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Comparison of health-related quality of life with epirubicin, cisplatin plus 5-fluorouracil and docetaxel, cisplatin plus 5-fluorouracil chemotherapy regimens as first-line systemic therapy in locally advanced inoperable or metastatic gastric or gastro-esophageal junction adenocarcinoma: A prospective study from South India

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Abstract

Background: Health-related quality of life (HRQOL) is an important oncologic end point for upper gastrointestinal malignancies. Unfortunately, till date, there is no published prospective data from India, comparing the HRQOL parameters between first-line chemotherapy regimens in advanced/ metastatic gastric cancer. **Materials and Methods:** The present study aimed to compare the HRQOL of first-line systemic chemotherapy with epirubicin, cisplatin plus 5-FU (ECF) and docetaxel, cisplatin plus 5-FU (DCF) regimens in patients with locally advanced inoperable or metastatic gastric or gastro-esophageal junction adenocarcinoma. The secondary end points were overall response rate, progression-free survival (PFS), overall survival (OS), and toxicity profile. **Results:** Between December 2014 and December 2016, 65 patients were treated with ECF (*n* = 34) or DCF (*n* = 31) regimen. The baseline HRQOL scores were comparable between the two study groups, with the exception of significantly poor pain and sleep difficulties symptom score in the DCF group. After three cycles of treatment, both the groups showed improvements in most of the quality of life (QOL) parameters including global QOL score, compared with their baseline status. After six cycles of chemotherapy, the ECF group showed nonsignificant deterioration for most of the QOL parameters; but on the contrary, the DCF group maintained improved scores for most of the QOL parameters. The median survival until a definitive deterioration of global QOL score was significantly better in the DCF arm in comparison to the ECF arm (7.1 vs. 5.6 months, respectively, *P* = 0.000). The median OS was 9.2 months with ECF and 12.5 months with DCF regimen (*P* = 0.000), while median PFS was 5.7 and 7.4 months with ECF and DCF regimens, respectively (*P* = 0.002). **Conclusions:** This prospective study highlighted a better impact of DCF chemotherapy on the HRQOL of patients with advanced/metastatic gastric cancer and showed the importance of QOL assessments in clinical trials to complement the risk–benefit judgment.

Key words: Cisplatin plus 5-fluorouracil regimen, docetaxel, cisplatin plus 5-fluorouracil regimen, epirubicin, gastric cancer, quality of life

Introduction

Gastric cancer is the fourth most common type of cancer worldwide, and despite advances in the diagnosis and treatment, it is often diagnosed at an advanced stage and remains the world's second highest cause of cancer-related deaths.[1] Patients with metastatic disease have a poor prognosis, with a median survival time of 3–5 months with best supportive care and 7–9 months with systemic chemotherapy.[2,3]

Given the poor prognosis and debilitating course of the disease, interventions for metastatic gastric cancer are typically palliative in nature and thus survival may not be the only significant clinical end point. Recently, health-related quality of life (HRQOL) has emerged as an increasingly important outcome to be considered in clinical trials along with traditional oncologic end points such as survival, toxicity, and disease control.[4-7] Defining quality of life (QOL) is a matter of debate, and no universally accepted definition exists till date. Schipper *et al.* proposed to define QOL as "the functional effect of an illness and its consequent therapy upon a patient, as perceived by the patient."[8] In general, however, the triad "physiological," "psychological," and "social" effects are considered to represent the QOL. Understanding and assessing QOL is critical in the holistic management of patients and may assist clinicians to determine an optimal treatment regimen.[9] Keeping in mind the fact that most patients with advanced gastric cancer are

not cured and many first-line chemotherapy regimens have similar efficacy in terms of traditional oncologic outcomes, differences in QOL may help to determine which regimen is to be preferred.[10] QOL is typically assessed through self-reported questionnaires completed by the patient or through proxy. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, (EORTC QLQ)-C30, is one of the best-known cancer-specific questionnaires for measuring QOL in cancer patients.[11]

Till date, there is no published prospective data from India, comparing HRQOL between different first-line chemotherapy regimens in patients with advanced gastric cancer. In the present study, we presented the results of QOL assessments in Indian patients with locally advanced inoperable or metastatic gastric or gastro-esophageal junction (GEJ) adenocarcinoma, enrolled in a prospective trial of epirubicin, cisplatin plus 5-FU (ECF) versus docetaxel, cisplatin plus 5-FU (DCF), at our institute.

Materials and Methods

Patient selection

Patients older than 18 years of age were eligible for inclusion in this prospective single-center study; if they

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had histologically confirmed locally advanced inoperable or metastatic adenocarcinoma of the stomach or GEJ; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2; adequate renal, hepatic, and hematologic function; and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). Major exclusion criteria were previous chemotherapy for metastatic or locally advanced disease, congestive heart failure, concurrent second malignancy, and evidence of brain metastases.

Treatment assignment

Patients who fulfilled all the eligibility criteria were allocated (1:1) to either ECF or DCF chemotherapy regimen, by alternating assignment. Both the regimens were given for every 3 weeks. The ECF regimen comprised epirubicin 50 mg/m^2 (1 h intravenous infusion) plus cisplatin 60 mg/m^2 (1–2 h intravenous infusion) on day 1, followed by 5-fluorouracil (5-FU) 750 mg/m^2/day (continuous intravenous infusion over 6 h) for 5 days, and the DCF regimen comprised docetaxel 75 mg/m^2 (1 h intravenous infusion) on day 1, along with cisplatin and 5-FU doses, same as that of the ECF regimen. All the patients also received appropriate hydration, premedication, and primary prophylactic G-CSF (5 µg/kg/day, subcutaneously for 5 days, starting from day 6). Chemotherapy dose adjustments and treatment delays were allowed and were at the discretion of the treating physician. A 25% dose reduction in subsequent cycles was done in patients developing any Grade 4 or life-threatening toxicity. Treatment was continued until disease progression, unacceptable toxicity, death, or patient withdrawal. After first-line chemotherapy had failed, second-line chemotherapy was recommended to all the patients if their PS was preserved.

Evaluation and outcomes

Before treatment assignment, a complete evaluation was carried out; including full medical history, physical examination, complete blood count, serum biochemical analysis, electrocardiography, and two-dimensional echocardiography. Baseline tumor assessments, including upper-gastrointestinal endoscopy and contrast-enhanced computed tomography (CECT) of the thorax, abdomen, and pelvis, were performed within 28 days before treatment initiation. CECT scans were repeated after three and six cycles of primary chemotherapy as a routine departmental strategy. After the active treatment phase of the study, subsequent CT scans have been performed every 12 weeks (±2 weeks) or whenever needed depending on the symptoms. QOL was assessed before the first cycle of chemotherapy, and within 2 weeks after the third and sixth cycles of chemotherapy, using the EORTC QLQ-C30 (version 3). Responses to chemotherapy were reported according to the RECIST 1.1. The primary end point was QOL. The secondary end points were overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and toxicity profile.

Statistical analysis

The QLQ-C30 responses were scored and analyzed according to the scoring manual provided by the EORTC Study Group on QOL.[11] First, the mean baseline scores for each treatment group were calculated and compared between the two treatment arms. Then, after three and six cycles of chemotherapy, the mean QOL scores were calculated for all patients and compared with the baseline scores. *t*-test was used for statistical comparison of QOL parameters between two arms. Kaplan–Meier method was used to estimate the survival distributions, and survival of two treatment groups was compared using the log-rank test. All statistical analyses were performed using IBM SPSS software version 17.0.

Results

Patient characteristics

Between December 2014 and December 2016, 67 patients were assigned to chemotherapy, at the Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India. Only 65 patients (34 in the ECF arm and 31 in the DCF arm) were included in the current analysis, as two patients did not complete the QOL questionnaires. Both the treatment groups were well balanced for baseline characteristics [Table 1]. The median age was 52 years and majority of the patients (64.6%) were male. ECOG PS was determined as ≤1 in most of the patients (93.8%). Fifty-two patients (80%) had metastatic disease at baseline. The most common site of metastases was liver (66.2%) followed by peritoneum (41.5%). Approximately two-third of the patients had ≥3 metastatic disease sites at baseline, mostly involving the liver and peritoneum.

Chemotherapy characteristics

The median number of first-line chemotherapy cycles received was 6 (range: 3–11). Second-line treatment with docetaxel was given in 12 patients (34.3%) of the ECF arm, and irinotecan was administered to three patients (8.6%) in the ECF arm and eight patients (25.8%) in the DCF arm. Overall, five patients (two patients of ECF arm and three patients of DCF arm) received third-line chemotherapy with capecitabine.

Quality of life assessments

The baseline QOL scores of both the study groups were shown in Table 2. At baseline, patients in both the groups showed impairment of global QOL score and most of the functional scores except for cognitive functioning. The baseline QOL scores were comparable between the two groups, with the exception of significantly poor pain (*P* = 0.04) and sleep difficulties (*P* = 0.03) symptom score in the DCF group. The mean scores of different QOL parameters after three and six cycles of ECF and DCF chemotherapy were depicted in Tables 3 and 4, respectively. In the ECF arm (*n* = 34), after three cycles of chemotherapy, eight patients had progressive disease and offered second-line treatment. Hence, for the QOL assessment after six cycles of chemotherapy, only the patients who completed six cycles of ECF (*n* = 26) were included.

After three cycles of chemotherapy, both the groups showed improvements in most of the QOL parameters compared with their baseline status, except for social functioning, diarrhea, and financial difficulties in the ECF arm, and constipation, diarrhea, and financial difficulties in the DCF arm, which showed deterioration. The improvements in QOL (after three cycles of chemotherapy) were nonsignificant for most of the parameters, except for pain (*P* = 0.02) and sleep difficulties (*P* = 0.01) in the ECF arm; and global QOL (*P* = 0.013), pain (*P* = 0.007),

Table 1: Patient characteristics at baseline

Variables	ECF (*n*=34)	DCF (*n*=31)	Total (*n*=65)
Median age in years (range)	53 (35-62)	52 (31-60)	52 (31-62)
Male gender (%)	21 (61.8)	21 (67.7)	42 (64.6)
ECOG PS (%)			
0-1	31 (91.2)	30 (96.8)	61 (93.8)
2	3 (8.8)	1 (3.2)	4 (6.2)
Extent of disease at baseline (%)			
Locally advanced inoperable	6 (17.6)	7 (22.6)	13 (20)
Metastatic	28 (82.4)	24 (77.4)	52 (80)
Site of primary tumor (%)			
GEJ	2 (5.9)	2 (6.5)	4 (6.2)
Body of the stomach	24 (70.6)	23 (74.2)	47 (72.3)
Pylorus and antrum	8 (23.5)	6 (19.3)	14 (21.5)
Grade of primary tumor (%)			
Grade 1	2 (5.9)	1 (3.2)	3 (4.6)
Grade 2	21 (61.8)	22 (71)	43 (66.2)
Grade 3	11 (32.3)	8 (25.8)	19 (29.2)
Site of metastases (%)			
Liver	22 (64.7)	21 (67.7)	43 (66.2)
Nonregional lymph node	8 (23.5)	8 (25.8)	16 (24.6)
Lung	4 (11.8)	3 (9.7)	7 (10.8)
Peritoneum	14 (41.2)	13 (41.9)	27 (41.5)
Ovary	2 (5.9)	2 (6.5)	4 (6.2)
Number of metastatic sites involved (%)			
0 or 1	8 (23.5)	8 (25.8)	16 (24.6)
2	6 (17.6)	4 (12.9)	10 (15.4)
≥3	20 (58.9)	19 (61.3)	39 (60)

ECF=Epirubicin, cisplatin plus 5-FU, DCF=Docetaxel, cisplatin plus 5-FU, ECOG=Eastern Cooperative Oncology Group, GEJ=Gastro-esophageal junction, FU=Fluorouracil, PS=Performance status

Table 2: Baseline quality of life scores as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (version 3)

QOL parameters	Mean (SD)		*P*
	ECF group (*n*=34)	DCF group (*n*=31)	
Global QOL	51.2 (11.8)	46.5 (13.9)	0.31
Functional scores			
Physical functioning	62.5 (11.4)	61.7 (13.2)	0.80
Role functioning	66.8 (12.6)	67.2 (11.4)	0.89
Emotional functioning	58.3 (9.7)	55.2 (13.3)	0.43
Cognitive functioning	84.1 (10.5)	82.7 (14.1)	0.78
Social functioning	67.7 (12.9)	65.5 (11.7)	0.57
Symptom scores			
Fatigue	41.7 (13.8)	45.2 (11.2)	0.51
Nausea and vomiting	18.2 (18.4)	23.8 (19.1)	0.64
Pain	44.9 (10.3)	53.8 (8.5)	0.04
Dyspnea	6.2 (17.6)	8.3 (20.7)	0.53
Sleep difficulties	33.8 (14.9)	44.7 (12.1)	0.03
Appetite loss	41.3 (7.9)	44.8 (9.4)	0.38
Constipation	12.8 (18.7)	11.5 (21.3)	0.71
Diarrhea	5.4 (15.8)	7.8 (17.4)	0.44
Financial difficulties	47.9 (14.8)	51.3 (9.2)	0.27

QOL=Quality of life, ECF=Epirubicin, cisplatin plus 5-FU, DCF=Docetaxel, cisplatin plus 5-FU, SD=Standard deviation, FU=Fluorouracil

cycles of treatment, the DCF group maintained improved scores for most of the QOL parameters, except for constipation, diarrhea, and financial difficulties, which showed deterioration. The persistently improved QOL scores after six cycles of DCF were nonsignificantly better than the baseline values for most of the parameters, except for pain (*P* = 0.04) and sleep difficulties (*P* = 0.08), which were still significantly better. The global QOL score after six cycles of DCF chemotherapy was still better than that of the baseline, but the improvement was not statistically significant (*P* = 0.27), unlike the global QOL score after three cycles of DCF (*P* = 0.013).

The median survival until a definitive deterioration of global QOL score was significantly better in the DCF arm in comparison to the ECF arm (7.1 vs. 5.6 months, respectively, *P* = 0.000) [Figure 1]. Patients with proven postchemotherapy tumor regression most frequently had an improvement of global QOL scores also. After three cycles of chemotherapy, the mean global QOL scores were significantly better in responding patients (64.8 in the ECF arm and 63.2 in the DCF arm), in comparison to the nonresponding patients (50.3 in the ECF arm and 51.7 in the DCF arm).

Efficacy, survival, and toxicity

The ORR in the ECF group was 26.5% (0% complete remission [CR] and 26.5% partial remission [PR]) versus 48.3% (6.4% CR and 41.9% PR) in the DCF group (*P* = 0.24). Stable disease rates were 35.3% and 32.2%, respectively (*P* = 0.97). The median PFS was 5.7 months (95% confidence interval [CI]: 4.4–6.8) with ECF and 7.4 months (95% CI: 6.1–9.7) with DCF

and sleep difficulties (*P* = 0.004) in the DCF arm, which showed statistically and clinically significant improvements.

After six cycles of chemotherapy, the ECF group showed nonsignificant deterioration for most of the QOL parameters compared with their baseline status, except for cognitive functioning and constipation, which were still nonsignificantly better. On the contrary, after six

Table 3: Changes of mean quality of life scores after 3 and 6 cycles of epirubicin, cisplatin plus 5-fluorouracil chemotherapy

QOL parameters	At baseline (*n*=34)	At 3 months (*n*=34)	*P*	At 6 months (*n*=26)	*P*
Global QOL	51.2 (11.8)	56.8 (10.2)	0.11	47.8 (7.9)	0.29
Functional scores					
Physical functioning	62.5 (11.4)	65.4 (9.5)	0.28	57.3 (12.3)	0.37
Role functioning	66.8 (12.6)	67.3 (11.2)	0.71	61.5 (13.7)	0.29
Emotional functioning	58.3 (9.7)	59.2 (10.3)	0.96	54.9 (10.8)	0.18
Cognitive functioning	84.1 (10.5)	85.7 (11.2)	0.83	85.2 (12.4)	0.87
Social functioning	67.7 (12.9)	65.9 (10.7)	0.66	61.8 (8.8)	0.43
Symptom scores					
Fatigue	41.7 (13.8)	40.3 (14.5)	0.56	44.5 (13.1)	0.52
Nausea and vomiting	18.2 (18.4)	15.8 (17.6)	0.35	20.2 (20.2)	0.77
Pain	44.9 (10.3)	34.3 (12.1)	0.02	46.7 (15.3)	0.31
Dyspnea	6.2 (17.6)	5.3 (15.7)	0.88	8.1 (15.2)	0.65
Sleep difficulties	33.8 (14.9)	20.3 (17.5)	0.01	34.4 (16.9)	0.77
Appetite loss	41.3 (7.9)	34.7 (11.5)	0.18	48.3 (9.2)	0.21
Constipation	12.8 (18.7)	10.3 (15.6)	0.64	11.5 (14.8)	0.82
Diarrhea	5.4 (15.8)	13.7 (12.3)	0.11	11.2 (13.7)	0.25
Financial difficulties	47.9 (14.8)	52.6 (13.2)	0.29	53.7 (12.9)	0.38

QOL=Quality of life

Table 4: Changes of mean quality of life scores after 3 and 6 cycles of docetaxel, cisplatin plus 5-fluorouracil chemotherapy

QOL parameters	At baseline (*n*=31)	At 3 months (*n*=31)	*P*	At 6 months (*n*=31)	*P*
Global QOL	46.5 (13.9)	55.8 (11.6)	0.013	50.8 (10.3)	0.27
Functional scores					
Physical functioning	61.7 (13.2)	64.3 (11.7)	0.44	62.3 (8.5)	0.78
Role functioning	67.2 (11.4)	70.8 (8.2)	0.62	71.5 (17.8)	0.47
Emotional functioning	55.2 (13.3)	61.2 (10.3)	0.17	58.9 (10.8)	0.38
Cognitive functioning	82.7 (14.1)	84.3 (13.5)	0.65	85.3 (11.5)	0.51
Social functioning	65.5 (11.7)	68.3 (13.7)	0.43	67.8 (11.4)	0.58
Symptom scores					
Fatigue	45.2 (11.2)	41.3 (11.7)	0.28	42.8 (13.1)	0.42
Nausea and vomiting	23.8 (19.1)	21.8 (15.2)	0.45	22.2 (17.5)	0.67
Pain	53.8 (8.5)	41.4 (12.1)	0.007	44.8 (13.4)	0.04
Dyspnea	8.3 (20.7)	6.2 (13.8)	0.75	7.9 (10.2)	0.86
Sleep difficulties	44.7 (12.1)	32.3 (15.4)	0.004	37.4 (16.9)	0.08
Appetite loss	44.8 (9.4)	39.4 (12.7)	0.18	42.7 (11.9)	0.61
Constipation	11.5 (21.3)	13.5 (14.6)	0.44	13.8 (11.4)	0.42
Diarrhea	7.8 (17.4)	15.2 (12.3)	0.08	15.8 (17.3)	0.07
Financial difficulties	51.3 (9.2)	54.8 (10.5)	0.39	55.7 (8.9)	0.48

QOL=Quality of life

regimen (log-rank *P* = 0.002), while median OS was 9.2 (95% CI: 7.6–10.7) and 12.5 (95% CI: 11.2–15.8) months, respectively (log-rank *P* = 0.000). The majority of hematological and nonhematological adverse events were of Grade 1 and 2. As compared with the ECF, the DCF regimen was associated with more frequent Grade 3–4 toxicities – neutropenia (17.6% vs. 41.9%, *P* = 0.12), febrile neutropenia (14.7% vs. 19.3%, *P* = 0.75), mucositis (5.9% vs. 19.3%, *P* = 0.26), and diarrhea (5.9% vs. 16.1%, *P* = 0.43); but none of the differences were statistically significant.

Discussion

The EORTC QLQ-C30 is one of the best-known cancer-specific questionnaires for measuring QOL in cancer patients.[11] The questionnaire comprises 30 items assessing five functional domains (physical, role, emotional cognitive, and social), symptom scales (fatigue, nausea, and pain), and
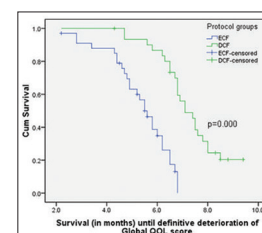

Figure 1: Kaplan–Meier plot showing survival (in months) until definitive deterioration of global quality of life score in patients treated with docetaxel, cisplatin plus 5-fluorouracil and epirubicin, cisplatin plus 5-fluorouracil regimens

six single items (dyspnea, sleep disturbances, appetite loss, constipation, diarrhea, and financial impact of the disease and treatment), and a single global QOL scale. Higher scores for functional scales and global QOL show improvement, and higher scores for symptom scales show deterioration. The EORTC QLQ-C30 was sensitive to detect HRQOL issues

that were important to patients within our specific treatment groups.

The addition of DCF regimen improved HRQOL of gastric cancer patients compared to cisplatin and 5-FU alone in V325 trial.[12] This multinational phase III trial randomized 445 patients with untreated advanced gastric cancer to receive either DCF or CF. Interestingly, better preservation of QOL occurred as a result of a significantly higher level of efficacy imparted by the addition of DCF compared with CF alone despite a higher incidence of some toxicities as a result of the addition of DCF. Time to 5% deterioration of global health status significantly favored DCF over CF (log-rank test, $P = 0.01$). Our current prospective study also revealed similar findings, favoring DCF.

This prospective study was planned primarily to determine whether DCF offered better efficacy and improvements of HRQOL parameters in comparison to the standard ECF treatment. QOL measures were assessed to provide patient-reported symptoms, as well as providing a general assessment of global well-being and functional status of patients treated with these first-line chemotherapy regimens. The study demonstrated a nonsignificantly better ORR and significantly better PFS and OS with the DCF regimen, without any significant increase in Grade 3 and 4 toxicities.

Although overall about 26.5% and 48.3% of the patients had major response to ECF and DCF chemotherapy, respectively, the QOL assessments suggested that improvement of HRQOL was achieved in a much larger percentage of patients, due to the palliative effect of chemotherapy. The lack of apparent impact of toxicity on global QOL of responding patients was clinically meaningful data that might assist the clinicians in treatment decision-making and patient counseling. Based on the current data, the DCF regimen was associated with a persistently improved HRQOL and global functioning, even after six cycles of treatment, which was clinically meaningful. To the best of our knowledge, the current study represents the first prospective comparison of HRQOL parameters between two commonly used first-line triplet chemotherapy regimens in advanced/metastatic gastric cancer patients from India.

The present study has several limitations also. First of all, this was a single-center, nonrandomized study restricted to the patients treated only in our department. Second, the posttreatment QOL parameters were assessed only after three and six cycles of chemotherapy, therefore there might be significant undetected variations of HRQOL in between the treatment cycles. Third, the sample size was not very large to draw any robust conclusion. Finally, because of logistic issues, reassessment of CECT studies was performed every 2–3 months in accordance with our routine departmental strategy; therefore, there might be bias in the PFS assessment.

Conclusions

QOL measures provide helpful information of patient-reported symptoms and functional status of patients, which are essential for clinical decision-making regarding a particular treatment option. This prospective study highlighted an improved QOL and global health with DCF chemotherapy in comparison to the ECF regimen, in patients with locally advanced inoperable or metastatic gastric or GEJ adenocarcinoma. Moreover, the improvements of HRQOL parameters with DCF regimen were persistently better even after six cycles of treatment and there were no apparent impact of toxicity profile on HRQOL in responding patients. Clearly, the present study showed the importance of QOL assessments in clinical trials to complement the risk–benefit judgment between different first-line chemotherapy regimens.

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Conflicts of interest
There are no conflicts of interest.

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