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ORIGINAL ARTICLE

Pemetrexed and cisplatin in patients with advanced gastric cancer: a Korean cancer study group multicenter phase II study

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Abstract
Background Pemetrexed is a multitargeted antifolate enzyme inhibitor, which has activity against a variety of tumors, including advanced gastric cancer (AGC). The aim of this study was to assess efficacy and safety of pemetrexed plus cisplatin (PemCis) combination in the treatment of AGC in Korean patients.
Patients and methods This was a multicenter, single arm, open label study. Patients with no prior palliative chemotherapy received pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 day 1, every 3 weeks plus folic acid and vitamin B_{12} supplementation. Response rate was assessed according to response evaluation criteria in solid tumors (RECIST) criteria.
Results Of the 50 patients evaluable for efficacy, 13 had partial response for an overall response rate of 26% (95% CI, 14.6–40.3%) and 15 (30%) had stable disease. Median time to progression was 2.8 months (95%CI, 2.2–4.4 months), and median overall survival was 6.6 months (95% CI, 4.8–10.4 months). Of the 51 patients evaluable for safety, the most frequent NCI-CTC grade 3/4 toxicities were neutropenia in 49% of patients (25% of cycles) and anorexia in 10% of patients (4% of cycles).
Conclusion PemCis has a modest activity and acceptable toxicity profile in patients with AGC. Clinical trials with different combinations and dose regimens are, therefore, warranted.

Keywords Advanced gastric cancer · Chemotherapy · Cisplatin · Pemetrexed · Phase II trial

Introduction

Gastric cancer remains the second leading cause of cancer mortality in the world [1] with a particularly high incidence in Eastern Asia, Eastern Europe, and parts of Central and South America [2]. It is the leading cause of cancer death in

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Korea [3–5]. The only potentially curative treatment is surgical resection of all gross disease. Despite this intervention, however, disease still recurs in both regional and distant sites in most patients [6].

Efforts to control disease recurrence have focused on combination chemotherapy, mostly based on 5-fluorouracil (FU), cisplatin, and an anthracycline. These include 5-FU, doxorubicin, mitomycin (FAM); 5-FU, doxorubicin, methotrexate (FAMTX); epirubicin, cisplatin, 5-FU (ECF); etoposide, leucovorin, 5-FU (ELF); and infusional 5-FU and cisplatin. Randomized trials evaluating these 2-and 3-drug regimens have achieved objective response rates of 10–51%, median times to progression of 2–7 months, median survival times of 6–10 months, and 1-year survival rates of about 30% [7–10]. Clearly, chemotherapy regimens that improve outcomes in patients with advanced gastric cancer are needed [11, 12].

Pemetrexed is a novel folate antimetabolite that predominantly inhibits the thymidylate synthase (TS) enzyme [13]. This multitargeted agent is also able to further inhibit folate-dependent enzymes such as dihydrofolate reductase and glycinamide ribonucleotide formyltransferase, the latter being involved in de novo purine biosynthesis [13]. Accordingly, it is possible that the ability of pemetrexed to act as a multitargeted enzyme inhibitor may confer a clinical advantage over single-target antifolates by increasing the spectrum of tumors with biochemical profiles potentially sensitive to the drug and discouraging the development of resistance. Activity has been seen in some patients with colorectal or pancreatic cancer who failed to respond to single-target antifolates, 5-FU or raltitrexed [14].

The broad range of clinical activity of pemetrexed against solid tumors such as colorectal cancer, pancreatic cancer, non-small cell lung cancer, mesothelioma, and breast cancer [15] prompted a phase II study of pemetrexed in patients with advanced gastric cancer [16]. The addition of high-dose oral folic acid (FA) to the treatment regimen—500 mg/m^2 pemetrexed over 10 min every 21 days—resulted in a highly satisfactory safety profile in the 30 patients who received FA supplementation. The overall response rate was 21% (of 36 evaluable patients); all responding patients were in the supplemented group. Adverse events reported during the trial were neutropenia, transient transaminase elevations, skin rash, mucosal toxicity, fatigue and diarrhea, which were similar to those reported previously [16].

Pemetrexed in combination with cisplatin has shown additive or synergistic activity in gastric cancer cells and human tumor xenografts [17–19]. The recent introduction of FA and vitamin B_{12} supplementation into a phase III clinical trial of pemetrexed and cisplatin in mesothelioma has made treatment with the combination safe and well tolerated [20].

On the basis of these considerations, we evaluated pemetrexed 500 mg/m^2 combined with cisplatin 75 mg/m^2 (plus vitamin B_{12}/FA supplementation) in patients with advanced gastric cancer. The primary objective was the evaluation of response rate. Secondary objectives included assessments of duration of response, time to disease progression, time to treatment failure, overall survival, and toxicity.

Patients and methods

Patient selection

Men or women with histologically or cytologically proven metastatic or locally advanced inoperable (stage IV) gastric adenocarcinoma not amenable to curative surgery were eligible for this study. Patients were required to be 18–70 years old with a life expectancy > 12 weeks, an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$1, and at least one target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria [21]. Prior adjuvant or neoadjuvant chemotherapy given before, after, or concurrent with radiotherapy was allowed if given with curative intent and completed > 12 months before enrolment; no prior palliative chemotherapy was allowed. At least 30 days must have passed since previous radiotherapy and 3 weeks from prior surgery. Patients were also required to have adequate organ function as defined by absolute neutrophil count (ANC) $\geq 1.5 \times 10^9\,l^{-1}$; platelet count of $\geq 100 \times 10^9\,l^{-1}$; hemoglobin $\geq$9.0 g/dl; serum total bilirubin $\leq 1.5 \times$ upper normal limit (ULN); serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase $\leq 3 \times$ ULN (AST, ALT, or alkaline phosphatase $\leq 5 \times$ UNL was acceptable if liver metastasis was present); and serum creatinine $\leq$140 μmol/l (calculated creatinine clearance, >45 ml/min, using the standard Cockcroft and Gault formula, if serum creatinine level was between 130 and 140 μmol/l).

Patients were excluded for known or suspected brain metastasis, concurrent administration of any other tumor therapy, active infection, serious concomitant disease, pregnancy or breast feeding, history of significant neurological or mental disorder, second primary malignancy, inability to interrupt aspirin or other nonsteroidal anti-inflammatory drugs during the treatment period, presence of clinically relevant third-space fluid collections that could not have been controlled by drainage or other procedures prior to study enrolment, and the inability or unwillingness to take FA, vitamin B_{12} supplementation, or dexamethasone.

All patients provided written informed consent, and the study was approved by the ethical review boards of the participating institutions.

Study design

In this multicenter, single-arm, open-label phase II study of pemetrexed/cisplatin, the primary endpoint was overall response rate. A response rate of 40–50% was anticipated for pemetrexed/cisplatin as first-line chemotherapy of advanced gastric cancer, and a response rate of 30% was considered the minimum activity level of interest for this patient population [22]. For an observed response rate of 50%, i.e., 25 of 50 patients showed an objective remission, the corresponding 95% confidence interval would be 35.5–64.5%. For a true response rate of 50%, there would be a 99.7% chance that the estimated response rate is >30%. Accordingly, for a true response rate of 42.4%, there would be at least a 95% chance that the estimated response rate is >30%.

Treatment plan

Patients initially received pemetrexed 500 mg/m^2 as a 10-min intravenous infusion followed by cisplatin 75 mg/m^2 administered as an intravenous infusion over approximately 1–2 h on day 1 of each 21-day cycle. Patients received adequate pre- and post-hydration according to local practice. All patients received routine prophylactic dexamethasone 4 mg orally twice a day, starting the day before and continuing until the day after pemetrexed administration. Supplemental oral FA 1 mg was given once daily approximately 1–2 weeks before the first dose of study drug until 3 weeks after the last dose of pemetrexed. Vitamin B_{12} 1 mg was given by intramuscular injection approximately 1–2 weeks prior to the first dose of study drug and approximately every 9 weeks until 3 weeks after the last dose of pemetrexed. Treatment was continued up to a maximum of six cycles unless there was documented disease progression, unacceptable adverse events, or withdrawal of consent

Dose adjustments were performed depending on the observed toxicity. Grade 4 neutropenia required a 25% dose reduction of both drugs. Grade 3 or 4 thrombocytopenia required a 50% dose reduction of both drugs. Grade 2 and 3 mucositis, pharyngitis, esophagitis, or diarrhea required a 25 and 50% dose reduction of pemetrexed, respectively. Patients were required to meet all the following criteria to begin the next cycle of treatment: absolute neutrophil count $\geq 1.5 \times 10^9\,l^{-1}$, platelet count $\geq 100 \times 10^9\,l^{-1}$, calculated creatinine clearance $\geq$45 ml/min, and resolution or improvement of stomatitis, pharyngitis, esophagitis, diarrhea, skin toxicity to grade 1 or 0. To start the next cycle, serum bilirubin, AST, ALT, and alkaline phosphatase should not be higher than the limits allowed for study enrolment, and patients should have no other ongoing grade 3 or 4 hematologic or nonhematologic toxicities. In patients with grade 2 neurosensory toxicity, cisplatin was reduced by 50%; for grade 3/4 neurosensory toxicity, cisplatin was discontinued. Patients who required dose reductions continued to receive the reduced doses for the remaining study period. Patients were discontinued from the study if they could not be retreated within 42 days from the last dose, or if a dose reduction was required after two previous dose reductions.

Baseline and treatment assessments

Pretreatment investigations, performed within 4 weeks of commencing treatment, included chest radiograph, with or without chest computed tomography (CT) scan, abdominal CT scan, and others as indicated. Within 8 days before the first infusion, a full history and examination, complete blood count, blood chemistry, and assessment of vital signs were performed.

All patients who met eligibility criteria, had measurable disease, and received at least one dose of study therapy were evaluated for tumor response rate. Response was evaluated according to RECIST criteria [21]. Tumor measurements during the study were done approximately every 6 weeks and prior to every other treatment cycle, using the same imaging methods conducted at baseline. In the event of an objective tumor response, confirmation of response was performed 4–5 weeks after the first documentation of response.

All patients who met eligibility criteria were included in the time-to-event analyses. Duration of overall tumor response was measured from the time of documentation of complete response (CR) or partial response (PR) (whichever came first) until the date of progressive disease (PD). Overall survival time was defined as the time from the date of study enrolment to the date of death from any cause. Time to treatment failure was defined as the time from the date of enrolment to the date of early discontinuation of study therapy for any reason, documented disease progression, or death from any cause. Time to disease progression was defined as the time from the date of enrolment to the date of documented disease progression.

All patients who received at least one dose of study therapy were evaluable for safety. All adverse events were assessed according to National Cancer Institute Common Toxicity Criteria (Version 2.0; NCI-CTC 1999).

Medians survival times at 6, 9, and 12 months were estimated using the Kaplan–Meier method. All estimates of treatment effects were conducted at a two-sided alpha level of 0.05, and 95% CIs were estimated for each variable.

Results

Patient characteristics

From October 2003 to September 2004, 51 patients were enrolled from eight investigational sites in Korea. One

patient who received study drug (one cycle) did not meet eligibility criteria (serum total bilirubin >1.5 × ULN); therefore, 50 patients were evaluated for efficacy and 51 for safety. Patient characteristics are summarized in Table 1. There were 38 males and 13 females with a median age of 56 years (range 24–69). Most patients (73%) had an ECOG performance status of 1. Among the 13 (25%) patients who had prior surgery, six patients were treated with palliative intent and seven patients were found to have relapsed disease after curative resection. Four of the seven patients with relapsed disease after curative surgery received prior adjuvant chemotherapy. Para-aortic lymph nodes and liver were the most common sites of metastases.

Efficacy

Of the 50 patients evaluable for efficacy, 13 (26%; 95% CI, 14.6–40.3%) had objective PR, 15 (29%) had stable disease (SD), 21 (42%) had PD, and 1 (2%) was classified as unknown (not evaluated). Of the 13 tumor responders, the median duration of response was 3.6 months (95% CI, 2.8–9.4). Median time to progression was 2.8 months (95% CI, 2.2–4.4 months); with a censoring rate was 18% ($n = 9$) (Fig. 1). Median time to treatment failure was 2.1 months (95% CI, 1.0–2.8 months), with a censoring rate of 2% ($n = 1$). The main reason for treatment failure was disease progression in 35 (71%) patients. Median overall survival was 6.6 months (95% CI, 4.8–10.4), with a censoring rate of 44% ($n = 22$) (Fig. 2). Kaplan–Meyer survival estimates were 55.6, 37.3, 32.7% at 6, 9, and 12 months, respectively.

Table 1 Patient characteristics

Total no. of patients	51
Median age in years (range)	56 (24–69)
Male/female, *n* (%)	38 (75%)/13 (25%)
ECOG performance status, *n* (%)	
0	14 (27%)
1	37 (73%)
Gastric adenocarcinoma, *n* (%)	
Undifferentiated	1 (2%)
Poorly differentiated	23 (45%)
Moderately differentiated	18 (35%)
Well differentiated	1 (2%)
Signet ring cell	6 (12%)
Unknown	2 (4%)
Previous treatment, *n* (%)	
None	38 (75%)
Surgery	13 (25%)
Palliative/curative	6/7
Chemotherapy	4 (8%)
Neoadjuvant + adjuvant/adjuvant	1/3
Sites of metastatic disease[a]	
Lymph nodes[b]	115
Liver	26
Lung	6
Bone	1
Peritoneum	12
Ovary	3
Pelvis	2
Others	11

[a] Patients could have had multiple sites of metastases

[b] Lymph nodes include: regional ($n = 31$); retropancreatic ($n = 10$), para-aortic ($n = 27$), portal ($n = 10$), retroperitoneal ($n = 9$), mesenteric ($n = 7$), others ($n = 21$)

Dose administration

A total of 212 cycles were administered to 51 patients; the median number of cycles was 4 (range 1–13 cycles). Fourteen patients (28%) completed at least six cycles of treatment. Eleven dose reductions (5% of doses administered) were reported for pemetrexed, and 13 dose reductions (6% of doses administered) for cisplatin. The most common reason for dose reduction was neutropenia. A total of 67 dose delays were reported of which most (72%) were due to hematologic toxicities. None of the doses were omitted. The mean dose intensities per week were 152 mg/m^2 for pemetrexed (91% of planned doses) and 22.6 mg/m^2 (91% of planned doses) for cisplatin, respectively.

Toxicity

Toxicities were generally mild (grade 1/2) (Table 2). The most common grade 3/4 hematologic toxicity was neutropenia in 25 (49%) patients and 52 (25%) cycles; however, grade 4 neutropenia was noted in seven patients (13.7%) and seven cycles (3.3%) and no patients developed febrile neutropenia. Grade 3 thrombocytopenia (no grade 4) occurred in three (6%) patients and three (1%) cycles. The most common grade 3/4 clinical toxicity was anorexia (grade 3 only) in five (10%) patients and eight (4%) cycles. A total of 10 (20%) patients discontinued treatment due to adverse events. Two patients died from their disease within 30 days of receiving their last dose of study drug.

Discussion

Of the 50 patients evaluable for response in this study, there were 13 PR, for an objective response rate of 26% (95% CI, 14.6–40.3%). Median time to progression was 2.8 months (95% CI, 2.2–4.4 months), and median overall survival was 6.6 months (95% CI, 4.8–10.4 months). Median time to

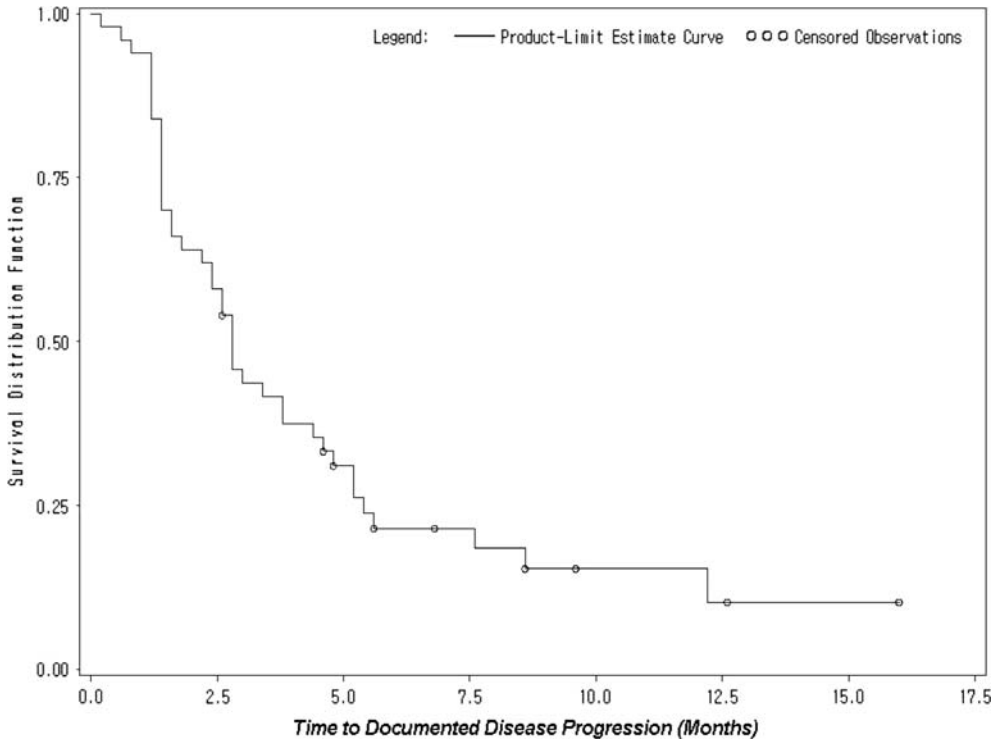

Fig. 1 Time to disease progression ($N = 50$)

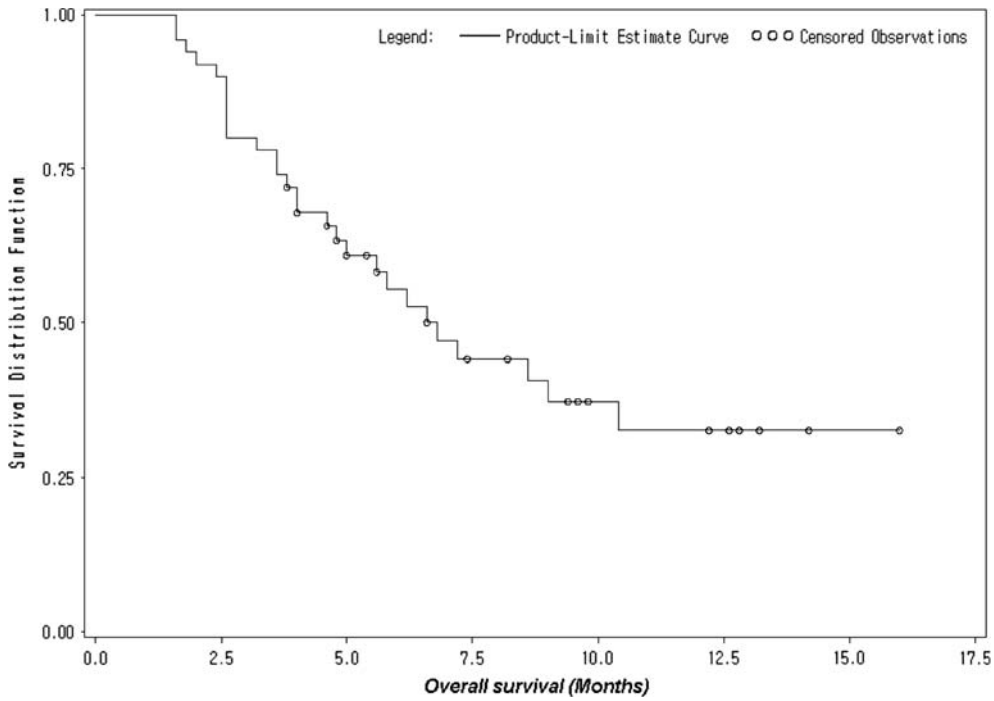

Fig. 2 Overall survival ($N = 50$)

treatment failure was 2.1 months (95% CI, 1.0–2.8 months), with disease progression being the main reason for treatment failure (70% of patients).

The overall response rate to the pemetrexed/cisplatin regimen evaluated in this study of 26% did not reach the minimal response rate of 30% expected for this study. Moreover, our anti-tumor activity was modest compared with that possible with 5-FU-based regimens (with or without anthracyclines) that are extensively used to treat gastric cancer (10–51%) [7–10].

Table 2 Toxicity (NCI-CTC)

Toxicity	Grade 1/2 (N = 51 patients)	Grade 3 (N = 51 patients)	Grade 4 (N = 51 patients)	Grade 3 (N = 212 cycles)	Grade 4 (N = 212 cycles)
Hematologic toxicity, *n* (%)					
Neutropenia	14 (27.5)	18 (35.3)	7 (13.7)	45 (21.2)	7 (3.3)
Leukopenia	26 (51.0)	10 (19.6)	0 (0.0)	13 (6.1)	0 (0.0)
Anemia	43 (84.3)	5 (9.8)	2 (3.9)	10 (4.7)	2 (0.9)
Thrombocytopenia	24 (47.1)	3 (5.9)	0 (0.0)	3 (1.4)	0 (0.0)
Nonhematologic toxicity, *n* (%)					
Anorexia	33 (64.7)	5 (9.8)	0 (0.0)	8 (3.8)	0 (0.0)
Nausea	33 (64.7)	4 (7.8)	0 (0.0)	4 (1.9)	0 (0.0)
Vomiting	24 (47.1)	4 (7.8)	0 (0.0)	4 (1.9)	0 (0.0)
Hyperglycemia	35 (68.6)	3 (5.9)	0 (0.0)	4 (1.9)	0 (0.0)
Alkaline phosphatase increased	27 (52.9)	2 (3.9)	0 (0.0)	3 (1.4)	0 (0.0)
Hyperbilirubinemia	11 (21.6)	2 (3.9)	0 (0.0)	2 (0.9)	0 (0.0)
Hyponatremia	7 (13.7)	8 (15.7)	0 (0.0)	12 (5.7)	0 (0.0)

NCI-CTC National Cancer Institute-Common Toxicity Criteria

Although a number of chemotherapeutic regimens have been tested in randomized studies, there is no internationally accepted standard of care, and uncertainty remains regarding the choice of regimen. In a recent meta-analysis, comparisons of 5-FU/cisplatin regimens with versus without anthracyclines, and 5-FU/anthracycline regimens with versus without cisplatin both demonstrated a significant survival benefit for the three-drug combination (hazard ratios [HR] = 0.77 and 0.83, respectively) [23]. In a recent randomized phase III trial; however, the small survival advantage for docetaxel/cisplatin/5-FU compared with cisplatin/5-FU as first-line therapy in gastric cancer, although statistically significant (median time to progression, 5.6 vs. 3.7 months, respectively; P <0.01; risk reduction, 32%), seems to be questionable in clinical relevance due to high incidence of severe neutropenia, neutropenic fever, and diarrhea [24].

The chemotherapeutic regimen most widely used in the routine care of patients with advanced gastric carcinoma in Korea is 5-FU combined with cisplatin. A pivotal prospective, randomized phase III Korean study compared the efficacy of two combinations—FU/cisplatin and FAM—versus single-agent 5-FU [10]. Compared with FAM and 5-FU, 5-FU/cisplatin achieved a significantly higher response rate (51 versus 25 versus 26%; P <0.01) and median time to progression (22 vs. 12 vs. 9 weeks; P <0.05), although overall survival was not statistically different for the three arms (37, 29, and 31 weeks for 5-FU). Various new agents have shown activity in gastric cancer in Korea, including docetaxel, paclitaxel, capecitabine, and irinotecan [25–28].

New oral fluoropyrimidines, such as capecitabine, with their convenient administration, have been used in place of 5-FU continuous infusion, which requires central venous access and portable pumps with uncomfortable schedules [29]. A platinum analog, oxaliplatin, has also shown comparable activity with cisplatin in this tumor type without the nephrotoxicity of cisplatin [30]. To date, however, none of the newer agents, alone, or in combination have been shown to improve efficacy over 5-FU combined with cisplatin.

The initial clinical experience with pemetrexed was complicated by severe adverse events, including neutropenia, thrombocytopenia, mucositis, diarrhea, and drug-related death [20, 31, 32] due to vitamin B_{12} and folate pool depletion. It is now established that the tolerability and therefore, the effectiveness of pemetrexed is related to the folate status of the patient, and that severe toxicity can be significantly reduced by vitamin B_{12} and FA supplementation. Preliminary results have suggested that patients with normal renal function tolerate much higher doses of pemetrexed (up to 1,000 mg/m^2 every 3 weeks) in the presence of folate and vitamin supplementation [33].

Although in the current study, the effectiveness of pemetrexed and cisplatin combination chemotherapy in gastric cancer was modest compared to that of historical regimens, the combination of pemetrexed and cisplatin was well tolerated in most patients. The most common grade 3/4 toxicity was neutropenia (50% of patients and 25% of cycles), with anorexia the most common clinical toxicity (10% of patients and 4% of cycles). The incidence of grade 3/4 neutropenia, although higher than that reported in other studies using the combination of pemetrexed and cisplatin, may be related to the weekly examination of blood counts conducted during the treatment period per protocol. Since

grade 4 neutropenia and/or grade 3 thrombocytopenia were infrequent, dose reductions were required in only 5 and 6% of the total administered doses of pemetrexed and cisplatin, respectively. Percentages of actual doses delivered were above 90% for both drugs.

The reduction of significant toxicity seen with pemetrexed in combination with vitamin B_{12} and FA supplementation and the convenience of administration (10 min infusion every 21 days) may offer a better chemotherapy alternative in this disease especially in previously non-responsive patients. Dose increments of pemetrexed may also be considered, especially given the acceptable toxicity profile made possible by vitamin/FA supplementation.

In conclusion, the combination of pemetrexed and cisplatin produces modest activity and an acceptable toxicity profile in patients with advanced gastric cancer. Further study is warranted using different combinations and doses with the aim of optimizing efficacy.

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