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ORIGINAL ARTICLE

Se Hoon Park · Woon Ki Lee · Min Chung
Soo-Mee Bang · Eun Kyung Cho · Jae Hoon Lee
Dong Bok Shin

Quality of life in patients with advanced gastric cancer treated with second-line chemotherapy

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Abstract *Objective*: Despite many trials of systemic chemotherapy in advanced gastric cancer, treatment after failure with first-line chemotherapy remains controversial. We prospectively assessed quality of life (QL) in gastric cancer patients treated with second-line chemotherapy. *Methods*: Forty-three patients who received second-line chemotherapy for advanced gastric cancer completed the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and hospital anxiety and depression scale (HADS) at baseline and at regular intervals during and after chemotherapy. *Results*: Compliance with QL questionnaire completion decreased to 72% after third cycle of treatment. In general, clinically meaningful improvements compared with baseline (change QLQ-C30 scores ≥10) were seen in a number of domains and items, including global health/QL, emotional function, cognitive function and all of the symptom scales and single items but appetite. There was no difference in QL between responders and non-responders ($P = 0.473$). At baseline, 27 (63%) patients were suspected to have anxiety or depressive disorder (HADS score ≥11), and this incidence decreased after chemotherapy (14.7 vs 9.5; $P < 0.001$). *Conclusion*: Improvements from baseline in QL measures and HADS scores were demonstrated in patients with advanced gastric cancer, treated with second-line chemotherapy.

Keywords Quality of life · Second-line chemotherapy · Gastric cancer

Conflict of interest: The Authors indicated no potential conflicts of interest to declare.

S. H. Park · S.-M. Bang · E. K. Cho · J. H. Lee · D. B. Shin (✉)
Division of Hematology and Oncology, Department of Internal Medicine, Gachon Medical School Gil Medical Center, Incheon, 405-760 Korea
E-mail: dbs@gilhospital.com
Tel.: +82-32-4603817
Fax: +82-32-4603233

W. K. Lee · M. Chung
Department of General Surgery, Gachon Medical School Gil Medical Center, Incheon, Korea

Introduction

Gastric cancer is the most frequently occurring malignancy in Korea and is one of the main causes of cancer death [1]. A complete surgical resection is the only way to offer a potentially curative therapy to patients with gastric cancer; however, even after a complete resection with negative margins, many patients will experience recurrence, in general only palliative therapy is possible. This reflects the fact that most cases are diagnosed at an advanced stage [2].

For patients with unresectable, recurrent, or metastatic disease, chemotherapy can provide significant palliation of symptoms [3, 4]. Most trials using varied combinations of chemotherapeutic agents have provided durations of survival ranging from 6 months to 10 months in patients with metastatic gastric cancer [5, 6]. None of these regimens, however, have been recognized as a standard or as superior to 5-fluorouracil alone in the treatment of metastatic gastric cancer [7–9].

Over half of patients with metastatic gastric cancer who received chemotherapy failed to achieve response and even in these responders, the duration of responses was as short as a few months [10]. Moreover, the treatment of metastatic gastric cancer patients after failure with first-line chemotherapy remains controversial. Patients with metastatic gastric cancer who fail to respond or have relapse after first line chemotherapy have a grim prognosis and a standard salvage treatment is not available.

Uncontrolled phase II trials suggested that pretreated patients might derive benefit from second-line chemotherapy [11–15]. In these trials tumor shrinkage has been the major endpoint and this may or may not correlate with patient benefit. Because benefits of treatment must outweigh risk, patient-oriented outcomes are important

in patients who have limited life expectancy [16]. Thus, we report the results of quality of life (QL) assessments obtained at baseline and throughout the therapy in patients with advanced gastric cancer, treated with second-line chemotherapy. We also wanted to assess the feasibility of measuring other endpoints such as anxiety and depression. These data were obtained using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and hospital anxiety and depression scale (HADS) instruments [17–20].

Patients and methods

Patients' eligibility

Second-line chemotherapy was defined by the requirements that the patient had received one prior regimen of chemotherapy for metastatic or recurrent gastric cancer, or relapse had occurred after completing adjuvant therapy and the patient had received one additional regimen for recurrent disease. The decision to commence second-line chemotherapy and the regimen to be used were determined by the patient and treating physician.

The only requirements for participation were that patients be receiving second-line chemotherapy for advanced gastric cancer, that they read and complete the questionnaires, and that they sign a written informed consent. This prospective analysis was reviewed and approved by Gil Medical Center institutional review board.

Assessment

Response rate was not a primary endpoint of this analysis, but was evaluated every two courses of chemotherapy if patient had at least one bidimensionally measurable lesion defined by physical or radiological examination. Toxicity was assessed for each cycle of chemotherapy using the National Cancer Institute Common Toxicity Criteria [21]. QL assessment was scheduled to be carried out at baseline, immediately before each chemotherapy cycle and at the end of the treatment. Validated Korean versions of EORTC QLQ-C30 and HADS questionnaires were used. EORTC QLQ-C30 contains 30 questions addressing various aspects of QL. It was decided that the primary endpoint for assessing QL would be a change in the global health/QL subscale score and that a 10 point change on this scale (0–100) would be important clinically [22, 23]. HADS is composed of each seven items for anxiety and depression scored from 0 (no problem) to 3 (maximum distress). Scores for anxiety and depression were ranged from 0 to 21, and scores from 11 to 21 were interpreted as cases of probable anxiety or depression disorders [24].

Missing items were analyzed using the method advocated by the EORTC Quality-of-Life Study Group [25]. If at least half of the items from a scale were completed, the values of missing ones were imputed as the mean value of the completed items. All questionnaires were distributed and collected by a research nurse.

Statistical analysis

QL was scored according to the EORTC QLQ-C30 scoring manual [25]. QL and HADS scores are presented as total number or means ± SD. Differences between baseline and average QL scores during and after chemotherapy were calculated with paired *t*-test. A *P* value of less than 0.05 was considered significant. All analyses were performed using SPSS for Windows 11.

Results

Patient characteristics

Forty-three patients who received second-line chemotherapy for metastatic gastric cancer were enrolled between June 2002 and July 2004. Baseline patients' characteristics are summarized in Table 1. All patients had received one prior chemotherapy for metastatic disease and five patients had received adjuvant chemotherapy. Thirty-nine (91%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. Objective response rate to their first-line chemotherapy was 26%, as documented in the patients' medical records.

Treatment outcomes

The most commonly used second-line chemotherapy regimen was ECF (epirubicin, cisplatin, infusional 5-fluorouracil or capecitabine). The median number of cycles of second-line chemotherapy administered was four (range, 1–8). Eleven of the 43 patients did not have measurable lesion and are not evaluable for tumor response using conventional criteria. Of the 32 patients with measurable disease, 6 (19%; 95% confidence interval [CI], 5–32%) achieved objective responses. At a median follow-up of 18.4 months (95% CI, 16.4–20.3 months), the median progression-free and overall survival were 3.7 months (95% CI, 3.1–4.4 months) and 7.2 months (95% CI, 5.1–9.3 months), respectively. Ten patients (23%) received at least one cycle of further third-line chemotherapy.

Twenty-one patients experienced grade 3 or 4 toxicity during the 182 cycles of treatment, which were predominantly hematologic or gastrointestinal. Grade 3 or 4 leukopenia occurred in 29% of chemotherapy courses. Two patients died early in their treatment courses due to disease progression.

Table 1 Patient characteristics at baseline

	No. of patients	%
Total	43	100
Evaluable for QL	35	81
Male gender	30	70
Age, years		
Median	59	
Range	35–75	
ECOG performance status		
0	7	16
1	32	74
2	4	9
Previous anticancer treatment		
Adjuvant chemotherapy	5	12
Salvage surgery	9	21
Cisplatin-based first-line chemotherapy	5	12
Response to first-line chemotherapy	11	26
Interval from the completion of prior chemotherapy, months		
Median	1.1	
95% CI	0–2.4	
Second-line chemotherapy regimen		
Cisplatin, 5-fluorouracil	9	21
Taxanes, 5-fluorouracil	12	28
Taxanes, 5-fluorouracil, cisplatin	2	5
Taxanes, cisplatin	2	5
Irinotecan, cisplatin	3	7
Epirubicin, cisplatin, 5-fluorouracil (or capecitabine)	15	35
Number of cycles given		
Median	4	
Range	1–8	
Chemotherapy subsequent to second-line (ten patients)		
Oral fluoropyrimidines	6	
Irinotecan-based	2	
Oxaliplatin-based	2	

Quality of life

Questionnaires were to be completed at baseline and at the start of each cycle of chemotherapy. Seven patients were excluded from the QL analysis because of the patients' poor compliance with the questionnaire. Four of these had early tumor progression and three patients declined further chemotherapy. Compliance decreased to 72% after the third cycle of treatment. The EORTC QLQ-C30 data indicated that patients assigned good scores to the functional scales at baseline (Table 2). The score for the global health/QL scale (56.9) was slightly lower than most of the functional scales. The highest scores of the symptoms scales and single items were assigned to fatigue (33.0), constipation (32.4), and economic impact (29.5).

Change in QL was defined as the difference between the baseline and average score reported for each subscale during and after chemotherapy (Fig. 1). After chemotherapy, the global health/QL score was improved (i.e., increase of 10 points or more) in 13/35 patients (37%; 95% CI, 21–53%). Moreover, significant improvements were observed in the emotional function scale (69.0–85.5; $P = 0.001$) and the cognitive function scale (78.0–90.8; $P = 0.004$). In the symptoms scale scores and single items, all scales and items but appetite decreased significantly (Table 2). In general, we observed no difference in QL between responders and non-responders during and after the completion of chemotherapy ($P = 0.473$).

All the 43 patients completed the HADS questionnaire at baseline. Twenty-seven patients (63%) were suspected to have anxiety or depressive disorder (i.e., HADS score of 11 points or more). This relatively high incidence decreased after three cycles of chemotherapy (mean ± SD, 14.7 ± 8.7 vs 9.5 ± 7.6; $P < 0.001$).

Discussion

The present study demonstrates that it is feasible to measure pragmatic outcomes such as QL in patients with advanced gastric cancer who are about to receive second-line chemotherapy for metastatic disease. Compliance with completion of QL questionnaires was high at baseline but decreased during and after completion of treatment. The patients in our study experienced such an improvement of their global health/QL after second-line chemotherapy. In addition, the emotional and cognitive function scale scores showed a clinically important

Table 2 Patients mean scores on EORTC QLQ-C30

	Baseline		After chemotherapy		*P**
	Mean	SD	Mean	SD	
Global health/QL[a]	56.9	27.1	69.4	19.3	0.052
Functional scales[a]					
Physical	81.7	15.9	81.7	12.9	0.797
Role	75.7	25.3	81.2	21.0	0.105
Emotional	69.0	25.1	85.5	16.0	0.001
Cognitive	78.0	19.3	90.8	14.2	0.004
Social	72.4	26.5	79.7	19.5	0.182
Symptom scales and items[b]					
Fatigue	33.0	21.1	26.8	20.9	0.038
Nausea/vomiting	13.8	20.4	4.3	10.5	0.039
Pain	22.8	25.9	8.1	19.2	0.001
Dyspnea	15.2	29.5	4.3	16.7	0.006
Insomnia	24.7	31.7	8.6	19.2	0.017
Appetite loss	24.7	29.6	24.7	25.8	0.614
Constipation	32.4	33.9	5.3	12.4	<0.001
Diarrhea	18.9	20.2	4.3	11.3	<0.001
Economic impact	29.5	27.8	17.0	16.8	0.018

[a]Scores range from 0 to 100, with a higher score representing a higher level of function
[b]Scores range from 0 to 100, with a higher score representing a higher level of symptoms*$P < 0.05$ was regarded as statistically significant

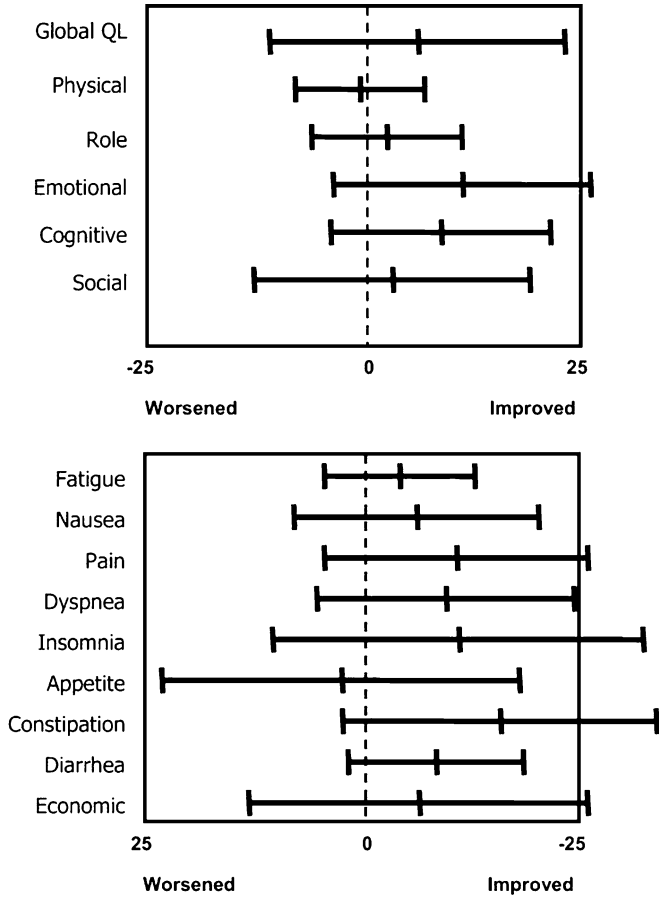

Fig. 1 Changes in QL scores from baseline (mean ± SD)

improvement. All of the symptom scales and the single items but appetite loss were high at baseline and decreased significantly. Fatigue is the most frequently reported symptom in these patients, probably due to the cancer itself.

Metastatic and/or recurrent gastric cancer is an incurable condition where the aim of treatment is to improve survival and to palliate symptoms. Disease may respond to several types of chemotherapy initially, and these treatments have been shown to provide palliation as indicated by improvement in duration and/or quality of survival [3, 4]. However, response rates for chemotherapy subsequent to first-line regimens in patients with metastatic disease are lower. It is unlikely that second-line chemotherapy in patients with metastatic gastric cancer will result in substantial prolongation of survival and there is potential for toxicity from the treatment. Despite favorable outcomes seen in some phase II trials of second-line chemotherapy for advanced gastric cancer, the results from phase II trials may not be generalized to the routine clinical situation [26]. Eligibility criteria tend to result in the recruitment of a relatively good prognostic group and little or no data concerning other efficacy endpoints. The therapeutic effect on tumor volume is most frequently used as the primary end point in clinical oncologic trials. However, over the last decades, the effect of therapy on the self-reported QL has also become an important (secondary) end point.

Physicians treating patients with advanced cancer should always consider the delicate balance between survival and QL. QL is an important outcome in patients receiving chemotherapy and with metastatic disease in particular. In patients with shorter expected survival, QL becomes even more important. The improvement seen in QL during the treatment of these patients might be an important and valid measure of benefit which justifies the use of chemotherapy in this group of patients, despite a low rate of objective tumor response. Our data are consistent with the trials of second-line chemotherapy in other types of cancer [27].

In a prospective study assessing the changes in QL for patients with solid tumors, palliative chemotherapy improved cancer-related symptoms and did not disturb the QL [28]. To the authors' knowledge, this is the first study describing QL data of second-line chemotherapy in patients with metastatic gastric cancer. We did not have control group for comparison in this study. Although it is recognized that there is a declining probability of response with subsequent chemotherapy regimens, most patients and their physicians would have difficulty in accepting randomization to supportive care only that did not include specific antitumor therapy.

It is of note that despite clinical responses, the QL scores after chemotherapy were not different between responders and non-responders. Within the limitation of a small sample size, a mix of different second-line chemotherapy regimens and thus different side effect profiles, there was clinically significant improvement in QL and disease-related symptoms, which was documented both in patients with objective response and in those without tumor regression. One might speculate that responding patients had often received more courses of chemotherapy than in non-responders, and thus they might suffer from more therapy-related toxicity. Or even in non-responders, patients with stable disease in particular, their tumors might be adequately controlled by chemotherapy itself.

In conclusion, we found that second-line chemotherapy improved the QL and HADS scores in patients with metastatic gastric cancer, regardless of objective tumor response. Besides this positive effect on the general well-being, specific functional scales and symptoms improved. Chemotherapy subsequent to first-line regimens is justified in patients physically able and willing to receive further chemotherapy. These findings are clearly different from other traditional endpoints, like the effect of treatment on tumor volume and performance status, and therefore give additional insight into the effect of the chemotherapy on the normal daily life of our patients with incurable disease.

References

1. Bae JM, Won YJ, Jung KW, Park JG (2002) Annual report of the Korean central cancer registry program 2000. Cancer Res Treat 34:77–83
2. Meyer HJ, Jahne J, Pichlmayr R (1994) Strategies in the surgical treatment of gastric carcinoma. Ann Oncol 5(Suppl 3):33–36
3. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M (1995) Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 71:587–591
4. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, Svensson C, Enander LK, Linne T, Sellstrom H, Heuman R (1997) Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 8:163–168
5. Van Cutsem E (2004) The treatment of advanced gastric cancer: new findings on the activity of the taxanes. Oncologist 9(Suppl 2):9–15
6. Bamias A, Pavlidis N (1998) Systemic chemotherapy in gastric cancer: where do we stand today?. Oncologist 3:171–177
7. Cullinan SA, Moertel CG, Wieand HS, O'Connell MJ, Poon MA, Krook JE, Mailliard JA, Tschetter LK (1994) Controlled evaluation of three drug combination regimens versus fluorouracil alone for the therapy of advanced gastric cancer North Central Cancer Treatment Group. J Clin Oncol 12:412–416
8. Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H, Yoshida S (2003) 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 21:54–59
9. Vanhoefer U, Rougier P, Wilke H, Ducreux MP, Lacave AJ, Van Cutsem E, Planker M, Santos JG, Piedbois P, Paillot B, Bodenstein H, Schmoll HJ, Bleiberg H, Nordlinger B, Couvreur ML, Baron B, Wils JA (2000) Final results of a randomized phase III trial of sequential high-dose methotrexate, fluorouracil, and doxorubicin versus etoposide, leucovorin, and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer: a trial of the European Organization for Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. J Clin Oncol 18:2648–2657
10. Van Cutsem E, Haller D, Ohtsu A (2002) The role of chemotherapy in the current treatment of gastric cancer. Gastric Cancer 5(Suppl 1):17–22
11. Kinoshita K, Yonemura Y, Sawa T, Miyata T, Sakuma H, Matsuki N, Tanaka S, Fushida S, Fujimura T, Mok YJ, Kim BS, Lee JI, Choi DW, Song YJ, Yang DH, Kwon SJ, Tanaka M, Miyazaki I (2003) 5-Fluorouracil, methotrexate, leucovorin, CDDP and epirubicin (FEPMTX): a wide-spectrum regimen of salvage chemotherapy for high-grade advanced gastric cancer. Hepatogastroenterology 50:1716–1719
12. Park SH, Kang WK, Lee HR, Park J, Lee KE, Lee SH, Park JO, Kim K, Kim WS, Chung CW, Im YH, Lee MH, Park CH, Park K (2004) Docetaxel plus cisplatin as second-line therapy in metastatic or recurrent advanced gastric cancer progressing on 5-fluorouracil-based regimen. Am J Clin Oncol 27:477–480
13. Ohtsu A, Yoshida S, Saito D, Shimada Y, Miyamoto K, Fujii T, Yoshino M, Yoshimori M (1991) An early phase II study of 5-fluorouracil combined with cisplatinum as a second line chemotherapy against metastatic gastric cancer. Jpn J Clin Oncol 21:120–124
14. Giuliani F, Gebbia V, De Vita F, Maiello E, Di Bisceglie M, Catalano G, Gebbia N, Colucci G (2003) Docetaxel as salvage therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico Italia Meridionale (GOIM). Anticancer Res 23:4219–4222
15. Schmitz SH, Voliotis DL, Schimke J, Diehl V (1994) Continuous 5-fluorouracil and leucovorin as a second-line therapy for advanced gastric carcinoma. Oncology 51:502–506
16. Stephens RJ, Hopwood P, Girling DJ (1999) Defining and analysing symptom palliation in cancer clinical trials: a deceptively difficult exercise. Br J Cancer 79:538–544
17. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC et al (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376
18. Yun YH, Park YS, Lee ES, Bang SM, Heo DS, Park SY, You CH, West K (2004) Validation of the Korean version of the EORTC QLQ-C30. Qual Life Res 13:863–868
19. Skarstein J, Aass N, Fossa SD, Skovlund E, Dahl AA (2000) Anxiety and depression in cancer patients: relation between the hospital anxiety and depression scale and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire. J Psychosom Res 49:27–34

20. Oh SM, Min KJ, Park DB (1999) A study on the standardization of the hospital anxiety and depression scale for Koreans: a comparison of normal, depressed and anxious groups. J Korean Neuropsychiatr Assoc 38:289–296
21. Ajani JA, Welch SR, Raber MN, Fields WS, Krakoff IH (1990) Comprehensive criteria for assessing therapy-induced toxicity. Cancer Invest 8:147–159
22. King MT (1996) The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Qual Life Res 5:555–567
23. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 16:139–144
24. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–370
25. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A (2001) EORTC QLQ-C30 scoring manual, 3rd edn. EORTC Quality of Life Group, Brussels
26. Antman K, Amato D, Wood W, Carson J, Suit H, Proppe K, Carey R, Greenberger J, Wilson R, Frei E III (1985) Selection bias in clinical trials. J Clin Oncol 3:1142–1147
27. Dancey J, Shepherd FA, Gralla RJ, Kim YS (2004) Quality of life assessment of second-line docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy: results of a prospective, randomized phase III trial. Lung Cancer 43:183–194
28. Bang SM, Park SH, Kang HG, Jue JI, Cho IH, Yun YH, Cho EK, Shin DB, Lee JH (2005) Changes in quality of life during palliative chemotherapy for solid cancer. Support Care Cancer