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THE COMPARISON OF EFFICACY BETWEEN CAPECITABINE AND CISPLATIN REGIMEN VERSUS GEMCITABINE AND CISPLATIN REGIMEN, AS PALLIATIVE *C*HEMOTHERAPY FOR ADVANCED BILIARY TRACT CARCINOMA

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ABSTRACT

Background: Biliary tract cancers refer to as group of cancers that arise from epithelial lining of the gall bladder and bile ducts perihilar and extra hepatic biliary tree and periampullary tumors. Though biliary tract cancer is a rare entity. **Objective:** In this study our main goal is to evaluate the efficacy between Capecitabine and Cisplatin regimen versus Gemcitabine and Cisplatin regimen, as palliative *c*hemotherapy for advanced biliary tract carcinoma. **Method:** This quasi-experimental study were conducted in Department of Oncology Bangabandhu Sheikh Mujib Medical University, Dhaka Medical College and National Institute of Cancer Research and Hospital, Dhaka from January 2018 to June 2019. 78 patients with advanced biliary tract carcinoma (Stage IV), attending the out-Patient department were selected as sample in *both* arm*s, in arm A 39 patients and in arm B 39 patients*. Where Arm A patients received - Oral Capecitabine 1250 mg/m^2 twice daily on days 1–14 plus Cisplatin 60 mg/m^2, 2 hour infusion with proper hydration on day 2 every 3 weeks *for 6 cycles* and Arm B patients received - Gemcitabine 1250 mg/m^2 by 30 minute infusion on days 1, 8 plus Cisplatin 75mg/m^2 2 hour infusion with proper hydration on day 1 every 3 weeks *for 6 cycles*. **Results:** Most of the patients in both the arms suffered from Grade1 and 2 anemia. It was 41.02% in Arm A and 51.28% in Arm B. Grade 2 anemia was experienced by 12.83% of the Arm A and 28.20% of the Arm B patients. Grade 3 anemia was experienced by 7.69% of the Arm B patients.64.10% patients from Arm A and 58.9*8*% patients from Arm B did not suffer from fatigue. 25.64% and 30.76% patients from Arm A and Arm B suffered from Grade1. And also*10.26*% in Arm A and 10.2*6*% in Arm B Grade 2 fatigue respectively. most of the patients in both the arms suffered from Grade1 and 2 Anorexia. It was 6*4.10*% in Arm A and 53.85% in Arm B. Grade 2 Anorexia was experienced by 33.3*4*% of the Arm A and 38.4*7*% of the Arm B patients. Only 1 patient of the Arm A and 3 patients of the Arm B patients did not have anorexia during the treatment period. **Conclusion:** We can say that treatment with Capecitabine-Cisplatin regimen is quiteeffective and convenient in palliation of symptoms and loco regional control of advanced biliary tract cancer.

KEYWORD: Advanced biliary tract carcinoma, palliative chemotherapy.

INTRODUCTION

Biliary tract cancers are a highly aggressive human malignancy that is difficult to diagnose. Most patients present with locally advanced or metastatic disease as a very advanced stages at the time of initial diagnosis with a limited treatment option. Only a minority of patients with this aggressive tumor present with respectable stage.[1]

Biliary tract cancer patients who underwent surgery eventually had recurrent disease. Because of its late clinical manifestation and frequent recurrence after curative surgery, palliative systemic chemotherapy is the mainstay of treatment for biliary tract cancers. In metastatic or recurrent biliary tract cancers, systemic chemotherapy has been shown to improve overall survival (OS) and the quality of life.[2]

It is now well recognized that, combination chemotherapy regimens improve advanced biliary tract cancers patient outcomes, but a global standard regimen is yet to be developed. Currently Gemcitabine plus

Cisplatin regimen is widely used for the treatment of advanced biliary tract cancers. For the administration of this chemotherapy regimen patients need to visit hospital twice on day 1 and 8. On the contrary Capecitabine is an oral drug when combined with cisplatin is more feasible as well as less expensive for the patient. In addition, it reduces the frequency of hospital visit. If Capecitabine – Cisplatin combination gives the better or similar result to Gemcitabine-Cisplatin it can be regarded as a standard regimen in advanced biliary tract cancers in low resource country like Bangladesh.[3]

In this study our main goal is to evaluate the efficacy between Capecitabine and Cisplatin regimen versus Gemcitabine and Cisplatin regimen, as palliative chemotherapy for advanced biliary tract carcinoma.

METHODOLOGY

Types of study

- It was a quasi-experimental study.

Place and period of the study

- The study were conducted in Department of Oncology Bangabandhu Sheikh Mujib Medical University, Dhaka Medical College and National Institute of Cancer Research and Hospital, Dhaka from January 2018 to June 2019.

Sample size and population

- 78 patients with advanced biliary tract carcinoma (Stage IV), attending the out-Patient department were selected as sample in both arms, in arm A 39 patients and in arm B 39 patients. Where Arm A patients received - Oral Capecitabine 1250 mg/m^2 twice daily on days 1–14 plus Cisplatin 60 mg/m^2, 2 hour infusion with proper hydration on day 2 every 3 weeks for 6 cycles and Arm B patients received - Gemcitabine 1250 mg/m^2 by 30 minute infusion on days 1, 8 plus Cisplatin 75mg/m^2 2 hour infusion with proper hydration on day 1 every 3 weeks for 6 cycles.

Sampling technique

- Convenientt type of purposive sampling.

Inclusion criteria

- Clinically diagnosed and histopathologically proved advanced biliary tract carcinoma (AJCC Stage IV).

Data analysis

- The information that emerged was interpreted. Thereafter the conclusion and recommendation were drawn, in order to address the objectives of the study. The possibility of bias in the study was acknowledged and limited as much as possible. The data were tabulated in separate tables for both Arm A and B. Thereafter, they were checked, edited, coded manually. Data analysis was done according to the objectives of the study by using the SPSS (Statistical Package for Social Science) software program for Windows, Version 24.0 available in the institute. The statistical data were analyzed by Chi-square test, Fishers exact test and by T-test, where applicable. The p-value, less than 0.05, was taken significant.

RESULTS

In table-1 shows sociodemographic status of the patients where the majority of the patients were in the 50 to 59 years age groups in both the arms. Range 37 -70 years. 53.85% of patients from Arm A and 74.36% of patients from Arm B were males. On the other hand, 46.15% of patients from Arm A and 25.64% of patients from Arm B were female. The following table is given below in detail:

Table-1: Sociodemographic status of the patients.

Age group	Arm A, %	Arm B, %
30-39 years	53.85%	74.36%
40-49 years	46.15%	25.64%
50-59 years	38.47%	56.42%
60-69 years	23.08%	20.51%
Gender	**Arm A, %**	**Arm B, %**
Male	53.85%	74.36%
Female	46.15%	25.64%

Intable-2 showsdistribution of patients on the basis of neutropenia. It was implied that most of the patients in both the arms suffered from Grade1 and 2 Neutropenia. It was 25.65% in Arm A and 41.02% in Arm B. Grade 2 Neutropenia was experienced by 20.51% of the Arm A and 30.77% of the Arm B patients. Grade 3 Neutropenia was experienced by 2.56% of the Arm A patients and 10.26% of the Arm B patients.51.28 % of the Arm A and 17.95% of the Arm B patients did not have Neutropenia during the treatment period. The following table is given below in detail:

Table 2: Distribution of patients on the basis of Neutropenia.

Neutropenia Toxicity Grade	Arm				Total	
	Arm A (XP)		Arm B (GP)			
	n (39)	%	n (39)	%	n (78)	%
No Toxicity	20	51.28	7	17.95	27	34.61
Grade 1	10	25.65	16	41.02	26	33.34
Grade 2	8	20.51	12	30.77	20	25.64
Grade 3	1	02.56	4	10.26	5	06.41
Total	39	100.00	39	100.00	78	100.00
Chi Square test	**10.2439**					
p-value	*0.0166*					

In table-3 shows distribution of the patients on the basis of Leukopenia. Most (46.15%) of the patients of Arm A and 20.51% Arm B did not have any leukopenia at all. It was grade 1, 38.46% for Arm A and 30.77% for Arm B separately. Also, it was grade 2, 12.83% for Arm A and 38.48% for Arm B. From arm A, 1 patient had Grade 3, and Arm B, 4 patients had suffered from Grade 3 leukopenia

Table 3: Distribution of the patients on the basis of Leukopenia.

Leukopenia Toxicity Grade	Arm				Total	
	Arm A (XP)		Arm B (GP)			
	n (39)	%	n (39)	%	n (78)	%
No Toxicity	**18**	**46.15**	**8**	**20.51**	**26**	**33.33**
Grade 1	**15**	**38.46**	**12**	**30.77**	**27**	**34.62**
Grade 2	**5**	**12.83**	**15**	**38.47**	**20**	**25.64**
Grade 3	**1**	**2.56**	**4**	**10.25**	**5**	**6.41**
Total	**39**	**100.00**	**39**	**100.00**	**78**	**100.00**

In table-4 shows distribution of the patients on the basis of Fatigue. Here 64.10% patients from Arm A and 58.98% patients from Arm B did not suffer from fatigue. 25.64% and 30.76% patients from Arm A and Arm B suffered from Grade1. And also10.26% in Arm A and 10.26% in Arm B Grade 2 fatigue respectively. The following table is given below in detail:

Table-4: Distribution of the patients on the basis of Fatigue.

Anorexia Toxicity Grade	Arm				Total	
	Arm A (XP)		Arm B (GP)			
	n (39)	%	n (39)	%	n (78)	%
No Toxicity	1	2.56	3	7.69	4	5.12
Grade 1	25	64.10	21	53.85	46	58.98
Grade 2	13	33.34	15	38.46	28	35.90
Total	39	100.00	39	100.00	78	100.00
Chi Square test	1.4907					
p-value	*0.474*					

In table-5 shows distribution of the patients on the basis of Anorexia. It was implied that most of the patients in both the arms suffered from Grade1 and 2 Anorexia. It was 64.10% in Arm A and 53.85% in Arm B. Grade 2 Anorexia was experienced by 33.34% of the Arm A and 38.47% of the Arm B patients. Only 1 patient of the Arm A and 3 patients of the Arm B patients did not have anorexia during the treatment period. The following table is given below in detail:

Table-5: Distribution of the patients on the basis of Anorexia.

Anorexia Toxicity Grade	Arm				Total	
	Arm A (XP)		Arm B (GP)			
	n (39)	%	n (39)	%	n (78)	%
No Toxicity	1	2.56	3	7.69	4	5.12
Grade 1	25	64.10	21	53.85	46	58.98
Grade 2	13	33.34	15	38.46	28	35.90
Total	39	100.00	39	100.00	78	100.00
Chi Square test	1.4907					
p-value	*0.474*					

In table-6 shows distribution of the patients on the basis of nausea. It was implied that most of the patients in both the arms suffered from Grade1 and 2 Nausea. It was 38.46% in Arm A and 51.28% in Arm B. Grade 2 Nausea was experienced by 25.65% of the Arm A and 15.38% of the Arm B patients. Grade 3 Nausea was experienced by 5.12% of the Arm A patients and 7.69% of the Arm B patients. 30.77 % of the Arm A and 25.65% of the Arm B patients did not have Nausea during the treatment period. The following table is given below in detail:

Table 6: Distribution of patients on the basis of Nausea in both arm.

Nausea Toxicity Grade	Arm				Total	
	Arm A (XP)		Arm B (GP)			
	n (39)	%	n (39)	%	n (78)	%
No Toxicity	12	30.77	10	25.65	22	28.20
Grade 1	15	38.46	20	51.28	35	44.88
Grade 2	10	25.65	06	15.38	16	20.51
Grade 3	02	05.12	03	07.69	05	06.41
Total	39	100.00	39	100.00	78	100.00
Chi Square test	2.0961					
p-value	*0.5527*					

In table-7 shows 1st response assessment at before3rd cycle of CT where1st assessment of response was found according to clinical examination and investigation findings. The following table is given below in detail:

Table-7: 1st response assessment at before3rd cycle of CT.

1st assessment	Arm				Total	
	Arm A (XP)		Arm B (GP)			
	n (39)	%	n (39)	%	n (78)	%
PR	1	2.56	2	5.13	3	3.85
SD	37	94.88	36	92.31	73	98.59
PD	1	2.56	1	2.56	2	2.56
Total	39	100.00	39	100.00	78	100.00
Chi Square test	**0.347**					
p-value	***0.847***					

In table-8shows 2nd response assessment after 4th cycle of CT where 2nd assessment of response was found according to clinical examination and investigation findings. The following table is given below in detail:

Table-8: 2nd response assessment after 4th cycle of CT.

2nd assessment	Arm				Total	
	Arm A (XP)		Arm B (GP)			
	n (39)	%	n (39)	%	n (78)	%
PR	09	23.07	9	23.07	18	23.07
SD	22	56.41	24	61.54	46	58.98
PD	08	20.52	06	15.39	14	17.95
Total	39	100.00	39	100.00	78	100.00
Chi Square test	0.3727					
p-value	*0.8299*					

In table-9 shows 3rd (final) response assessment after 6 weeks of completion of 6 cycles of C where 3rd (final) assessment of response was found according to clinical examination and investigation findings. The following table is given below in detail:

Table-9: 3rd (final) response assessment after 6 weeks of completion of 6 cycles of C.

3rd assessment	Arm				Total	
	Arm A (XP)		Arm B (GP)			
	n (39)	%	n (39)	%	n (78)	%
PR	20	51.28	16	41.02	36	46.15
SD	14	35.89	8	20.52	22	28.20
PD	5	12.83	15	38.46	20	25.65
Total	39	100.00	39	100.00	78	100.00
Chi Square test	7.0808					
p-value	*0.029*					

DISCUSSION

Most (33.33%) of the patients of both arms did not have any leukopenia at all. It was 46.15%for the patients of Arm A and 20.51% for Arm B separately. In arm A 38.46% patients had Grade 1 and 30.77% of arm B patients had Grade 1 leucopenia. 12.83% patients of Arm A and 38.47% patients of arm B suffered from Grade 2 leukopenia. Only 1 patient from Arm A and 4 patients from arm B had grade 3 leukopenia.

In terms of nausea, the majority of the patients from both the arms suffered from Grade 1 nausea. 38.46% patients from Arm A and 51.28% patients from Arm B had Grade 1 nausea. 25.65% patients from Arm A and 15.38% patients from Arm B had Grade 2 nausea. Only two patients from Arm A and three patients from Arm B suffered from Grade 3 nausea. Around 28% of patients from both the arms did not have any nausea.

According to the data, the majority of the patients from both the arms suffered from anorexia. Grade 1 anorexia is experienced by 64.10% and 53.85% patients in Arm A and B respectively. 35% of patients in both the arms had Grade 2 anorexia. Meanwhile, no patient from both Arm had Grade 3 and Grade 4 anorexia. It was seen that 5% of patients from both arms did not have anorexia.

64.10% patients from Arm A and 58.98% patients from Arm B did not suffer from fatigue. 25.64% and 10.26% patients from Arm A suffered from Grade 1 and Grade 2 fatigue respectively. On the other hand, 30.76% and 10.25% patients in Arm B had Grade 1 and Grade 2 fatigue respectively. Meanwhile, no patient from both the Arms had Grade 3 and Grade 4 fatigue.

So from the discussion till now, we can say that Capecitabine-Cisplatin (XP) chemotherapy was well tolerated as Gemcitabin-Cisplatin (GP). Both regimens had a similar safety profile and there was no unexpected toxic effect. As per the characteristic of fluoropyrimidine-based therapy, gastrointestinal adverse events were the most frequent toxic effects in both the treatment arms. According to one study in patients aged 70 years or older, grade 3-4 anemia (22.2%) was the dominant toxicity in the GP arm and grade 3-4 hand-foot syndrome (8.3%) was the most common toxicity in the XP arm.[4]

The occurrence of neutropenia was more in Gemcitabine-Cisplatin (GP) arm. No patient from both the arms discontinued treatment due to the adverse toxicity. Most of the patients from both arms suffered from low-grade toxicities. The number of patients who had a higher grade of toxicities was very few. All the toxicities were duly managed. Though the number of cases who experienced toxicities was arithmetically more in the Gemcitabine-Cisplatin (GP) arm, the difference between the arms in term of toxic events were not statistically significant. Most of these findings correlate with the findings other of many studies.[5-6]

Three assessments were done during and after the treatment were given. They took place before 3rd cycle, after 4th cycle and 6 weeks after completion of 6th cycles of chemotherapy.

In the 1st assessment, 2.56% patients from Arm A and 5.13% patients from Arm B showed PR. Other patients were in SD. In both the arms 2.56% patients showed PD. Pearson's Chi-Square test was used to calculate *p*-value which was insignificant.

In the 2nd assessment, 23.07% patients from both the Arm A and B showed PR. A total of 56.41% and 61.54% of patients from Arm A and Arm B showed SD. 20.52% in arm A and 15.39% in arm B showed PD. Pearson's Chi-Square test was used to calculate *p*-value which was insignificant.

In the 3rd Assessments, 51.28% patients in Arm A and 41.02% patients in Arm B showed PR. 35.89% and 20.52% patients from Arm A and B showed SD respectively. 12.83% patients from the Arm A showed PD, while 38.46% patients from the Arm B were in the same state. Pearson's Chi-square Test was needed to determine the *p*-value. P value was 0.02. It is significant.

Nevertheless, the current study indicates that Capecitabine-Cisplatin (XP) is effective and well-tolerated as the first-line treatment to palliate the symptoms and loco regional control of the inoperable cases of advanced biliary tract carcinoma. Capecitabine has the advantage of avoiding the inconvenience and a complication associated with in fusional Gemcitabine and offers the potential for a simplified dosing schedule. The patient load is very high in the cancer treatment centers of our country.

CONCLUSION

In conclusion we can say that, treatment with Capecitabine - Cisplatin regimen is quite effective and more convenient in palliation of symptoms and loco regional control than Gemcitabine – Cisplatin regimen in advanced biliary tract cancer.

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