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***Prospective Study***

**Modified docetaxel, cisplatin and capecitabine for stage IV gastric cancer in Japanese patients: A feasibility study**

Maeda O *et al.* DCX for gastric cancer in Japanese patients

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**Abstract**

***AIM***

To evaluate the feasibility of chemotherapy including fluoropyrimidine, platinum and taxane with modified dosages for unresectable gastric cancer in Japanese patients.

***METHODS***

We performed a feasibility study of a modified docetaxel, cisplatin and capecitabine (DCX) regimen for stage IV gastric cancer. In particular, 30 or 40 mg/m2 of docetaxel on day 1, 60 mg/m2 of cisplatin on day 1, and 2000 mg/m2 of capecitabine for 2 wk were administered every three weeks.

***RESULTS***

Three patients were treated with modified DCX (mDCX) with 30 mg/m2 docetaxel, and five patients were treated with this regimen with 40 mg/m2 docetaxel. Grade 3 or 4 neutropenia was observed in six of the eight patients; no patients exhibited febrile neutropenia. Partial response (PR) was achieved in four of the eight patients. Three patients underwent gastrectomy, which achieved R0 resection without residual tumors in dissected lymph nodes. In one of these three patients, resected specimens revealed pathological complete response in the primary lesion and in lymph nodes.

***CONCLUSION***

mDCX was well tolerated by Japanese patients with stage IV gastric cancer. This regimen might be useful for allowing gastric cancer patients with distant lymph node metastasis to undergo conversion surgery.

**Key words:** Gastric cancer; Docetaxel; Cisplatin; Capecitabine

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**Core tip:** A combination of fluoropyrimidine and platinum is a standard treatment for unresectable gastric cancer. Although the addition of a taxane to this doublet is expected to improve effectiveness, research has demonstrated that such triplet regimens often cause adverse effects, including neutropenia. To reduce adverse events but maintain therapeutic effectiveness, we devised a triplet regimen with modified dosages. Modified docetaxel, cisplatin and capecitabine treatment was safe and effective for stage IV gastric cancer. Three of the eight treated patients underwent conversion surgery and achieved long-term survival without recurrence.

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**INTRODUCTION**

The prognosis of stage IV gastric cancer is poor, and the median overall survival time is approximately one year. The standard treatment for Stage IV gastric cancer is chemotherapy with agents such as fluoropyrimidines and platinum compounds. In Japan, the oral fluoropyrimidine S-1 plus cisplatin (SP) is the standard regimen for HER2-negative advanced gastric cancer because SP was proven to be superior to S-1 alone in a phase III randomized trial[1]. Because capecitabine, similarly to S-1, is an effective oral fluoropyrimidine, capecitabine plus cisplatin (XP) is also a possible regimen[2].

The addition of docetaxel to fluoropyrimidine and cisplatin was expected to improve therapeutic efficacy. A combination of docetaxel, cisplatin and 5-fluorouracil (DCF) produced longer overall survival than cisplatin plus 5-fluorouracil; however, the use of DCF is limited due to severe side effects, including hematologic toxicity[3]. Various modified DCF regimens have been tested in attempts to improve tolerability without losing efficacy[4-8]. Research has also examined regimens that replace the infusion of 5-fluorouracil with an oral fluoropyrimidine, such as docetaxel, cisplatin and S-1 (DCS)[9] and docetaxel, cisplatin and capecitabine (DCX)[10]. Although DCX has been reported to be effective for unresectable gastric cancer, this regimen often causes adverse events, including hematologic toxicities[10-12]. We believed that a modification of the doses used for DCX might reduce toxicity but maintain effectiveness. In previous reports, doses of docetaxel used for DCX ranged from 60 mg/m2 to 75 mg/m2[10-12]. In certain studies of DCS, the dose of docetaxel was set to 30-40 mg/m2, and good effectiveness and adequate safety were achieved[13-15]. In the present study, we set the dose of docetaxel to 30 or 40 mg/m2, which was a lower dose than that used in previous reports on DCX, and evaluated the safety and efficacy of our modified DCX (mDCX) regimen in Japanese patients.

**MATERIALS AND METHODS**

***Patient eligibility***

The eligibility criteria included stage IV unresectable HER2-negative gastric cancer, an age of 20-75 years, Eastern Cooperative Oncology Group (ECOG) performance status 0-1, conserved organ functions, and no prior chemotherapy.

***Treatment***

The treatment regimen, which consisted of 1,000 mg/m2 capecitabine twice per day on days 1-14, 60 mg/m2 cisplatin on day 1 and 30 or 40 mg/m2 docetaxel on day 1, was administered every three weeks. The dosage of docetaxel was 30 mg/m2 for the first three patients and was planned to increase to 40 mg/m2 for subsequent patients if no dose-limiting toxicities (DLTs) were observed after the first three patients’ first treatment cycle. The treatment was continued until the disease progressed, patients experienced intolerable side effects, or curative resection was expected.

Treatment was interrupted if a patient developed grade ≥ 3 hematologic toxicity. If a patient experienced grade 4 neutropenia for more than 5 days or grade 3 febrile neutropenia, the dosage of all agents was decreased to 75% for the next course. If a patient exhibited grade 4 thrombocytopenia, dosages of all agents were decreased to 50%. If a patient had grade ≥ 2 diarrhea and/or grade ≥ 2 hand-foot syndrome, the treatment course was interrupted. If creatinine clearance (Ccr) was < 60 mL/min and ≥ 50 mL/min, cisplatin was decreased to 75%. If Ccr was < 50 mL/min and ≥ 40 mL/min, cisplatin was decreased to 50%. If Ccr was < 40 mL/min, the treatment protocol was terminated. Supportive treatment, including G-CSF and anti-emetics, was permitted.

***Safety and anti-tumor activity assessments***

Adverse events were assessed using the National Cancer Institute’s CTCAE v4.0. DLTs were defined as adverse events that occurred after the beginning of the first cycle and before the beginning of the second cycle that satisfied any of the following criteria: (1) non-hematologic toxicities ≥ grade 3 that did not resolve to grade 0 or grade 1 within two consecutive days, except for nausea, vomiting, anorexia and asymptomatic electrolyte imbalance; (2) neutropenia ≥ grade 3 for > 5 consecutive days; (3) febrile neutropenia (absolute neutrophil count < 1.0 × 109/L and fever ≥ 38 °C); (4) grade 4 thrombocytopenia or platelet transfusion; or (5) delay of the treatment cycle for > 2 wk.

Radiological tumor assessments were conducted using computed tomography every eight weeks in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

**RESULTS**

Three patients received mDCX with 30 mg/m2 of docetaxel. Because no DLTs were observed in the first three patients, treatment with 40 mg/m2 docetaxel was administered to five subsequent patients.

The patients’ characteristics and clinical courses are summarized in Table 1, and adverse events are summarized in Table 2. No DLTs were observed after the first treatment cycles in any patient. The relative dose intensities of docetaxel, cisplatin and capecitabine were 90.6%, 90.0% and 76.2%, respectively. Four of the eight patients exhibited a partial response (PR). Three patients (cases 2, 5 and 8) underwent gastrectomy with lymph node dissection; for all of these patients, R0 resection was achieved, and no viable tumors were detected in resected lymph nodes (ypN0). Case 2 achieved pathological complete response in both the primary lesion and lymph node metastasis. Regarding case 5, the observed therapeutic effect was grade 2, and she received capecitabine for ten weeks as adjuvant chemotherapy. The clinical courses of three representative cases are presented below.

***Case 1***

A 64-year-old man had type III advanced cancer in the fornix of the stomach and multiple liver metastases (Figure 1). Biopsy specimens were pathologically diagnosed as moderately and poorly differentiated adenocarcinoma. The patient received three courses of mDCX, and the liver metastases shrank, a phenomenon judged to be PR. After five courses, PR was confirmed. After seven courses, shrinkage of the liver metastases was sustained. The treatment protocol was discontinued due to grade 2 sensory peripheral neuropathy. Other adverse events were grade 2 anemia, grade 1 aspartate aminotransferase elevation, grade 1 alanine aminotransferase elevation, and grade 1 anorexia. The patient received post-protocol treatment that included irinotecan and weekly paclitaxel. He died 22 mo after enrollment in the study.

***Case 2***

A 59-year-old man had type III advanced cancer at the small curvature of the angulus with lymph node metastasis along the superior mesenteric artery (#14a; Figure 2). Biopsy specimens were pathologically diagnosed as moderately and poorly differentiated adenocarcinoma. After three courses of mDCX, the lymph node metastasis shrank; after five courses, PR was confirmed. Adverse events included grade 2 leukopenia, grade 3 neutropenia, and grade 2 anemia. The patient underwent subtotal gastrectomy with lymph node dissection. Pathological findings revealed no residual carcinoma, and the observed therapeutic effect was grade 3. He received S-1 for one year as adjuvant chemotherapy. He remains alive without any findings indicative of recurrence four years after enrollment.

***Case 8***

A 63-year-old woman had type III advanced cancer at the gastric antrum with lymph node metastasis that included left supraclavicular lymph nodes and para-aortic lymph nodes (Figure 3). Biopsy specimens were pathologically diagnosed as moderately and poorly differentiated adenocarcinoma. After two courses of mDCX, the lymph nodes shrank; after four courses, PR was confirmed. Adverse events included grade 2 leukopenia, grade 4 neutropenia, grade 3 anorexia, and grade 3 diarrhea. Because the patient’s lymph node metastasis became undetectable by computed tomography, she underwent subtotal gastrectomy with D2 dissection; the para-aortic lymph nodes were not dissected. Pathological findings revealed no residual tumors in the lymph nodes, and the observed therapeutic effect was grade 1b. As adjuvant chemotherapy, she underwent two courses of capecitabine plus oxaliplatin which were discontinued due to grade 2 nausea and fatigue. She subsequently received S-1 for one year. The patient remains alive without any findings indicative of recurrence two years after enrollment.

**DISCUSSION**

Reports have described the effectiveness of DCX for unresectable gastric cancer[10,16], as preoperative chemotherapy[17], as adjuvant chemotherapy[18] and as perioperative chemotherapy[12]. These reports indicate that DCX is highly effective but also rather toxic, particularly in hematologic respects. To our knowledge, no prior reports have described a DCX trial in Japan.

In the present study, six of the eight patients (75%) experienced grade 3 or grade 4 neutropenia, although no patients experienced febrile neutropenia. Although the modifications to the DCX regimen decreased the dose of docetaxel to 30 or 40 mg/m2, the frequency of hematologic toxicity in this study was similar to those reported in prior studies of DCX (neutropenia ≥ grade 3, 40%-76.5%; Table 3). However, we regarded the observed side effects as tolerable because no DLT was observed after the first cycle, and all patients were able to receive three or more courses of treatment with appropriate supportive care. In addition, the median admission period was five days (data not shown), indicating that for the most part, admission was primarily necessary for hydration due to the administration of cisplatin.

Three of the five patients with only distant lymph node metastasis underwent conversion surgery, and all three patients have remained alive for more than two years without recurrence. Therefore, we believe that intensive treatment with a triplet regimen could be a useful preoperative treatment that enables conversion surgery for patients with distant lymph node metastasis. However, in certain cases, survival time was shorter than one year; in particular, one case died 7.7 mo after the start of treatment, although PR was achieved. It is necessary to identify certain biomarkers to select patients suitable for a triplet regimen. Furthermore, a randomized control study is needed to evaluate whether the proposed triplet regimen is superior to a standard platinum and oral fluoropyrimidine doublet.

In conclusion, mDCX is safe and effective for Stage IV gastric cancer in Japanese patients.

**COMMENTS**

***Background***

For stage IV gastric cancer, doublet regimens including fluoropyrimidine and platinum agents are standard chemotherapy. The addition of taxanes to the doublet regimen may improve effectiveness but may also increase toxicity.

***Research frontiers***

The addition of a smaller amount of docetaxel than previously reported to capecitabine and cisplatin was evaluated.

***Innovations and breakthroughs***

The authors set the dose of docetaxel to 30 or 40 mg/m2, which was a lower dose than used in previous reports on docetaxel, cisplatin and capecitabine (DCX).

***Applications***

Intensive treatment with a triplet regimen could be a useful preoperative treatment that allows for conversion surgery in patients with distant lymph node metastasis.

***Terminology***

DCX: A combination chemotherapy regimen including docetaxel, cisplatin and capecitabine. Conversion surgery: Surgical operation for patients with cancer that was unresectable before chemotherapy and became to be resectable after chemotherapy.

***Peer-review***

The authors designed the dose of docetaxel to 30 or 40 mg/m2, which was a lower dose than used in previous reports on DCX, and evaluated the safety and efficacy.

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**Table 1 Patient characteristics and prognoses**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Age** | **Sex** | **Macroscopic type** | **Histopathology** | **Metastasis** | **Number of courses** | **Objective tumor response** | **Prognosis (mo)** | **Conversion** |
| **surgery** |
| 1 | 64 | M | 3 | tub2/por | Liver, LNs | 7 | PR | 21.9 | Dead |  |
| 2 | 59 | M | 3 | tub2/por | LNs | 5 | PR | 50.9 | Alive | Yes |
| 3 | 62 | M | 2 | por | Liver, LNs | 6 | SD | 7.4 | Dead |  |
| 4 | 65 | M | 3 | por | LNs | 5 | PR | 7.7 | Dead |  |
| 5 | 67 | F | 3 | tub2/por | LNs | 3 | non-CR/non-PD | 31.3 | Alive | Yes |
| 6 | 66 | M | 3 | por | LNs | 4 | non-CR/non-PD | 12 | Dead |  |
| 7 | 62 | M | 2 | por | Liver, LNs | 3 | SD | 5.4 | Dead |  |
| 8 | 63 | F | 2 | tub2/por | LNs | 4 | PR | 24.4 | Alive | Yes |

tub2: Moderately differentiated tubular adenocarcinoma; por poorly: Differentiated adenocarcinoma; LNs: Lymph nodes; PR: Partial response; SD: Stable disease; CR: Complete response.

**Table 2 Hematologic and non-hematologic adverse events *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Any grade**  | **Grade 3**  | **Grade 4**  |
|  | Leukopenia |  | 7 | (87.5) |  | 2 | (25) | 0 |
|  | Neutropenia |  | 7 | (87.5) |  | 4 | (50) |  | 2 | (25) |
|  | Anemia |  | 6 | (75) |  | 1 | (12.5) | 0 |
|  | Thrombocytopenia |  | 7 | (87.5) | 0 | 0 |
|  | Hyperbilirubinemia |  | 3 | (37.5) | 0 | 0 |
|  | Elevated serum aspartate aminotransferase |  | 6 | (75) | 0 | 0 |
|  | Elevated serum alanine aminotransferase |  | 8 | (100) | 0 | 0 |
|  | Elevated serum creatinine  |  | 3 | (37.5) | 0 | 0 |
|  | Fever |  | 4 | (50) | 0 | 0 |
|  | Fatigue |  | 2 | (25) | 0 | 0 |
|  | Alopecia |  | 1 | (12.5) | 0 | 0 |
|  | Skin rash |  | 1 | (12.5) | 0 | 0 |
|  | Anorexia |  | 7 | (87.5) |  | 4 | (50) | 0 |
|  | Diarrhea |  | 4 | (50) |  | 2 | (25) | 0 |
|  | Nausea |  | 3 | (37.5) | 0 | 0 |
|  | Vomiting |  | 3 | (37.5) | 0 | 0 |
|  | Constipation |  | 1 | (12.5) | 0 | 0 |
|  | Peripheral neuropathy |  | 1 | (12.5) | 0 | 0 |
| 　 | Infection | 　 | 1 | (12.5) |  | 1 | (12.5) | 0 |

**Table 3 Previous reports regarding docetaxel, cisplatin and capecitabine**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Year** | **Setting** | **Capecitabine** | **Cisplatin** | **Docetaxel** | **Interval** | **Number** |  | **Grade 3-4** | **Febrile** | **RR (95%CI)** | **PFS (95%CI)** | **OS (95%CI)** |  |  |
| **(d)** | **of patients** |  | **neutropenia** | **neutropenia** | **(mo)** | **(mo)** |  |  |
| Kang *et al.* [10] | 2010 | metastatic or recurrent | 1875 mg, days 1-14 | 60 mg, day 1 | 60 mg, day 1 | 21 | 40 |  | 62.5% | 10% | 68%(53–83%) | 7.6(6.9–8.4) | 14.4(7.3–21.5) |  | pCR: 10% |
| Sym *et al*[17] | 2010 | neoadjuvant | 1875 mg,days 1-14 | 60 mg, day 1 | 60 mg, day 1 | 21 | 49 (36 resected cases) |  | 69% | 4% |  | R0: 54.3(0-112.9) | R0: not reached | R0 resection: 63% |  |
|  |  |  |  |  |  |
|  |  | non-R0: 5.1(3.6-6.6) | non-R0: 11.5(7.3-15.7) |  |  |
| Thuss-Patience *et al*[12] | 2012 | perioperative | 1875 mg,days 1-14 | 60 mg, day 1 | 75 mg, day1 | 21 | 51 | preoperative | 76.5% | 21.5% |  |  |  | R0 resection: 90.2% | pCR: 13.7% |
| postoperative | 62.9% | 11.1% |  |  |  |
| Polyzos *et al*[16] | 2012 | metastatic | 2000 mg, days 2-15 | 60 mg, day 1 | 60 mg, day 1 | 21 | 36 |  | 50% | 16% | 44.4%(28-60%) | 5(3-6)1 | 12(5-24) |  |  |
| Yoon *et al*[18] | 2015 | adjuvant for stage IIIB-IV | 1875 mg, days 1-14 | 60 mg, day 1 | 60 mg, day 1 | 21 | 46 |  | 40% | 15% |  | 26.9(7.5-46.4)2 | 43.9(29.2-58.7) |  |  |

1Time to progression; 2Relapse-free survival. RR: Response rate; PFS: Progression-free survival; OS: Overall survival; pCR: Pathological complete response.





**Figure 1 Case 1.** Endoscopic findings (A, B) and computed tomography images (C, D) before (A, C) and after (B, D) seven courses of modified docetaxel, cisplatin and capecitabine (DCX) (mDCX).







**Figure 2 Case 2.** Endoscopic findings (A, B) and computed tomography images (C, D, E, F) before treatment (A, C, E) and after (B, D, F) five courses of modified docetaxel, cisplatin and capecitabine (DCX) (mDCX). The primary lesion (A, B), swollen lymph nodes along the common hepatic artery (#8) (C, D) and lymph nodes along the superior mesenteric artery (#14a) (E, F) markedly shrank. Microscopic findings for the resected specimens of the primary lesion (E, magnification × 100) and lymph nodes (F, magnification × 400) revealed no residual tumor.



**Figure 3 Case 8.** Computed tomography images before (A, C) and after (B, D) four courses of modified docetaxel, cisplatin and capecitabine (DCX) (mDCX). Left supraclavicular nodes (A, B) and para-aortic nodes (C, D) became undetectable.