Gastric Cancer (2012) 15:389–395
DOI 10.1007/s10120-011-0128-z

ORIGINAL ARTICLE

Comparative analysis of the efficacy and safety of chemotherapy with oxaliplatin plus fluorouracil/leucovorin between elderly patients over 65 years and younger patients with advanced gastric cancer

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Received: 6 April 2011 / Accepted: 3 December 2011 / Published online: 12 January 2012

Abstract
Background A chemotherapy regimen with oxaliplatin, fluorouracil, and leucovorin is commonly used to treat advanced gastric cancer (AGC). This study was designed to compare the efficacy and the safety of oxaliplatin plus fluorouracil/leucovorin administered biweekly (mFOLFOX6) between elderly patients aged over 65 years and younger counterparts with AGC.
Methods This analysis included 82 AGC patients (≥65:31, <65:51). Patients with previously untreated chemo-naïve advanced adenocarcinoma of the stomach received oxaliplatin 85 mg/m^2, 5-FU bolus 400 mg/m^2 on day 1 and 5-FU 1,500 mg/m^2, leucovorin 75 mg/m^2 22 h infusion on days 1 and 2 every 2 weeks. The aim of the study was to compare efficacy and safety, including response rate (RR), progression-free survival (PFS), overall survival, and grade ≥3 adverse events, between patients aged ≥65 years and patients aged <65 years.
Results Median progression-free survival (PFS) was not significantly different between both groups (≥65: 5.8 months, <65: 5.7 months, respectively, HR 0.77, 95% CI: 0.44–1.16, $P = 0.18$). Median overall survival was not significantly different between both groups (≥65: 10.3 months, <65: 9.5 months HR 0.83, 95% CI: 0.50–1.37, $P = 0.46$). The rate of grade 3 or 4 neutropenia did not differ with age group (≥65: 51.6%, <65: 43.1%); nor did the rates of neutropenic fever (≥65: 16.1%, <65: 5.9%), and infection without neutropenia (≥65: 3.2%, <65: 3.9%). Rates of grade ≥3 toxicities such as thrombocytopenia, nausea/vomiting, or peripheral neuropathy were not significantly different between the two groups.
Conclusions mFOLFOX6 maintains its efficacy and safety in elderly patients aged over 65 years in comparison with AGC patients aged <65 years. Its judicious use should be considered regardless of age.

Keywords Stomach cancer · Aged · Oxaliplatin · Combination chemotherapy

Introduction

Cancer incidence among the elderly is rapidly increasing [1, 2]. Clinical trial data involving only elderly cancer patients are rare—not because of a lack of efficacy but because of a lack of evidence and resources [3–5]. It has been suggested that chemotherapy among elderly patients is as effective as chemotherapy among younger groups. However, most studies have focused on breast cancer and colorectal cancer [6–9]. Moreover, most studies were accomplished in an adjuvant setting. Research on the effect of palliative chemotherapy for advanced gastric cancer in the elderly is rare.

Gastric adenocarcinoma is frequent in Asia and Eastern Europe, and accounts for more than 800,000 new cases per year worldwide. It is the second most common cause of death from cancer [10, 11]. Since early detection is practiced in Japan and Korea, the incidence of advanced gastric cancer (AGC) is decreasing. However, advanced metastatic gastric cancer is still common in Asia. Inoperable or metastatic gastric cancer is an incurable disease, and little progress has

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been made in its treatment. Despite the introduction of several new-generation chemotherapeutic agents, the median overall survival is less than 10 months in AGC due to short durations of response [12–15]. An oxaliplatin plus 5-fluorouracil combination chemotherapy regimen is favored because of its manageable toxicity and its modest efficacy [13–18]. Oncologists are sometimes reluctant to administer chemotherapy to even young patients with a poor performance status because of the relatively short-term improvement in overall survival and PFS that it provides. Therefore, many oncologists are reluctant to administer chemotherapy to older patients because of its potential toxic effects, which may affect their quality of life, and the questionable survival prolongation it affords.

In this clinical setting, it is very important to determine whether elderly patients with AGC would benefit from conventional chemotherapy. However, it is difficult to conduct a prospective randomized clinical trial in elderly cancer patients. To address this practical issue specifically for a regimen of oxaliplatin plus fluorouracil/leucovorin administered biweekly (modified FLOFOX6) in AGC, we conducted a retrospective, age-based analysis that compared the effects of chemotherapy in elderly AGC patients aged over 65 years with its effects in younger patients. The aim of our study was to compare the PFS of modified FOLFOX6 (mFOLFOX6) chemotherapy and the overall survival duration (OS) between patients aged >65 years and their younger counterparts. The second aim was to compare the toxicities and response rate (RR) of these two groups.

Patients and methods

Patients

Between June 2006 and January 2010, a total of 82 patients (31 elderly patients, 51 young patients) with metastatic or locally advanced AGC were analyzed in this retrospective study. Eighty-two patients were administered a mFOLFOX-6 regimen consisting of a 2 h infusion of oxaliplatin 85 mg/m^2 (day 1), 5-FU 400 mg/m^2 bolus infusion (day 1), 5-FU 1,500 mg/m^2 22 h continuous infusion (days 1, 2), and leucovorin 75 mg/m^2 continuous infusion (days 1, 2) as a first-line palliative chemotherapy. Treatment was repeated every 2 weeks until disease progression, patient refusal, or unacceptable adverse reactions.

Eligibility criteria included: (1) pathologically confirmed gastric adenocarcinoma with a measurable or evaluable lesion; (2) no prior chemotherapy except for adjuvant chemotherapy administered more than 6 months previously; (3) ECOG performance 0–2; (4) adequate bone marrow, hepatic, and renal functions. Figure 1 shows a flow chart of the analysis. ECOG performance status was defined as follows: ECOG 0: fully active, able to carry out all pre-disease activities without restriction; ECOG 1: restricted in terms of physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature; ECOG 2: ambulatory and capable of self-care, but unable to carry out any work activities; ECOG 3: capable of only limited self-care, confined to a bed or chair for >50% of the patient's waking hours; ECOG 4: completely disabled.

Patients received a blood test for toxicity every cycle and were re-evaluated every 3 cycles by abdominal computed tomography. The tumor responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST). Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE, version 3.0). The dose of 5-FU was reduced by 20% for diarrhea or mucositis exceeding grade 2. 5-FU and oxaliplatin were reduced by 20% for NCI-CTC grade 3 or 4 neutropenia or thrombocytopenia. Peripheral sensory neuropathy was also graded according to the same toxicity criteria. A 20% dose reduction of oxaliplatin was planned if the patient experienced grade 2 sensory neuropathy, and we strictly followed the protocol that permitted the initiation of chemotherapy after recovery from all toxicities lower than grade 2.

Evaluation of efficacy outcomes

Responses were classified according to RECIST [19]. The proposed RECIST methods included determining the product of the unidimensional measurement of tumors, summing these dimensions over all tumors, and then categorizing changes in these summed products as follows: complete response—tumor has disappeared for at least 4 weeks; partial response—30% or greater reduction in the sum of tumor diameters of target lesions from baseline confirmed at 4 weeks; stable disease—neither partial response nor complete response nor progressive disease; and progressive disease—at least a 20% increase in tumor size in sum of tumor diameters of target lesions, with no complete response, partial response, or stable disease documented before an increase in size, or the development of new tumor sites. Computed tomography of target areas was performed before the start of the treatment and repeated every 8 weeks in both arms. Patients who discontinued the study were evaluated every 2 months. PFS was measured from the date of start of chemotherapy until disease progression or death from any cause. Overall survival (OS) was measured from the start date of chemotherapy until death from any cause.

Statistical analysis

The primary end point was to compare PFS and OS and toxicity between patients aged >65 years and younger

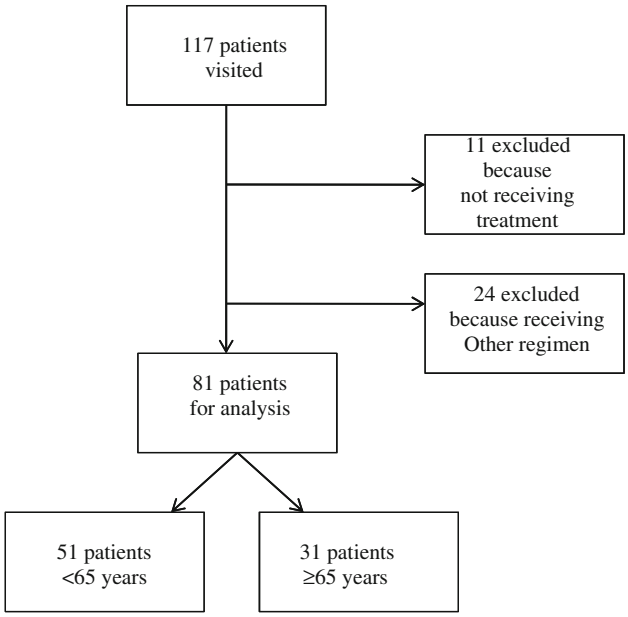

Fig. 1 Flow chart of the analysis

patients. Survival data were calculated using the Kaplan–Meier method on the intent-to-treat (ITT) population which received at least one cycle of chemotherapy. The safety analysis included all patients who received chemotherapy. Quality-of-life data were not collected in a uniform manner, and quality-of-life measures are not considered in this analysis.

PFS and OS were compared using the logrank test. Toxicities and RRs were compared with the χ^2 test and Fisher's exact test. All analyses were conducted using the SPSS system (version 17.0), and $P < 0.05$ was employed to denote statistical significance.

Results

Efficacy

A total of 82 patients (≥65, 31 patients; <65, 51 patients) were enrolled from a single unit: Konkuk University Medical Center in Korea. Eighty-two patients were eligible for OS analysis on an ITT basis; 81 patients were eligible for PFS analysis. We initially recommend the mFOLFOX6 regimen to all AGC patients who visit the Department of Hemato-oncology in Konkuk University Medical Center. A total of 117 AGC patients were referred. Eleven patients did not receive chemotherapy because of their refusal or poor performance status. Twenty-four patients did not want a biweekly regimen or intravenous chemotherapy. Twenty-four patients received oral TS-1 monotherapy or TS-1 plus cisplatin combination chemotherapy. The decision about the chemotherapy regimen depended on the patient's preferred schedule or convenience. It did not depend on the patient's performance status or degree of cancer metastasis. Figure 1 shows a flow chart for this analysis. Median follow-up duration was 24 months. Baseline and demographic data are summarized by age group in Table 1. The two groups were well balanced in terms of pretreatment characteristics. The median ages of the groups were 73 and 49 years (Table 1). Performance status was well balanced between both groups.

RR was analyzed by age group. The RR for the elderly patients was not significantly different from that for the younger patients (elderly group: 50% vs. young group 42%). The PFS for the elderly patients was 5.8 months (95% CI: 3.8–7.8 months). The PFS for the younger patients was 5.7 months (95% CI: 4.8–6.6 months) (Fig. 2). There was no significant difference in PFS according to the logrank test (HR 0.77, 95% CI: 0.44–1.16, $P = 0.18$). The median overall survival among elderly patients undergoing chemotherapy with mFOLFOX6 was 10.3 months (95% CI: 3.6–17.0 months). The median overall survival among younger patients was 9.5 months (95% CI: 7.7–11.3 months) (Fig. 3). Overall survival duration (OS) did not show a significant difference between the groups (HR 0.83, 95% CI: 0.50–1.37, $P = 0.46$). After the end of treatment with the oxaliplatin and 5-fluorouracil combination regimen, a second-line chemotherapy regimen [including taxane-based, TS-1-based (TS-1 only or TS-1 plus cisplatin), or irinotecan-based chemotherapy] was given to 31 of the 51 (62.7%) young patients and 12 of the 31 (38.7%) elderly patients ($P = 0.0867$). Forty-three of the 82 patients (52.4%) were given second-line chemotherapy. S1-based chemotherapy was given to 21 (25.6%) patients, irinotecan-based chemotherapy was given to 12 (14.6%) patients, and taxane-based chemotherapy was given to 10 (12.2%) patients.

Toxicities

Rates of grade ≥3 adverse events by age group for patients treated with mFOLFOX6 are listed in Table 2. The rates of grade ≥3 hematologic toxicity, including neutropenia (51.6% ≥65 vs. 43.1% <65) and thrombocytopenia (6.4% ≥65 vs. 3.9% <65), did not differ with age group. The rate of neutropenic fever/infection seemed higher in the elderly group (16.1 vs. 5.9%), but there was no statistically significant difference ($P = 0.30$). The rates of nausea/vomiting did not differ with age group; nor did the rate of grade ≥3 neurologic adverse events (16.1% ≥65 vs. 17.6% <65, $P = 0.56$). The rate of infection without neutropenia did not differ with age group. Early cessation due to patient refusal was more common in the elderly group, but there was no statistical significance (12.9% ≥65 vs. 3.9% <65, $P = 0.14$). The median number of chemotherapy cycles

Table 1 Characteristics of the patients by age group

Characteristics	Elderly, ≥65		Young, <65	
	Number	%	Number	%
Total number	31	37.8	51	62.2
Age, years				
Median	73		49	
Range	65–79		32–64	
Sex				
Male	23	74.2	32	62.7
Female	8	25.8	19	37.3
ECOG status				
Median	1		1	
0–1	16	51.6	33	64.7
2	15	49.4	18	35.3
Dose intensity[a] (%)	88.4		93.8	
Cycle number				
Median	9		9	
Range	1–12		1–12	

[a] Mean percentage dose of drug administered per cycle

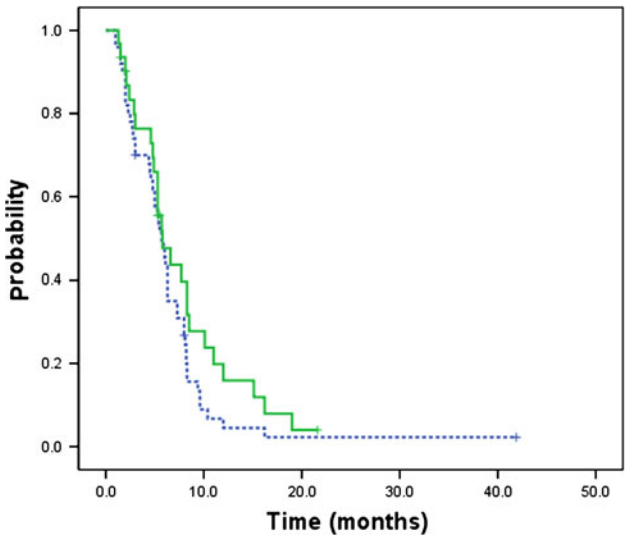

Fig. 2 Kaplan–Meier plots of progression-free survival (PFS) for mFOLFOX6 by age group. Median PFS: age <65 (*dot*), 5.7 months; age ≥65 (*solid*), 5.8 months. $P = 0.16$

was 9 in both groups (Table 1). Dose reductions of any drug were required in 51.6% of the elderly patients and 35.4% of the young patients. However, the dose intensity of each cycle (mean percentage dose of the drug administered per cycle) did not differ with age group (88.4% ≥65 vs. 93.8% <65) (Table 1). Treatment discontinuation due to toxicity was low in both groups (elderly group: 12.9%, young group: 3.9%, $P = 0.14$). Treatment delays of at least 7 days occurred in 8 (25.8%) of the 31 elderly patients and 8 (15.7%) of the 51 young patients. There was no

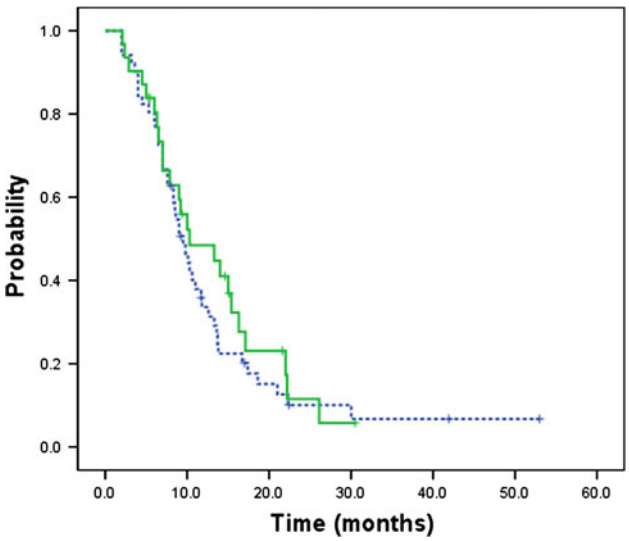

Fig. 3 Kaplan–Meier plots of overall survival (OS) for mFOLFOX6 by age group. Median OS: age <65 (*dot*), 9.5 months; age ≥65 (*solid*), 10.3 months. $P = 0.45$

statistically significant difference in the incidence of treatment delays of at least 7 days between both groups, nor in the incidences of neutropenic fever and treatment discontinuation, while the incidence of treatment delays of at least 7 days due to toxicity seemed to be higher in the elderly group, although there was no statistically significant difference. In addition to this, neither group had any treatment-related deaths.

Discussion

This study has shown that the efficacy of chemotherapy with the mFOLFOX6 regimen among elderly gastric cancer patients aged over 65 years is not inferior to the efficacy among younger gastric cancer patients in terms of RR, PFS, and overall survival. In addition to the efficacy of chemotherapy, toxicities are not more severe among elderly AGC patients compared to younger patients. Therefore, this study demonstrated that palliative chemotherapy with the mFOLFOX6 regimen in AGC is beneficial even when the patient is aged over 65 years.

Several phase II trials have indicated that oxaliplatin-based doublets (oxaliplatin/FU/leucovorin combinations) are an effective and well-tolerated treatment for patients with AGC [13, 16–18]. Our study also showed similar median PFS and OS values to those reported in studies with oxaliplatin-based doublets. There was no significant statistical difference between the two groups in terms of PFS (elderly: 5.8 vs. younger: 5.7 months) and OS (elderly 10.3 vs. younger: 9.5 months). This study of patients on the mFOLFOX6 regimen achieved similar RRs to those seen in

Table 2 Percentages of the patients in each group who experienced NCI-CTC grade ≥3 adverse events

Adverse events	Age ≥65 ($n = 31$)		Age <65 ($n = 51$)		P
	%	Number	%	Number	
Neutropenia	51.6	16	43.1	22	.45
Neutropenic fever	16.1	5	5.9	5	.49
Infection without neutropenia	3.2	1	3.9	3	1.0
Thrombocytopenia	6.4	2	3.9	2	.63
Nausea/vomiting	6.4	2	2.0	1	.55
Neurotoxicity	16.1	5	17.6	9	.86
Early cessation	12.9	4	3.9	2	.19

Early cessation: early cessation of chemotherapy due to patient refusal or toxicity

other studies. There was no statistically significant difference in response between the two groups (elderly: 50% vs. younger: 42%).

The rates and types of adverse events observed in our study with mFOLFOX6 were consistent with those previously reported for oxaliplatin-based doublets, though our study showed slightly higher incidences of neutropenia and neutropenic fever. The higher proportion of patients with poor performance (ECOG PS 2) was assumed to cause the higher incidences of grade 3 and 4 neutropenia and neutropenic fever in comparison to those seen in other phase 2 clinical trials. However, toxicities were manageable, and treatment-related death was not observed in either group. The incidence of febrile neutropenia was less than 8% in other phase 2 clinical trials with oxaliplatin-containing regimens [13–15].

In contrast to other clinical trials, this study is a retrospective analysis. Despite the limitations of retrospective analysis, it is clear that this study can minimize the selection bias of clinical trials, which are performed in healthier and younger patients. The median age of the patients in the elderly group of our study was 74 years old. In addition, the proportion of patients with poor performance status (ECOG PS 2) was substantial in our our study compared to others. The percentage of ECOG PS 2 patients was 49.4% among the elderly population. In most of the reported clinical trials, the median age of the population was 60–64 years old. The percentage of ECOG PS 2 patients was less than 10% in these studies partly because they were prospective clinical trial based studies. Taking into account these characteristics of the study population, we suggest that a modified FOLOX6 regimen should be considered for elderly gastric cancer patients because of the manageable toxicity rate. Treatment discontinuation due to toxicity was low (elderly group: 12.9%, young group: 3.9%). Most cases of neutropenic fever were detected early and managed successfully with broad-spectrum antibiotics and granulocyte colony-stimulating factor. Most patients with neutropenia recovered within 2 or 3 days. Dose reduction was able to prevent a relapse of febrile neutropenia.

According to Al-Batran's study, an oxaliplatin-based doublet (FLO) regimen showed favorable activity in elderly patients compared to the FLP regimen (5-FU/cisplatin/leucovorin) [14]. The FLO regimen resulted in significantly superior RR (41.3 vs. 16.7%), PFS (6.0 vs. 3.1 months) and overall survival (13.9 vs. 7.2 months) values compared to the FLP regimen among patients older than 65 years. Our study confirmed that oxaliplatin-based doublets produce favorable activity and manageable toxicities, even in elderly gastric cancer patients. However, this point should be considered within the limitations of retrospective analysis. The results of our study showed that mFOLFOX6 was at least as effective in elderly gastric cancer patients as in younger patients. As we pointed out, overall, our study population presented a worse performance status and were older. In spite of their older age and worse performance status, their PFS and OS values did not differ from those seen in other clinical trials. Therefore, we can assume that the mFOLFOX6 regimen is at least as effective in elderly gastric cancer patients as it is in young gastric cancer patients. However, elderly patients with poor performance status should be monitored thoroughly considering their high incidences of neutropenia and neutropenic fever. Prophylactic administration of granulocyte colony-stimulating factor might be helpful for elderly gastric cancer patients at a high risk of developing neutropenia after a comprehensive geriatric assessment.

In the face of limited progress in new and improved stategies for treating AGC, the focus has shifted to making treatments safer while aspiring to prolonged overall survival. Particularly among elderly patients, safety is a very important factor when deciding whether to start palliative chemotherapy and which regimen to administer. The mFOLFOX6 regimen did not show a difference in toxicity profile between our elderly patients and our younger patients. It is therefore feasible to administer the mFOLFOX6 regimen even in elderly gastric cancer patients. According to Al-Batran's study, 5-fluorouracil plus cisplatin combination chemotherapy showed inferior activity in an elderly group because of the early cessation of chemotherapy due to toxicities and patient refusal [14]. Our

study showed that the median number of mFOLFOX6 cycles in elderly AGC patients was the same as in the younger group (median cycle number: 9 cycles), and the dose intensity was not compromised in the elderly group (88.4% ≥65 vs. 93.8% <65). With this mind, we can say that mFOLFOX6 had tolerable toxicity profiles without compromising dose intensity and treatment duration, even in elderly patients aged over 65. Oxaliplatin-based chemotherapy has been suggested to be preferable to cisplatin-containing regimens because it leads to significantly fewer cases of toxicity and a trend toward improved median PFS was observed for patients on it [14, 20]. TS-1 monotherapy and TS-1-containing chemotherapy regimens are widely used in Asia, including Korea and Japan. TS-1 monotherapy and TS-1-containing chemotherapy also showed tolerable toxicity profiles and good effects of chemotherapy in terms of PFS and OS [21, 22]. We cannot discern which of these regimens would be preferable for the elderly population because there has been no clinical trial. It is clear that there is a paucity of prospective information on elderly gastric cancer patients. Clinical trials focusing on younger, healthier patients have left us devoid of useful data, even with which to treat elderly gastric cancer patients in an evidence-based fashion. The undertreatment of elderly gastric cancer patients could be problematic. While our efforts in this study are only a first step, we believe that our results offer some insight into the effect of palliative chemotherapy with the mFOLFOX6 regimen in elderly gastric cancer patients. In particular, it is important to recognize that the mFOLFOX6 regimen can be a reasonable option for elderly gastric cancer patients.

Another limitation is that we did not perform a comprehensive geriatric assessment and quality of life study. Age cannot be the only factor when deciding whether to administer palliative chemotherapy to AGC patients. Before administering chemotherapy in elderly AGC patients, a comprehensive geriatric assessment and quality of life data are crucial to increasing the efficacy of the treatment and decreasing toxicity rates. A prospective study including a comprehensive geriatric assessment and quality of life data is absolutely necessary to elucidate the role of chemotherapy in elderly gastric cancer patients. We hope that this article is able to provide an impetus to perform further clinical trials in elderly AGC patients.

In conclusion, palliative chemotherapy using oxaliplatin-based doublets in elderly gastric cancer patients is safe and effective. Therefore, the judicious use of oxaliplatin-based chemotherapy should be considered in elderly gastric cancer patients.

Acknowledgments This work was supported by a Konkuk University Grant 2010.

References

1. Edwards BK, Howe HL, Ries LA, Thun MJ, Rosenberg HM, Yancik R, et al. Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on U.S. cancer burden. Cancer. 2002;94:2766–92.
2. Levi F, Lucchini F, Negri E, Boyle P, La Vecchia C. Mortality from major cancer sites in the European Union, 1955–1998. Ann Oncol. 2003;14:490–5.
3. Lichtman SM, Balducci L, Aapro M. Geriatric oncology: a field coming of age. J Clin Oncol. 2007;25:1821–3.
4. Kemeny MM, Peterson BL, Kornblith AB, Muss HB, Wheeler J, Levine E, et al. Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol. 2003;21:2268–75.
5. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. J Clin Oncol. 2004;22:4626–31.
6. Christman K, Muss HB, Case LD, Stanley V. Chemotherapy of metastatic breast cancer in the elderly. The Piedmont Oncology Association experience [see comment]. JAMA. 1992;268:57–62.
7. Extermann M. Management issues for elderly patients with breast cancer. Curr Treat Options Oncol. 2004;5:161–9.
8. Goldberg RM, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. J Clin Oncol. 2006;24:4085–91.
9. Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. N Engl J Med. 2001;345:1091–7.
10. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006;56:106–30.
11. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
12. Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28:1547–53.
13. Al-Batran SE, Atmaca A, Hegewisch-Becker S, Jaeger D, Hahnfeld S, Rummel MJ, et al. Phase II trial of biweekly infusional fluorouracil, folinic acid, and oxaliplatin in patients with advanced gastric cancer. J Clin Oncol. 2004;22:658–63.
14. Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008;26:1435–42.
15. Chao Y, Yeh KH, Chang CJ, Chen LT, Chao TY, Wu MF, et al. Phase II study of weekly oxaliplatin and 24-h infusion of high-dose 5-fluorouracil and folinic acid in the treatment of advanced gastric cancer. Br J Cancer. 2004;91:453–8.
16. de Vita F, Orditura M, Matano E, Bianco R, Carlomagno C, Infusino S, et al. A phase II study of biweekly oxaliplatin plus infusional 5-fluorouracil and folinic acid (FOLFOX-4) as first-line treatment of advanced gastric cancer patients. Br J Cancer. 2005;92:1644–9.
17. Lordick F, Lorenzen S, Stollfuss J, Vehling-Kaiser U, Kullmann F, Hentrich M, et al. Phase II study of weekly oxaliplatin plus infusional fluorouracil and folinic acid (FUFOX regimen) as first-line treatment in metastatic gastric cancer. Br J Cancer. 2005;93:190–4.

18. Louvet C, Andre T, Tigaud JM, Gamelin E, Douillard JY, Brunet R, et al. Phase II study of oxaliplatin, fluorouracil, and folinic acid in locally advanced or metastatic gastric cancer patients. J Clin Oncol. 2002;20:4543–8.
19. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000;92:205–16.
20. Montagnani F, Turrisi G, Marinozzi C, Aliberti C, Fiorentini G. Effectiveness and safety of oxaliplatin compared to cisplatin for advanced, unresectable gastric cancer: a systematic review and meta-analysis. Gastric Cancer. 2011;14:50–5.
21. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9(3):215–21.
22. Narahara H, Iishi H, Imamura H, Tsuburaya A, Chin K, Imamoto, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). Gastric Cancer. 2011;14(1):72–80.