capecitabine 1,000 mg/m$^2$ twice daily on days 1 to 14 for every 3 weeks were chosen being based on patients economic status, because capecitabine is not covered by the medical insurance system of our country.

The clinical target volume for radiotherapy consisted of the gastric bed (with stomach remnant, when present), anastomoses, and draining lymph nodes, as described in the Intergroup 0116 study (Macdonald et al., 2001). Some patients had computed tomographic-based dose calculation with construction of dose volume histograms. Dose constraints for critical organs were with a mean liver dose less than 30 Gy and for kidneys sparing at least two thirds of one kidney receiving a dose less than 40% of the total dose. All patients were treated in a supine position without immobilization measures on linear accelerators. Patients were seen weekly by their radiation oncologist.

Hematologic and serum creatinine values were checked weekly. Antiemetics were given on a prophylactic basis, and antacid and antidiarrheal drugs were prescribed when needed.

For evaluation of acute and late toxicities, during the chemoradiotherapy period, clinical examinations as blood counts and serum chemistries have been weekly carried out and then, while the adjuvant chemotherapy courses, these examinations have been carried out in every 3 weeks. Following the treatment, these examinations have been repeated at the end of the 1st month. Beginning from the 3rd month, these counts with abdominal CT have been carried out every 6 months plus endoscopic examinations if needed. The acute toxicities seen during and after therapy enlisted in the files were determined according to the Radiation Therapy Oncology Group (RTOG), Acute Radiation Morbidity Scoring Criteria.

*Ethical consideration*

As to follow legal and penal codes in the country, it is mandatory to have a signature bearing certificate of each patient stating their personal approval to be enrolled in such study.

*Statistical analysis*

The patients characteristics, toxicities, downstaging, sphincter preservation were compared among two groups using the chi-square test, Fisher exact test or student t test and Kruskal Wallis test for which p values less than 0.05 were considered to be statistically significant.

Kaplan-Meier method was used to estimate disease free and overall survivals. Survival differences between two groups were tested by log-rank test. Hazard ratios, 95% confidence intervals (CI) and p values were calculated. All statistical analyses were conducted using the SPSS (Version 10.0) statistical software program. Cox regresion analysis was used to determine the effected factors to disease free and overall survivals.

## Results

*Patient characteristics*

Median age is 54 (range,34-70) and the patient characteristics are shown in Table 1.

*Acute toxicity*

The highist grades of acute toxicity during chemoradiotherapy in each group are shown in Table 2. Patients treated with FU had a higher rate of Grade 2 gastrointestinal toxicity but with no statistical significance (diarrhea, abdominal pain and mucositis) (9.5% and 4.5%, p: 0.387); whereas CA group had a statistically significant higher rate of Grade 1 dermatologic toxicity (18% and 4.2%, p: 0.030). In addition, FU group had a statistically significant higher rate of Grade 2 and 3 hematologic

**Table 1. Patient Characteristics**

| Patient Characteristics | | | FU Group n (%) | CA Group n (%) | p |
|---|---|---|---|---|---|
| Gender | Male | | 18 (75) | 17 (77) | 0.224 |
| | Female | | 6 (25) | 5 (23) | |
| Age | Median | | 54 | 54 | 0.476 |
| | Range | | 34-70 | 34-69 | |
| Type of Surgery | | | | | |
| | Total gastrectomy | | 13 (54.2) | 10 (45.5) | 0.575 |
| | Subtotal gastrectomy | | 11 (45.8) | 12 (54.5) | |
| Tumor Localization | | | | | |
| | Antrum | | 13 (54.2) | 13 (59) | 0.508 |
| | Corpus | | 10 (41.6) | 8 (36.4) | |
| | Cardia | | 1 (4.2) | - | |
| | Linitis Plastica | | - | 1 (4.6) | |
| Pathology | Adenocarcinoma | | 6 (62.5) | 13 (59.1) | 0.172 |
| | Signet ring cell carcinoma | | 8 (33.3) | 5 (22.8) | |
| | Musinous carcinoma | | 1 (4.2) | 4 (18.2) | |
| Type of dissection | | 0 | 12 (50) | 10 (45.5) | 0.790 |
| | | 1 | 10 (41.7) | 10 (45.5) | |
| | | 2 | 2 (8.3) | 2 (9.1) | |
| Surgical margin | | Positive | 3 (12.5) | 2 (9.1) | 0.913 |
| | | Negative | 21 (87.5) | 20 (90.9) | |
| Grad | | I | 2 (8.4) | 1 (4.5) | 0.639 |
| | | II | 11 (45.8) | 10 (45.5) | |
| | | III | 11 (45.8) | 10 (45.5) | |
| | | Unknown | - | 1 | 4.5 |
| T stage | | T1- 2 | 4 (16.7) | 3 (13.7) | 0.613 |
| | | T3 | 18 (75) | 17 (77.2) | |
| | | T4 | 2 (8.3) | 2 (9.1) | |
| Lymph Node | | 0 | 2 (8.3) | 2 (9.1) | 0.945 |
| | | 1-3 | 10 (41.7) | 8 (36.4) | |
| | | 4 | 12 (50) | 12 (54.5) | |
| Stage | | IB | 2 (8.3) | - | 0.147 |
| | | II | 3 (12.5) | 6 (27.3) | |
| | | IIIA | 10 (41.7) | 8 (36.4) | |
| | | IIIB | 7 (29.2) | 5 (22.7) | |
| | | IV | 2 (8.3) | 3 (13.6) | |
| Surgery-Chemotherapy/Radiotherapy | | | | | |
| Interval (days) | | Median | 36 | 42 | 0.484 |
| | | Range | 16 -70 | 19-69 | |
| Total RT Dose (cGy) | | Median | 4680 | 4500 | 0.198 |
| | | Range | 4140-5040 | 4500-5040 | |
| Follow-up (months) | | Median | 19 | 18 | 0.424 |
| | | Range | 6-59 | 3-59 | |

**Table 2. Grades of Acute Toxicity During Chemoradiotherapy**

| Toxicity | FU | | | CA | | | p |
|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G1 | G2 | G3 | |
| Gastrointestinal | | | | | | | |
| | 3 (12.5%) | 2 (9.5%) | 1 (4.2%) | 2 (9.1%) | 1 (4.5%) | - | 0.387 |
| Hematologic | | | | | | | |
| | 2 (8.3%) | 7 (29.2%) | 3 (12.5%) | 3 (13.6%) | 2 (9.1%) | - | 0.048 |
| Dermatologic | | | | | | | |
| | 1 (4.2%) | - | - | 4 (18.2%) | 1 (4.5%) | - | 0.030 |

**Table 3. Relaps**

| 5-y rate | FU Group (%) | CA Group (%) | p |
|---|---|---|---|
| Local control | 83.3 | 87.5 | 0.510 |
| Distant control | 70.8 | 72.7 | 0.721 |

**Table 4. Survivals**

| | | All Patients | FU Group | CA Group | p |
|---|---|---|---|---|---|
| Overall survival | 1-year (%) | 64.9 | 65.7 | 62.2 | |
| | 3-year (%) | 39 | 39.5 | 43.2 | 0.865 |
| Disease free survival | 1-year (%) | 55 | 53.3 | 57.5 | |
| | 3-year (%) | 39.5 | 36.9 | 42.5 | 0.984 |

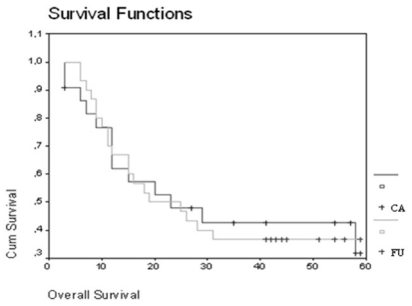


**Figure 1. Kaplan–Meier Estimates of Overall Survival of Patients Treated with Adjuvant FU+RT Compared with Adjuvant CA+RT**

toxicities (p: 0.048).

When evaluating the total therapy period in regard of therapy interruption, the need to end therapy was not seen whereas 13 (28.3%) patients needed to have a break. The median duration of therapy interruption was 8 days (range: 4-13).

Those patients who had to take a break, 11 (45.8%) were in the FU arm and two (9.1%) were in the CA arm. When comparing the patients who had a break, the difference was statistically significant (p=0.023). But, there was no statistically significant difference between groups in median duration of therapy interruption (p=0.427). None of the patients needed to quit therapy, yet in 13 patients it had to be interrupted and in these patients supportive therapies were given to provide the completion of therapy.

*Relapses and survivals*

During a median follow-up period of 19 months (range: 3-59), seven patients (15.2%) had local recurrences and 13 patients (28.3%) developed distant recurrences. Four patients (16.7%) with local recurrences were seen in the FU group and three patients (12.5%) in CA group. There was no statistically significant difference between groups in local recurrence rates (p=0.510) (Table 3).

Distant metastasis was seen in seven (29.2%) of the cases treated with FU versus the patients treated with CA developing six (27.3%) distant metastasis. Similar to the result with metastasis, no statistically significant difference was found in distant metastasis frequency rates (p=0.721) (Table 3). There were no cases that had both a local and distant component of failure.

During the follow-up, 27 patients (58.7%) died. Fifteen (62.5%) were in the FU arm, while 12 (54.5%) were in the CA arm. Again no statistically significant difference was found between death rates (p=0.756).

For all patients, OS duration was 23 (±6.08) months and median DFS duration was 18 (±5.09) months. The OS for all patients were 64.9 and 39% after 1 and 3 years, respectively, and for the DFS the ratios were 55 and 39.5% after, 1 and 3 years, respectively (Table 4).

The 1-3 year disease-free survival rates in the FU arm were 53.3 and 36.9%, while in the CA arm the rates were 57.5 and 42.5% (p=0.948) (Table 4). One to 3-year OS rates in cases treated with FU were 65.7 and 39.5%, as in cases treated with CA 62.2 and 43.2% (p=0.865) (Figure 1). There was no statistically significant difference

between DFS and OS rates in both arms.

All prognostic factors listed below for DFS and OS rates have been evaluated by univariate analysis and no statistically significant differences have been found regarding age, gender, pathology, type of operation, location of the tumor, surgical margin, dissection type, the number of lymph nodes removed during operation, tumor grade, the time therapy started and interruption of therapy.

## Discussion

Due to the contribution of the INT 0116-SWOG 0008 study to survival, postoperative chemoradiotherapy has become a standard approach in gastric cancer. However, toxicity during and even after therapy is a considerable problem in centers accepting this therapy as "the standard" and this was also true for the above-mentioned study (Macdonald et al., 2001).

In this study, patients were treated to 45 Gy using radiation fields that covered a large portion of the upper and mid-abdomen to encompass the preoperative tumor bed and regional lymph nodes, leading to significant side effects. As a result, 17% did not complete their therapy due to toxicity. In addition, 33% of the patients experienced grade 3 or higher GI toxicities. Given the formidable size of standard 2D or 3D fields, the desire to avoid the risk of acute toxicity likely contributed in part to the 35% deviations of the radiation plans that required corrections in that trial.

The outcomes for gastric cancer continue to be poor, and the toxicity caused by the treatment with chemotherapy and 2 CRT is high. There is a need to improve the treatment for gastric cancer due to treatment-related morbidity. 3D RT and IMRT may allow us to increase dose in hopes of improving disease control while decreasing the toxicity profile previously observed with 2D CRT, and the toxicity noted in the other series compares favorably with the Intergroup 0116 trial (Marcenaro et al., 2006; Milano et al., 2006; Minn et al., 2010). Also, no treatment breaks were needed among patients treated with IMRT compared with those treated with 3D CRT.

Compared with the 41% rate of grade 3 toxicity, the 32% rate of grade 4 toxicity and the 1% rate of grade 5 toxicity noted in the Intergroup study, the IMRT patients in the Minn et al. (2010) had a 26% rate of grade 3 and no grade 4 or 5 GI toxicity. There was 10% grade 3 hematologic toxicity with no grade 4 or 5 toxicities, and these were typically observed at the initiation of RT, suggesting that these may be related to pre-RT chemotherapy treatment. Although differences in the chemotherapy regimens may confound this type of direct comparison, the toxicity profile with IMRT does appear to be tolerable. It should be noted, however, that the group of patients in the this study who were treated with 3D CRT also experienced a similarly low rate of grade 3 toxicity. In our department as well, the use of 3-D conformal radiotherapy and the difficulty in protecting critical organs might have caused the similar results in both therapy arms of our study.

Modification in FU doses have been tried and oral agents were introduced in order to decrease this toxicity (Van Cutsem et al., 2001; Dahan et al., 2005; Lee et al., 2006; Jansen et al., 2007). With their utilization toxicity has decreased to a certain rate but this has no reflection on local control and survival rates. There is no outstanding difference between the different therapy protocols used (Lee et al., 2006).

Conformal RT plus modification in CT regimens (postoperatively with three cycles FU and cisplatin, followed by a concomitant LV5FU2 chemotherapy) schedule seems to be feasible (Dahan et al., 2005). CT dose reduction is urged in a lesser number of patients with the favour of this schedule and the toxicity is less frequently observed when compared with the INT 0116 study, thus leading to a more satisfying therapeutic feasibility. Furthermore; conformal RT and IMRT technique helps reducing the toxicity by reducing the therapeutic volume.

Capecitabine with daily administration of FU analogue, concurrent with radiotherapy was shown to be capable of inducing relevant tumor responses in upper gastrointestinal and rectal cancers (Van Cutsem et al., 2001; Lee et al., 2006; Jansen et al., 2007). The combination of radiotherapy with daily capecitabine alone or plus oxaliplatin has been shown to be safe and tolerable in patients with locally advanced gastric cancer in two phases I-II trials (Van Cutsem et al., 2001; Jansen et al., 2007; Tham et al., 2010; Kim et al., 2011).

In our study as well, toxicity did not decrease significantly with the use of oral CA, whereas the interruption rate decreased significantly. The comparison between patients who had an interruption or a continuous treatment showed that the local and distant control and survival was not affected by this interruption. The interruption of therapy or its ending due to toxicity decreases the probability of applying adjuvant therapy to patients following chemoradiotherapy. In our study as well, median 2 courses (range: 2-3) of adjuvant chemotherapy could have been given to patients following concurrent chemoradiotherapy. It is reported that insufficient adjuvant chemotherapy decreases locoregional control (Lim et al., 2004).

According Ohri et al. (2013) meta-analyses, adjuvant radiation therapy provides an approximately 20% improvement in both DFS and OS. This benefit is in no way clearly related either to chemotherapy use, dissection type, nodal status or to geographical region in separate. Thus; it has been believed that radiation therapy should be evidently considered as part of the multidisciplinary treatment approach depending on its benefits in outcomes for most patients with resectable gastric cancer. Other two meta-analyses have investigated the efficacy of adjuvant RT for gastric cancer (Fiorica et al., 2007; Valentini et al., 2009). Both evaluated mortality at 5 years, with reported odds ratios of 0.54 and 0.79 in favor of RT. That findings are similar to those reported in the study of California Cancer Registry, where the use of RT was associated with a 20% decrease in overall mortality (Kunz et al., 2012).

Although these studies contributed to improving results of gastric cancer treatment, many questions remain without clear responds concerning the optimal treatment, especially about the optimal type and sequencing of

chemotherapy and implementation of new radiotherapy and surgical techniques (Ohri et al., 2013).

In conclusion, therapy compliance in adjuvant chemoradiotherapy which is accepted as the standard treatment of gastric cancer is still questionable. Frequent breaks is likely to be given during therapy; meanwhile oral CA use can obviously decreases the toxicity disadvantage although there is no difference between FU and CA regarding therapy results. New randomized studies in this domain will help determine optimal therapy in gastric cancer.

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