Original Research Article

Are taxane based regimens better than non-taxane fluoropyrimidine based regimens in advanced gastric cancer? Findings from an observational multicentre study, South India

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ABSTRACT

Background: Capecitabine, 5 Fluorouracil, platinum agents and taxanes are either used alone or in combination in advanced gastric cancers (AGC). Data on tolerability and efficacy of these regimens are minimal. We aimed to report proportion of AGC patients opting for best supportive care upfront and tolerability and efficacy of taxane and non-taxane fluoropyrimidine based regimens from three oncology centers, South India.
Methods: Case records of AGC patients initiated on either taxane or non-taxane fluoropyrimidine based chemotherapy during May 2016 to Dec 2017 in three private tertiary cancer care centers across two states in south India were reviewed. Information on clinical characteristics, regimen used, radiological and clinical response, toxicity and its related hospital admissions were extracted. Statistical analysis was done by categorical variables that were summarized using proportions. Median survival was calculated using Kaplan Meier curves and comparison between the groups were done using log-rank test.
Results: Of 88 AGC patients, 27 patients (30.7%) opted for best supportive care; 19 and 41 patients received paclitaxel based and non-taxane fluoropyrimidine based regimens respectively. There was no statistically significant difference in pain symptoms, vomiting, hospital admissions and intensive care admissions between the two regimens. Median (inter quartile range) survival of patients receiving best supportive care, taxane based regimen and non-taxane fluoropyrimidine regimen were 3.1 (1.5-16.1), 7.4 (1.6-15.0) and 11.6 (3.2-29.3) months respectively. Median (range) survival on any chemotherapy was 10.3 (1.6-29.3) months and it was significantly higher compared to best supportive care (p<0.001)
Conclusions: AGC patients on chemotherapy had improved overall survival compared to stand alone best supportive care. Fluoropyrimidine based regimens offered better survival than taxane based regimen.

Keywords: Carboplatin, CMOG, Paclitaxel, Radiological response, Survival, SORT IT, Toxicity

INTRODUCTION

Globally, gastric cancers are the fifth most commonly diagnosed cancer with 1,000,000 cases in 2018 and the third leading cause of death accounting for 1 out of 12 deaths.[1] Despite the advancements in multimodality treatment options, the survival continues to be dismal due to late presentation and systemic recurrence after curative treatment.[1-4] Five year overall survival (OS) is 27%, however it is 3% for unresectable and metastatic cancers and the same is observed in India as well.[5-7]

Chemotherapy is an important option for symptom relief in patients with advanced gastric cancer (AGC). When the general condition of the patient and the advanced stage of tumor render chemotherapy ineffectual, 'best supportive care' is provided for symptom control.[7-9] Globally, there is no consensus on standard regimen for chemotherapy in AGC.[10-12] Evidence suggests that patients who received chemotherapy showed better OS compared to those who received best supportive care.[8,10,13]

Multiple cytotoxic chemotherapeutic agents like platinum agents, taxanes, fluoropyrimidines, irinotecan, anthracyclines, etoposide, monoclonal antibodies are active in AGC.[14,15] Taxane and fluoropyrimidine (5-FU: 5Fluorouracil or Capecitabine) based regimens are commonly used in treating AGC. Combination of 5FU and Cisplatin are commonly used in first line chemotherapy of AGC.[16-19]

Administration of infusional fluoropyrimidine based regimens needs prolonged hospital admission and insertion of central venous access devices (CVADs) like peripherally inserted central venous catheter (PICC) or chemoport adding to the treatment costs.[20] Patients with CVADs need regular care of device and management of complications of CVAD (infections, venous thrombosis, device dislodgment, device failure etc).[21,22]

Although 5FU based regimens are reported to have more gastrointestinal toxicity compared to other regimens, it is preferred in majority of the oncology centers in India.[23-25] On the other hand, taxane based regimens (monotherapy or doublet protocols) have an advantage over fluoropyrimidines because of their dosage convenience, tolerability and ease of administration.[14,26,27] Indian data on outcomes of taxane (especially paclitaxel) based first line chemotherapy regimen in AGC patients is scarce.[28-30]

Therefore, in this study, we aimed to assess the treatment outcomes, toxicity and overall survival between taxane and non-taxane fluoropyrimidine based regimens in patients with advanced gastric cancer and to characterize the proportion of patients opting for best supportive care upfront.

METHODS

It was a cohort study involving review of patient records. The study was conducted in three private tertiary cancer care centers across two states in south India namely Karnataka (Bengaluru) and Tamil Nadu (Chennai and Madurai). The cancer centrein Bengaluru is in a medical college and teaching hospital with a full-fledged oncology department. The other two centers are private hospitals in Tamil Nadu state with oncology units.

Study setting

Gastric cancer is managed according to the standard guidelines of National Comprehensive Cancer Network (NCCN) and European Society and Medical Oncology (ESMO) in the study centers.[31] Only those patients who are fit and opt for chemotherapy are treated with one of the first line palliative chemotherapy regimens.

Study population

Adults diagnosed with AGC at the three study centres between May 2016 and December 2017 were included in the study. We included only patients who were initiated on treatment with either taxane based (monotherapy or combination with platinum agent) or non-taxane fluoropyrimidine based (Cape-ox: Capecitabine oxaliplatin, ECF: Epirubicin Cisplatin 5-FU, EOX: Epirubicin Oxaliplatin Capecitabine, FOLFOX: 5FU Leucovorin Oxaliplatin, 5-FU/LV: 5-Fluorouracil Leucovorin, single agent capecitabine) regimens.

Data variables and sources of data

Baseline clinical presentations, clinical response and radiological response were retrieved from patient records. Information on common toxicology criteria (CTC) grade 3 and 4 toxicities and its associated hospital admissions (ward and ICU) were collected. Date of diagnosis, date of initiation of chemotherapy and date of death/lost to follow-up were obtained.

Data analysis

Data were entered using Epicollect5 (a free mobile application for data collection, Imperial College, London) and were analyzed with STATA (version 12.1, copyright 1985-2011 StataCorp LP USA). Continuous variables were expressed as mean (SD). Categorical variables like gender, symptoms and type of regimen were expressed as proportions.

Patients opting for best supportive care, details on clinical response, radiological response and toxicity were summarized as proportion with 95% confidence interval (CI). The difference in the outcome variables between the two groups (taxane vs. non-taxane fluoropyrimidine) was assessed using chi-square test. The date of censoring for

survival was 31st March, 2019. Median duration of survival in each group was estimated using Kaplan-Meir curves and compared using log rank test. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

Demographic and clinical characteristics

Among 88 patients with AGC, 64 (72.7%) were male and 24 (27.3%) were female with a mean (SD) age of 53(13) years (Table 1).

Of 88 patients, 27 patients (30.7% (95% CI: 21.3-41.4)) opted for best supportive care. Of 61 patients who received first line chemotherapy, 41(67.2%) patients

received fluoropyrimidine based regimen, 19(31.1%) patients received taxane based regimen and one patient received Docetaxel 5FU Cisplatin (DCF) regimen. Treatment options chosen by the patients and their outcomes are described in Figure1.

Chemotherapy regimens and number of cycles

Details of first line chemotherapy regimens and the number of cycles administered are described in Table 2. Of 19 patients who received taxane based regimens, 12 patients (63.1%) received paclitaxel carboplatin, 6 patients (31.5%) received paclitaxel monotherapy and one patient was on docetaxel carboplatin. Of the 41 patients who received 5FU based regimen, 46.6% received capecitabine oxaliplatin

Table 1: Demographic and clinical characteristics of patients with advanced gastric cancer registered in three cancer centres in South India, 2016-2018 (n=88).

Variables	Categories	Total		Best supportive care		Chemotherapy	
		n	(%)	n	(%)	n	(%)
Total		**88**	**(100.0)**	**27**	**(30.6)**	**61**	**(69.4)**
Gender	Male	64	(72.7)	23	(35.9)	41	(64.0)
	Female	24	(27.3)	4	(16.6)	20	(83.3)
Age (years)	Mean (SD)	53	(13.0)	55.8	(12.0)	51.6	(12.8)
BMI (kg/m^2)	Mean (SD)	21	(4.1)				
ECOG PS	1	62	(75.6)	10	(16.1)	52	(83.8)
	2	19	(23.2)	15	(78.9)	4	(21.0)
	3	1	(1.2)	1	(100)	0	(0)
	Not recorded	6	(6.8)	1	(16.6)	5	(83.3)
Presenting symptoms							
Abdominal pain (n=86)		83	(96.5)	25	(30.1)	58	(69.8)
	Nausea/vomiting (n=86)	65	(76.5)	21	(32.3)	44	(67.6)
	Anorexia (n=87)	72	(82.8)	25	(34.7)	47	(65.3)
	Abdominal distention (n=75)	34	(45.3)	7	(20.5)	27	(79.4)
	Constipation (n=83)	29	(34.9)	15	(51.7)	14	(48.2)
	Diarrhoea	1	(1.1)	0	(0)	1	(100)
	Others	6	(6.4)	2	(33.3)	4	(66.6)
Comorbidity							
	Diabetes mellitus	19	(21.6)	2	(10.5)	17	(89.4)
	Hypertension	9	(10.2)	0	(0)	9	(100)
	Ischemic heart disease	6	(6.8)	2	33.3)	4	(66.6)
Hb (gm/dl)	Mean (SD)	10	(2.3)	13.8	(5.0)	10.5	(3.5)
Alb (gm/dl)	Median (IQR)	3.5	(1.5-9)	9	(6.5)	3.5	(6.1)
Site of lesion (n=84)							
	Proximal	29	(34.5)	3	(10.3)	26	(89.6)
	Distal	49	(58.5)	22	(44.8)	27	(55.1)
	Diffuse	6	(7.0)	1	(16.6)	5	(83.3)
Metastatic site							
	Peritoneum/ascites	56	(63.6)	19	(33.9)	37	(66.0)
	Non-regional lymph nodes	53	(60.0)	10	(18.8)	43	(81.1)

Continued.

Variables	Categories	Total		Best supportive care		Chemotherapy	
		n	(%)	n	(%)	n	(%)
	Liver	42	(47.7)	11	(26.1)	31	(73.8)
	Lung	12	(13.6)	2	(16.6)	10	(83.3)
	Bone	7	(8.0)	1	(14.2)	6	(85.7)
	Pleural effusion/pleural deposit	7	(8.0)	2	(28.5)	5	(71.4)
	Brain	2	(2.3)	0	(0)	2	(100)
Staging (n=85)							
	III	5	(5.9)	0	(0)	5	(100)
	IV	80	(94.1)	26	(32.5)	54	(67.5)
Histology (n=87)							
	Adenocarcinoma	64	(73.6)	21	(32.8)	43	(67.1)
	Signet ring cell	15	(17.3)	2	(13.3)	13	(86.6)
	Poorly differentiated	7	(8.0)	2	(28.5)	5	(71.4)
	Squamous cell	1	(1.1)	1	(100)	0	(0)

SD – Standard Deviation, BMI – Body Mass Index, ECOG PS -Eastern Co-operative Oncology Group – Performance Status, IQR – Inter Quartile Range, Hb-Hemoglobin, Alb-Albumin
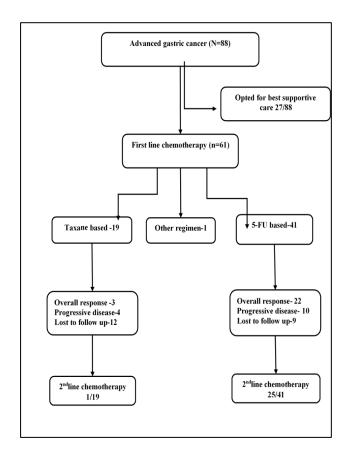

Figure 1: Flow chart describing management and outcomes among patients with advanced gastric cancers in three cancer centres in South India, 2016-2018 (n=88).

Table 2: First line chemotherapy regimens and number of cycles received by patients with advanced gastric cancer registered in three cancer centres in South India, 2016-2018 (n=61)

Chemotherapy regimen	Total		Number of cycles		
	N	(%)	<3	5-Apr	≥ 6
Total	61	100	15	11	35
Taxane based regimens (n=19)					
Paclitaxel Monotherapy	6	31.5	4	0	2
Paclitaxel Carboplatin	12	63.1	3	4	5
Docetaxel Carboplatin	1	-5.2	0	0	1
5FU based regimens (n=41)					
Capecitabine Oxaliplatin	19	46.3	2	3	14
EOX/ ECF	16	-39	3	2	11
FOLFOX	1	-2.4	0	0	1
5FU-LV	1	-2.4	0	1	0
Single agent capecitabine	4	-9.7	3	1	0
Other (DCF)	1	-	0	0	1

DCF – DocitaxelCisplatinum 5-Fluorouracil, EOX/ECF – EpirubicinOxaliplatinCapecitabine/EpirubicinCisplatinum 5-Fluorouracil, FOLFOX - 5-Fluorouracil Leucovorin Oxaliplatin, 5-FU-LV - 5-Fluorouracil Leucovorin

Table 3: Toxicity related to Taxane and 5FU based chemotherapy and associated hospital admissions in patients with advanced gastric cancer registered in three cancer centres in South India, 2016-2018 (n=61).

CTC grade 3 and 4 toxicity and hospital admission	Chemotherapy				P value
	Taxane based (n=19)		5 FU based (n=41)		
	N	%	N	%	
Hb (<8 gm/dl)	2	13.3	5	16.7	0.81
WBC (<3000)	9	-50	19	46.3	0.8
Platelet count	1	-5.6	1	-2.5	0.62
Echo EF (<55%)	2	12.5	2	-6.5	0.53
Neuropathy	2	11.8	13	33.3	0.07
Mucositis	2	11.8	12	32.4	0.12
Vomiting episode (>1/24 hrs)	0	(-)	11	32.3	-
ICU admission	1	-5.9	6	15.4	0.37
Hospital admission	7	43.8	11	33.3	0.14

CTC-Common Terminology Criteria for adverse events, Hb-Hemoglobin (gram/decilitre), WBC-White Blood Cells, EF-Ejection Fraction, ICU-Intensive Care Unit, 5FU-5 Fluorouraci

Toxicity and hospital admissions

Grade 3 and 4 toxicity and related hospital admissions are presented in Table3. Hospital admissions were more among patients who received taxane based regimen (43.8% vs 33.3%; P= 0.14) and intensive care unit admissions were observed more among fluoropyrimidine based regimen group (15.4% vs 5.9%; P=0.37) but were not statistically significant. Similarly, there was no significant difference in any of the toxicities between the two regimens though patients who received fluoropyrimidine based regimen had more neuropathy, mucositis and vomiting episodes.

Clinical and radiological response

Symptomatic and radiologic responses to the first line chemotherapy regimens are described in Table4.

Table 4. Clinical and radiological imaging response to first line chemotherapy (Taxane and 5FU based) in patients with advanced gastric cancer registered in three cancer centres in South India, 2016-2018 (n=61).

Variables	Categories	Clinical and radiological response						P value
		Taxane-based (n=19)			5-FU-based (n=41)			
		Baseline	Post CT		Baseline	Post CT		
		N	N	%	N	N	(%)	
Presence of symptoms								
	Pain	18	13	-72.2	39	30	-76.9	0.71
Nausea/vomiting		11	8	-72.7	32	24	-75	0.87
	Anorexia	14	7	-50	32	28	-87.5	0.01
Radiological imaging†[1]			n=8			n=32		
Overall response‡*		-	4	-50	-	22	-68.8	0.34
CR		-	2	-25	-	2	-6.2	
PR		-	1	(12.5	-	19	-59.3	
Stable disease		-	1	-12.5	-	1	-3.1	
Upper GI endoscopy§			n=6			n=23		
Overall response‡		-	3	-50	-	19	-82.6	0.15
CR		-	2	-33.3	-	2	-8.6	
PR		-	1	-16.6	-	15	-65.2	
Stable disease		-	0	-	-	2	-8.6	

There was no statistically significant difference in pain symptoms and vomiting between the two groups. In fluoropyrimidine group, 28 patients (87.5%) out of 32 had significant improvement in anorexia compared to 7(50%) out of 14 in taxane group (p=0.01). In fluoropyrimidine group, 22 out of 32 patients (69%) who were assessed for radiological response showed overall response; 19 (59%) showed partial response, 2 had complete response and one had stable disease. Among the 23 patients who underwent upper gastrointestinal endoscopy, 19 patients (83%) showed overall response; 15 (65%) had partial response, 2 had complete response and 2 patients showed stable disease

Overall survival

The overall survival of patients opting for chemotherapy and best supportive care is depicted in Figure-2A.

Median (interquartile range) survival of patients receiving best supportive care, taxane based regimen and non-taxane fluoropyrimidine based regimen were 3.1 (1.5-16.1), 7.4 (1.6-15.0) and 11.6 (3.2-29.3) months respectively. The difference in median survival between taxane and fluoropyrimidine regimens was statistically significant (p<0.001). Median (range) survival of patients on any chemotherapy was 10.3 (1.6-29.3) months

and it was significantly higher compared to best supportive care (p<0.001). Those who received second line chemotherapy (irrespective of type of first line therapy) had median survival of 13.5 (5.7-24.9) months compared to 7.7 (1.6-29.3) months in those receiving first line alone (p<0.001) (Figure-2B). The impact of number of cycles of chemotherapy given on overall survival of patients is depicted in Figure-2C and Figure-2D.
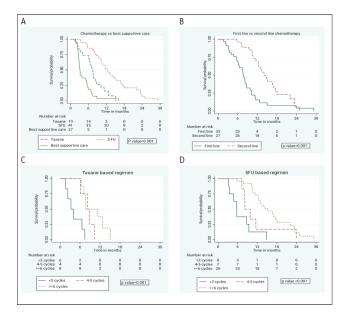

Figure 2: Overall survival of patients with advanced gastric cancer received chemotherapy and best supportive care in three cancer centres in South India, 2016-2018 (n=87).

Statistically significant differences were observed based on number of chemotherapy cycles received in both taxane and fluoropyrimidine based regimen.

DISCUSSION

In our study, 70% of the AGC patients received chemotherapy upfront and had significantly better overall survival than patients who opted for best supportive care. Fluoropyrimidine based regimen had better overall survival compared to the taxane group. Among the patients who received non-taxane fluoropyrimidine-based regimens, those who received at least 6 or more cycles and among the taxane group, those who received more than 4 cycles had better overall survival.

This study adds on to the limited evidence regarding efficacy and tolerability of paclitaxel based therapy (monotherapy and doublet) as first line therapy in AGC patients in India. Selection bias inherent in retrospective studies is a limitation of our study.

Radiologic imaging and gastrointestinal endoscopy were not performed in all patients due to financial constraints and logistic issues and hence there were missing data in assessment of radiological response. The small sample size in the taxane based regimen did not allow us to do adjusted analysis for overall survival. The mean age of patients in our study was 53 years, similar to other Indian studies.[5,23,32-34] In our study, two fold higher prevalence of AGC has been observed in male gender in accordance with other Indian and global findings.[1,35-,39] Studies have shown that distal stomach cancer is most prevalent in European and Asian countries and our study had similar findings: 58.5% with distal followed by 34.5% with proximal.[6,37,38,40-42] Abdominal pain was the most common symptom similar to other studies in contrast to some studies reporting anorexia and weight loss to be the most common presenting symptom.[5,23,33,36,39,43]

In recent Indian studies, ECF has been administered for an average of 5 cycles, EOX with a median of 8 cycles and Cape Ox with a median 6.5 cycles.[31,32,44] In our study, about 75% of patients received a minimum of 4 cycles of paclitaxel carboplatin consistent with other studies.[28,45,46] Paclitaxel monotherapy has also been shown to have anti tumor activity in AGC.[11,16] In our study, one-third of the patients in taxane based regimen (6 out of 19, 31.5%) received paclitaxel monotherapy due to financial constraints.

Grade 3 and 4 (CTC adverse event) mucositis has been reported to be 3% by Babu et al, and it was higher in the present study with12% in taxane group and 32% in 5FU group. Prithviraj et al., reported 14.2% Grade 3 and 4 neutropenia, 3.7% neuropathy and 2.2% anemia.[26] Neutropenia has been reported to be 40% and anemia 8% whereas in our study neutropenia was 46.3% and anemia was 16.7%.[23,24,32]

On the other hand, patients put on chemotherapy did better because of the response rate obtained from the first line regimen.[2,19] Higher response rate has been correlated with better overall survival.[47] Some single agent chemotherapy agents show response activity in the range of 16-18% (oral etoposide, cisplatin, hydroxyurea, doxorubicin, epirubicin).[14]

Single agent paclitaxel shows an overall response rate (ORR- CR+PR+ Stable disease) of 17-23% and single agent docetaxel shows ORR of 17-29%.[29,48-50] Doublet regimens (paclitaxel carboplatin) showed an ORR of 33%, triplet regimens like ECF have a higher ORR like 71%.[51] In our study, 50% of the patients who underwent response assessment in the taxane based regimen group were found to have overall response.

In a Phase II trial of paclitaxel carboplatin in advanced gastric cancer, combination resulted in 33% response rate in 27 patients, with a median survival of nine months.[52] In our study, patients receiving taxane based regimens had a median overall survival of 7.4 months. Multiagent chemotherapy regimens have shown to have a better median OS when compared to single agent chemotherapy (8.3 vs 6.7 months).[18] In our study, of the patients receiving fluoropyrimidine based regimen, 22 out of 32

patients (69%) who were assessed for radiological response showed overall response; 19 (59%) showed partial response, 2 had complete response and one had stable disease. These findings are encouraging and better than that reported in the previous studies.

A review study done on the efficacy of chemotherapy in AGC patients has revealed that chemotherapy increased the overall survival by 6.7 months in comparison to best supportive care which is analogous with our study where the median OS of chemotherapy receiving group was 11.4 months while it was 4.3 months with BSC group.[8,14]

CONCLUSION

To conclude, our study has demonstrated that non-taxane based fluoropyrimidine regimens offer better survival in AGC patients than taxane based regimens although there were no significant differences in the chemotherapy induced toxicity. Receiving chemotherapy in AGC patients had also substantially improved OS in comparison to the group that received standalone best supportive care. Further randomized trials with large sample size may provide evidence on the efficacy of non-taxane fluoropyrimidine and taxane based regimens in the management of AGC.

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