계명의대학술지 제36권 1호
Keimyung Med J
Vol. 36, No. 1, June, 2017

Triple Combination Chemotherapy in Elderly Metastatic Gastric Cancer Patients

Jin Young Kim, M.D., Jung Min Lee, M.D., Hong Suk Song, M.D.

Division of Hemato-Oncology, Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea

Received: March 27, 2017
Revised: May 11, 2017
Accepted: May 31, 2017
Corresponding Author: Hong Suk Song, M.D.,
Department of Internal Medicine,
Keimyung University School Medicine,
56 Dalseong-ro, Jung-gu, Daegu 41931, Korea
Tel: +82-53-250-7436
E-mail: shs7436@dsmc.or.kr

• The authors report no conflict of interest in this work.

This study was conducted in order to evaluate the response rate, progression free survival (PFS), overall survival (OS), safety and prognostic factors of weekly S-1, paclitaxel plus cisplatin chemotherapy in patients older than 65 years. We administered the triple regimen to patients older than 65 years with recurrent or metastatic gastric cancer. The response rate, PFS, safety of triple combination chemotherapy was evaluated. Clinical outcomes of the elderly group (≥65 years old; n = 28) were compared with those of the non-elderly group (<65 years old; n = 68). The common metastatic lesions were abdominal lymph nodes (57.1%). The median number of cycle was 3.3 cycles (range; 1~9). The disease response rate was 50.0%. The median PFS was 6.2±0.46 months and median OS was 7.6±1.46 months. This treatment was moderately tolerated with grade 3/4 neutropenia in 67.9%, grade 3 anemia in 21.4%. Non-hematologic toxicities were grade 3 general weakness in 25.0% of patients. Compare to younger patients, more grade 3/4 neutropenia, anemia and general weakness were observed. Treatment related mortality was 3.6%. Only body mass index (BMI) was correlated with overall survival by cox regression analysis (p = 0.043). Triple regimen in elderly gastric cancer patients showed relatively high disease response rate and survival duration similar to younger patients, but more frequent neutropenia, anemia and general weakness were seen as barriers to treatment in elderly patients. Especially in low BMI elderly patients, triple regimen chemotherapy must be used with caution.

Keywords: Drug therapy, Gastric neoplasm, Geriatric assessment, Prognosis

© Copyright
Keimyung University School of Medicine 2017

Introduction

Although the incidence and mortality of gastric cancer have been decreasing over the past a few decades, it is still the second most common cancer next to lung cancer around the world [1]. Korea is the area that has one of the highest incidence rates of gastric cancer. Despite of poor prognosis of advanced gastric cancer, systemic chemotherapy improves the quality of life and overall survival compared with the best supportive care alone [2]. In many countries, more than half of women and a third of men die after the age of 80 years [3]. Cancer is well recognized as a disease of old age and the process of tumorigenesis starts at around the age of 20 and detection of cancer is normally around the age of 50 or later [4]. Moreover, life expectancy is often underestimated, especially for the old patients and must be weighted against the natural history of the disease for which definitive treatment is being considered [5]. Recent studies have shown a considerable increase in the number of elderly patients with gastric cancer [6]. Older cancer patients are under-represented in clinical trials for new cancer therapies [7]. Therefore there is less evidence based data to guide the treatment of these patients.

Many combination regimens have shown a response rate (RR) of 35-45% and are able to achieve better RR compared with monotherapy [8]. However, most patients analyzed in these study were 70 years of age or younger. Aging is inextricably associated with physiological changes in functional status, organ function and drug pharmacokinetics but age itself is not a negative predictive, and treatment should not be omitted just on the basis of chronological age [9]. Although there has been increasingly recognition and acceptance of the importance of more active treatment for elderly advanced gastric cancer patients, the interactions between age, performance status and RR remains unknown.

Three drug combination regimen showed promising results in terms of quality of life, RR, time to progression (TTP) and overall survival (OS) in gastric cancer. These achieved at the cost of substantial toxicity. These results raised interest in whether the risk/benefit ratio could be improved by use of three drug combination regimen in elderly gastric cancer patients.

S-1 is a novel oral fluoropyrimidine consisting of a 5-fluorouracil (FU) prodrug, tegafur, and the dihydropyrimidine dehydrogenase inhibitor, 5-chloro-2, 4-dihydropyrimidine and the orotatephosphoribosyl transferase inhibitor, potassium oxalate, which suppress the gastrointestinal toxicity of tegafur [10]. S-1 already demonstrated significant activity in advanced gastric cancer, achieving RR of 26-49% with tolerable safety profile in several phase II trials [11].

Paclitaxel is an antitumor agent isolated from the bark of yew tree (Taxusbrevifolia) and acts on microtubules during mitosis, resulting in antitumor activity. The RR of 3-week intervals of intravenous paclitaxel was 20-23% [12]. In addition, weekly infusion of paclitaxel is also active in gastric cancer [13]. Several phase II studies have shown that paclitaxel, alone or in combination with cisplatin or 5-fluorouracil, is active against advanced gastric cancer [14,15]. And in our previous report [16], S-1, paclitaxel and cisplatin combination chemotherapy has good efficacy and favorable toxicity profile among young aged gastric cancer patients.

Therefore, this phase II study was conducted to evaluate efficacy, safety, clinical features and prognostic factors of weekly S-1/paclitaxel plus cisplatin combination regimen in patients older than 65 years.

Materials and Methods

Patient eligibility

From May 2008 to May 2011, 28 patients were enrolled to receive triplet chemotherapy regimen in Dongsan Medical Center. All patients in this study had histologically confirmed metastatic or recurrent gastric adenocarcinoma with at least one unidimensionally measurable lesion, age ≥ 65 years and Eastern Cooperative Oncology Group (ECOG) of two or less. Laboratory criteria was adequate hematological (absolute neutrophil count above 1.5 × 10^3/μL, platelet count above 100 × 10^3/ μL), renal (below serum creatinine 1.5 mg/dL and above creatinine clearance 35 mL/min), and hepatic (total bilirubin 1.5 mg/dL and serum transaminase level 3 times the upper limit of the normal range) functions. Patients who had received adjuvant chemotherapy completed 1 year before entry were eligible. Patients were ineligible if they had previously received paclitaxel, S-1 chemotherapy or radiation therapy, or had other severe comorbid conditions, symptomatic brain metastasis, and another active malignancy. Patients were excluded if they received drugs with potential interactions with S-1 (allopurinol, phenytoin, warfarin), or were not able to comply with the requirements of the protocol. The following clinical data were collected from the medical records of each patients: a physical examination, body weight, body mass index (BMI), serum chemistry, imaging and medical information including response, toxicity profile, the date of progression, the last follow up and death were collected.

Treatment dose and schedule

S-1 (70 mg/m^2/day) was administered on days 1-14 of 21-day cycle. Patients received their assigned oral dose of S-1 divided in two, within 1 hour after meal. Paclitaxel 80 mg/m^2 and cisplatin 30 mg/m^2 were given as intravenous infusion for 1-hour on days 1 and 8. All patients were premedicated with a dexamethasone to prevent hypersensitivity reactions of paclitaxel. Antiemetic treatment was routinely given before each cycle of chemotherapy. The prophylactic use of a colony stimulating factor (CSF) was not allowed but in the case of neutropenic fever, the use of CSF was permitted. Treatment was continued until disease progression, patient refusal, or an unacceptable toxicity up to a maximum 9 cycles.

Dose modification

The next cycle of treatment was begun when the absolute neutrophil count was above 1.5×10^3/μL, the platelet count was above 100×10^3/μL, and any other treatment-related toxicities were less than or equal to grade 1: otherwise, treatment was withheld for up to 2 weeks. If adverse events did not improve to grade 0 or 1 after two weeks, the patients were excluded from the study.

For hematological toxicity, a dose modification for the next cycle was decided by the nadir count of the previous cycle. S-1 or paclitaxel were alternatively reduced by 5 mg/m^2/day or 10 mg/m^2/day, respectively. Paclitaxel was the first to be reduced for a grade 4 neutropenia, grade 3/4 thrombocytopenia, or neutropenic fever. On day 8, both drugs omitted in case of grade 4 neutropenia, grade 3/4 thrombocytopenia, neutropenic fever, or severe hemorrhage. On day 8, for grade 3 neutropenia or grade 2 thrombocytopenia or platelet counts less than 100×10^3/μL, paclitaxel dose was reduced by 10 mg/m^2/day without the reduction of S-1. The dose of S-1 was not reduced in the same cycle. We permitted to use of G-CSF in the case of febrile neutropenia.

For the non-hematological toxicity, S-1 for the

next cycle was reduced by 5 mg/m^2/day for grade 2 diarrhea or grade 3/4 abdominal pain and was withheld for grade 3 diarrhea. Paclitaxel was reduced by 10 mg/m^2/day for a grade 2 peripheral neuropathy and was discontinued for grade 3 peripheral neuropathy. Both drugs were reduced by grade 2 hyperbiliru-binemia, grade 3 liver dysfunction and grade 3 non-hematological toxicity except alopecia, nausea, vomiting, myalgia, and arthralgia. Both drugs were omitted for grade 3 hyperbilirubinemia, grade 4 liver dysfunction and grade 4 other non-hematological toxicity. The dose of S-1 was not changed in the same cycle. The drug dose could be reduced to the 50% of initially planned dose due to toxicity.

Study assessments

A screening assessment, including a medical history, physical examination, ECG, chest X-ray, and tumor assessment, conducted within 2 weeks before starting treatment. Other baseline evaluations conducted within 7 days before starting treatment included vital signs, an ECOG performance status, and laboratory tests. Complete blood counts were performed weekly during the first cycle and every cycle thereafter, and biochemical tests performed before each cycle. Response assessment was performed every two cycles until the tumor progressed. The tumor responses were classified according to the response evaluation criteria in solid tumors (RECIST) guidelines [17]. Patients with a complete response (CR) or partial response (PR) required a confirmatory disease assessment at least 4 weeks later. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0. Dose intensity was defined as the total amount of drug given (mg/m^2) divided by the number of weeks.

Statistical analysis

This trial is a retrospective study and compared with prior prospective, multicenter phase II triple combination chemotherapy study [16]. Prior prospective, multicenter phase II study was performed for advanced gastric cancer patients that the age was between 18-70 years. We want to compared with physically good status and relatively young patients. All enrolled patients were included in the intention-to-treat analysis of efficacy. The time to progression and OS were estimated using the Kaplan-Meier method. Other variables were expressed as relative and absolute frequencies. The comparison between variables was conducted using the chi-squared test and student's t-test for qualitative and quantitative variables, respectively. Analysis of variance (ANOVA), Cox regression and Pearson's square method were also used to compare qualitative variables for multiple layer quantitative analyses. *P* values less than 0.05 were considered statistically significant. Population parameter estimates were carried out at a Confidence Interval (CI) of 95%.

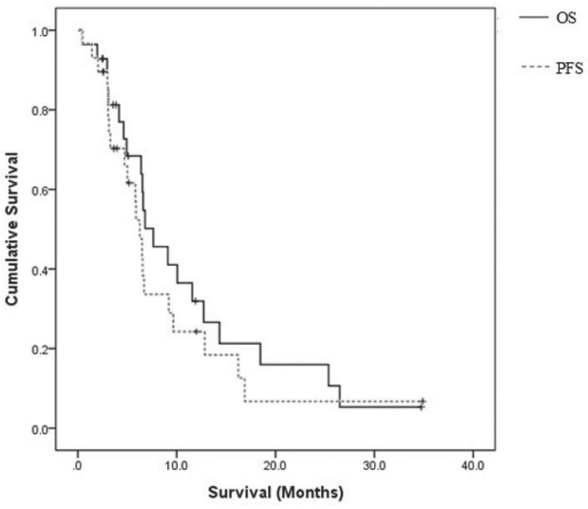

Fig. 1. Kaplan-Meier curves for median progression free survival (PFS) and overall survival (OS). The median PFS was 6.2 ± 0.46 (95% CI; 5.29-7.11) months and OS was 7.633 ± 1.46 (95% CI; 4.77-10.50) months.

Table 1. Patients characteristics

	Elderly/total patients	N (%)
Sex	Male/Female	22/6 (78.6/21.4%)
Age (yr)	Mean (range)	69.0 ± 36.2, (65-77)
	65-70	18 (64.3%)
	70-75	6 (21.4%)
	>75	4 (14.3%)
ECOG	1	21 (75.0%)
	2	6 (21.4%)
	3	1 (3.6%)
Weight loss	No	9 (32.1%)
	<10%	9 (32.1%)
	>10%	10 (35.7%)
Comorbidity	Total	15 (53.6%)
	1	7 (25.0%)
	2	5 (17.9%)
	3	3 (10.7%)
BMI index		22.91 ± 3.81
	Underweight	9 (32.1%)
	Normal	9 (32.1%)
	Overweight	9 (32.1%)
	Obese	1 (3.7%)
Creatinine clearance (mL/min)	> 75	4 (14.3%)
	50-75	9 (32.1%)
	<50	15 (53.6%)
Metastatic site	Lymph node	16 (57.1%)
	Liver	6 (21.4%)
	Peritoneum	5 (17.9%)
	Lung	2 (7.1%)
	Prostate, ureter, bone, esophagus, adrenal gland, spleen	1 (3.6%)
Cycle	<3	12 (42.9%)
	≥3	16 (57.1%)
	Total	93
	Mean	3.3 (1-8)

ECOG: eastern cooperative oncology group, BMI: body mass index.

Results

Patients' characteristics

From September 2007 to April 2011, 28 advanced gastric cancer patients older than 65 years had been treated. The clinical characteristics of these patients are shown in Table 1. The median age of the patients was 69 years (range, 65-77), and the male:female ratio was 3.7:1 (78.6:21.4%). The

median ECOG performance status (PS) was 1 (0-3), and mean BMI was 22.91 ± 3.80 and 9 patients (32.1%) were under weighted. One patient was ECOG 3 but other parameters were within normal range and the patient really want to receive triplet chemotherapy so investigators discussed about this case and permitted to include clinical tiral. The patients more than 10% weight loss were 10 patients (35.7%) and total 15 patients had comorbidities. Fifteen patients (53.6%) were below 75 mL/min in creatinine clearance and the most common metastatic site was lymph node and next was liver. The median cycle was 3.3.

Efficacy

Twenty-three (82.1%) of the 28 patients were available for the evaluation of the response, with the remaining 5 being lost to follow-up or patient refusal. All efficacy data are reported using the intent-to-treat patient population. One case of complete remission and 13 cases of partial remission were confirmed, giving an overall response rate of 50.0%. The tumor responses are shown in Table 2. The median duration of response in the 14 responding patients was 12.7 months (95% CI; 5.5-19.5). At a median follow-up of 13.9 months, the median PFS and median OS were 6.2 (95% CI; 5.29-7.11) months and 7.6 (95% CI; 4.77-10.50) months. Four patients (21.7%) received a second-line therapy, such as folfox (3 patients), xeloda (1 patient). Twenty-one patients had died at the time of the evaluation.

Toxicity

The hematologic and non-hematologic adverse events that occurred during this study are summarized in Table 3. A total of 93 cycles (mean 3.3, range 1-8 cycles) administrated in 28 patients were assessable for toxicity. For hematological toxicity, grade 3/4 neutropenia occurred in 2/17 (7.1%/60.7%) events in all 93 cycles. Febrile neutropenia developed in seven patients (25.0%). However, all cases were successfully treated with antibiotics and G-CSF. Compared with young patients, grade 3 anemia and grade 4 neutropenia were more developed. General weakness was the most common non-hematologic toxicities. Grade 2/3 general weakness was observed in 10.7%/25.0% of patients. One patient (3.6%) experienced grade 3 diarrhea and 4 patients (14.3%) developed dyspnea. Grade 3 general weakness, grade 2 anorexia, grade 3 dyspnea and pneumonia were more developed compared with young patients. No grade 4 non-hematologic toxicity was observed. Eight patients were hospitalized due to treatment related toxicities (5 due to febrile neutropenia, 3 due to pneumonia). The toxicity characteristics are shown in Table 3.

According to cox regression of OS, only BMI was correlated with OS. Median survival of under weighted patients was 6.4 months and normal and overweight was 12.7 months (Table 4). Factors related to hematologic toxicity were BMI, chemotherapy dosage, white blood cell and lymphocyte count (Table 5).

A total of 93 cycles were delivered to patients. Median cycle was 3.3 (range: 1-8). The mean dose of paclitaxel, cisplatin and S-1 were 54.0 mg/m^2/

Table 2. Tumor response (Intention-to-treat analysis)

Response	N (%)
Confirmed response	14 (50.0)
Complete response	1 (3.6)
Partial response	13 (46.4)
Stable disease	7 (25.0)
Progressive disease	2 (7.1)
Not assessable	5 (17.9)

Table 3. Hematologic and non hematologic adverse events

		Elderly	Young*	*p* value
Total		25 (89.3%)	68 (70.5%)	0.061
Hematologic				
Anemia	Grade 1	4 (14.3%)	19%	
	Grade 2	14 (50.0%)	3%	
	Grade 3	6 (21.4%)	1%	0.009
Leukopenia	Grade 3	4 (14.3%)	7.1%	
	Grade 4	14 (50.5%)	4.8%	0.122
Neutropenia	Grade 1	6 (21.4%)		
	Grade 2	3 (10.7%)	6%	
	Grade 3	2 (7.1%)	8%	
	Grade 4	17 (60.7%)	6%	0.005
Thrombocytopenia	Grade 1	1 (3.6%)		
	Grade 2	3 (10.7%)		
	Grade 3	1 (3.6%)	1%	0.770
Nonhematologic				
General weakness	Grade 2	3 (10.7%)	4.8%	
	Grade 3	7 (25.0%)		0.007
Anorexia	Grade 2	8 (28.6%)		0.000
Diarrhea	Grade 1	1 (3.6%)		
	Grade 2	3 (10.7%)	7.1%	
	Grade 3	1 (3.6%)		0.168
Dyspnea	Grade 2	4 (14.3%)		0.012
Nausea	Grade 2	3 (10.7%)	9.5%	0.871
Vomiting	Grade 2	2 (7.1%)		0.079
Neuropathy	Grade 2	2 (7.1%)		
	Grade 3		2.4%	0.335
Stomatitis	Grade 2	2 (7.1%)		0.079
Pain	Grade 2	1 (3.6%)		0.217
Neutropenic fever		7 (25.0%)	11.4%	0.154
Pneumonia		3 (10.7%)	0	0.030

* Young patients' data came from prior triplet chemotherapy [16].

Table 4. Cox regression of overall survival

	Relative Risk	Lower	Upper	*p* value
Body mass index	0.865	0.751	0.995	0.043
S-1 total dose	0.999	0.998	1.000	0.064

Table 5. Factors related to hematologic toxicity

	Pearson
Body mass index	0.015
Paclitaxel total dose	0.020
Cisplatin total dose	0.019
TS-1 total dose	0.048
White blood cell count	0.024
Lymphocyte count	0.003

week, 54.0 mg/m2/week and 55.0 mg/m2/week which were 95.0%, 92.0% and 96.0% of planned dose-intensity of protocol.

Discussion

Average life expectancy in Korea has progressively increased because of better living conditions, increased consumption of nutritious foods, and improved treatment of comorbidities and other diseases [18]. The incidence of gastric cancer as well as other cancers has increased in elderly patients. The increased age of the population is accompanied by an increase in age related disease. The analysis of chemotherapy versus best supportive care showed a significant OS of chemotherapy, and 5-FU based combination showed superior response compared with 5-FU monotherapy [19,20]. The data regarding elderly patients with metastatic gastric cancer seems to be limited. There is uncertainty about the use of systemic palliative chemotherapy in elderly patients because of the underrepresentation of this age group in clinical trials [21]. In the present study in advanced gastric cancer patients older than 65 years who had been treated with S-1, paclitaxel andcisplatin, the median PFS and median OS was 6.2 months and 7.6 months respectively with 50.0% overall response rate. These responses were consistent with previously reported data for first line chemotherapy in aged above 65 years with metastatic gastric cancer [22]. The European and Korean trials were also reported that there was no relationship between prognosis and age in gastric cancer [9,23]. These findings imply that chronological age may not influence treatment efficacy in metastatic gastric cancer. In comparison with young age triplet therapy group, it appeared shorter survival rate. In this study showed median PFS 6.2 months and median OS was 7.6 months, in young age triplet therapy group, median PFS was 9.4 months and median OS was 11.2 months.

There are limited data for prognostic factors in elderly patients with advanced gastric cancer. Kim *et al* [23] showed that the important prognostic factor was whether the patients had undergone a curative resection, and Lee *et al* [24] found that none of the potential prognostic factor (i.e. performance status, peritoneal or liver involvement and charlson comorbidity index) for OS in phase II trial of capecitabine versus S-1 in elderly patients. According to cox regression of OS, only BMI was correlated with survival in present study. The median survival of underweight patients was 6.4 months and normal and overweight was 12.7 months. The number of comorbidity or total dosage of chemotherapy was not significant independent prognostic factors for survival.

Toxicity is another important factor influencing oncologists' decision to treat. According to this study, physicians should pay more careful attention to toxicities especially in low body mass index patients. Kim *et al* [25] reported that there was no significant difference for RR and grade 3 or 4 adverse effect and OS between patients with combination and single agent as first-line therapy. Trumper *et al* [9] showed that chemotherapy-related toxicities such as neutropenia, anemia, stomatitis, and diarrhea occurred more frequently

in the elderly. In this study, total hematologic toxicity was occurred at 25 patients. Grade 3/4 neutropenia was 2/17 (7.1%/60.7%), grade 3 anemia was 6 (21.4%) and grade 3 thrombocytopenia was 1 (3.6%). Compared with young patients, grade 3 anemia and grade 4 neutropenia occurred more frequently in elderly patients. Total non-hematologic toxicity observed at 24 patients (85.7%) and it was similar with young patients (81.8%). The most common non-hematologic toxicity was general weakness (10 patients, 35.7%). Grade 3 general weakness was 7 (25.0%), grade 3 diarrhea was 1 (3.6%). Grade 3 general weakness, grade 2 anorexia, grade 3 dyspnea and pneumonia were more occurred in elderly patients compared with younger patients.

These results should be interpreted with caution. This study has limitations, such as being an analysis at a single institution, with a small number of patients, no comparative group who received double chemo-therapy. Further randomized prospective studies are needed to ascertain the role of triple combination chemotherapy in elderly patients.

Sumary

This study showed that patients older than 65 years in age with metastatic gastric cancer might derive a clinical benefit from S-1, paclitaxel and cisplatintriple combination chemotherapy. It showed relatively high disease response rate and survival duration similar to younger patients, but more frequent neutropenia, anemia and general weakness were seen as barriers to treatment in elderly patients. Physicians should pay attention to lower body weight patients because body mass index was correlated with OS.

Conflicts of Interest

Conflict of interest relevant to this article was not reported

References

1. Boyle P, Ferlay J. Cancer incidence and mortality in Europe 2004. *Ann Oncol* 2005:**16**:481-8.
2. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;**72**:37-41.
3. Manton KG, Vaupel JW. Survival after the age of 80 in the United States, Sweden, France, England, and Japan. *N Engl J Med* 1995;**333**:1232-5.
4. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer lett* 2008;**267**:133-64.
5. Ergina PL, Gold SL, Meakins JL. Perioperative care of the elderly patient. *World J Surg* 1993;**17**:192-8.
6. Roviello F, Marrelli D, De Stefano A, Messano A, Pinto E, Carli A. Complications after surgery for gastric cancer in patients aged 80 years and over. *Jpn J Clin Oncol* 1998;**28**:116-22.
7. 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.
8. Glimelius B, Hoffman K, Haglund U, Nyrén O, Sjödén PO. Initial or delayed chemotherapy with best supportive care in advanced gastric cancer. *Ann Oncol* 1994;**5**:189-90.
9. Trumper M, Ross PJ, Cunningham D, Norman AR, Hawkins R, Seymour M, *et al*. Efficacy and tolerability of chemotherapy in elderly patients with advanced oesophago-gastric cancer: a pooled analysis of three clinical trials. *Eur J Cancer* 2006;**42**:827-34.

10. Maehara Y. S-1 in gastric cancer: a comprehensive review. *Gastric Cancer* 2003;**6**:2-8.
11. Sakata Y, Ohtsu A, Horikoshi N, Sugimachi K, Mitachi Y, Taguchi T. Late phase II study of novel oral fluoropyrimidine anticancer drug S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) in advanced gastric cancer patients. *Eur J Cancer* 1998;**34**:1715-20.
12. Ohtsu A, Boku N, Tamura F, Muro K, Shimada Y, Saigenji K, *et al*. An early phase II study of a 3-hour infusion of paclitaxel for advanced gastric cancer. *Am J Clin Oncol* 1998;**21**:416-9.
13. Emi Y, Yamamoto M, Takahashi I, Orita H, Kakeji Y, Kohnoe S, *et al*. Phase II study of weekly paclitaxel by one-hour infusion for advanced gastric cancer. *Surg Today* 2008;**38**:1013-20.
14. Ajani JA, Fairweather J, Dumas P, Patt YZ, Pazdur R, Mansfield PF. Phase II study of Taxol in patients with advanced gastric carcinoma. *Cancer J Sci Am* 1998;**4**:269-74.
15. Bokemeyer C, Lampe CS, Clemens MR, Hartmann JT, Quietzsch D, Forkmann L, *et al*. A phase II trial of paclitaxel and weekly 24 h infusion of 5-fluorouracil/folinic acid in patients with advanced gastric cancer. *Anticancer Drugs* 1997;**8**:396-9.
16. Kim JY, Do YR, Park KU, Kim JG, Chae YS, Kim MK, *et al*. Multicenter phase II trial of S-1, paclitaxel and cisplatin triplet combination chemotherapy in patients with advanced gastric cancer. *Cancer Chemother Pharmacol* 2011;**67**:527-32.
17. 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.
18. McKenna RJ, Sr. Clinical aspects of cancer in the elderly. Treatment decisions, treatment choices, and follow-up. *Cancer* 1994;**74**:2107-17.
19. Glimelius B, Ekström K, Hoffman K, Graf W, Sjödén PO, Haglund U, *et al*. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;**8**:163-8.
20. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006;**24**:2903-9.
21. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;**341**:2061-7.
22. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, *et al*. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: the Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003;**21**:54-9.
23. Kim DY, Joo JK, Ryu SY, Park YK, Kim YJ, Kim SK Clinicopathologic characteristics of gastric carcinoma in elderly patients: a comparison with young patients. *World J Gastroenterol* 2005;**11**:22-6.
24. Lee JL, Kang YK, Kang HJ, Lee KH, Zang DY, Ryoo BY, *et al*. A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. *Br J Cancer* 2008;**99**:584-90.
25. Kim ST, Park KH, Oh SC, Seo JH, Shin SW, Kim JS, *et al*. Is chemotherapy in elderly patients with metastatic or recurrent gastric cancer as tolerable and effective as in younger patients? *Asia Pac J Clin Oncol* 2012;**8**:194-200.