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# The Outcome of Gemcitabine-Cisplatin Versus Gemcitabine-Oxaliplatin in The Treatment of Advanced Biliary Tract Carcinoma

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## Abstract

**Background**: Biliary tract carcinoma is highly fatal and one of the commonest cancers in Bangladesh. Chemotherapy is the mainstay of treatment as it is present in an advanced stage. Gemcitabine-Cisplatin association has been a standard of care for first-line regimens in advanced biliary tract cancer. Nevertheless, the Gemcitabine-Oxaliplatin regimen is frequently preferred. There has been no nationwide study to compare the effectiveness of these two platinum groups. Therefore, this study compared the efficacy and toxicities of Gemcitabine-Cisplatin (Gem-Cis) with Gemcitabine-Oxaliplatin (GEMOX) combination chemotherapy for the treatment of ABTC. **Material & Methods:** In this quasi-experimental study, a total number of eighty patients (40 patients in arm A and 40 patients in arm B), who had histopathologically or cytopathologically proven ABTC with no history of previous treatment were included. The study has done between the periods of January 2019 to June 2020. The patients received Gemcitabine (1000 mg/m2 i.v. on day 1 and day 8) plus Cisplatin (25 mg/m2 i.v. on day 1 and 8) every 3 weeks for 6 cycles in Arm A. In another group, Gemcitabine (1000 mg/m2 i.v. on day 1) plus Oxaliplatin (100 mg/m2 i.v. on day 2) every 2 weeks for 6 cycles in Arm B was given. All the patients were followed up according to the set follow-up criteria up to 6 weeks after completion of treatment. **Results:** At the end of the treatment, Response rates (CR+PR+SD) were analyzed. No patient from both the arms showed Complete Response (CR). 37.5% and 45% of patients of the Arm A and Arm B groups showed Partial Response (PR) respectively. Meanwhile, 45% and 40% of patients from Arm A and B showed Stable Disease (SD) respectively. P-value was 0.410 (>0.05). Seven patients (17%) in Arm A and six patients (15%) in Arm B developed Progressive disease (PD). The most common treatment-related grade 3 toxicities were more experienced in the Arm A group. For Arm A versus Arm B that were as follows: neutropenia (15% versus 5%), anemia (15% versus 8%), thrombocytopenia (10% versus 2.5%), nausea (10% versus 5%), vomiting (5%versus 2.5%), peripheral neuropathy (0% versus 15%) and renal toxicity (7.5% versus 0%). For none of them, the p-value was <0.05 except for neutropenia, anemia, thrombocytopenia, renal toxicity, and peripheral neuropathy in which the p-value was 0.042, 0.001, 0.014, 0.0001, and 0.00001 respectively. For both Arms, there were no treatment-related Grade 4 toxicities. **Conclusion:** The study exhibited that treatment with Gemcitabine-Oxaliplatin regimen was well tolerated, less toxic, and convenient with similar effectiveness compared to Gemcitabine-Cisplatin regimen in loco regional control of advanced biliary tract cancer.

**Keywords**:- Biliary tract carcinoma, Gemcitabine-Cisplatin (Gem-Cis), Gemcitabine-Oxaliplatin (GEMOX), Exhibited.

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## INTRODUCTION

According to Cancer Statistics 2020, published in the American Cancer Society Journal, the estimated new cancer cases will be 1.8 million, and 606,520 cancer deaths in the United States in 2020. Globally about 1 in 6 deaths is due to cancer. Approximately 70% of deaths from cancer occur in underdeveloped countries. Global Cancer Observatory (GLOBOCAN) 2018 reveals that there are about 150,000 new cases of cancer and about 108,000 cancer-related death occurred in Bangladesh in 2018. It also predicts that, by the year 2040, Bangladesh will have to deal with about 290,000 new cancer patients and 214,000 cancer-related deaths annually. Among these biliary cancer is expected to be considered as the number of these cases is increasing gradually. Though biliary tract cancers are considered rare tumors, they account for 3% of all gastrointestinal cancers worldwide with geographic variations. Biliary tract cancers are uncommon in Western countries but are relatively common in Central America, Northern India, and Asian countries.[1] The reported incidence is highest in South-East Asia, Israel & Japan.[2] In Bangladesh, it is the 6th most common cancer and annually 7,272 new cases are diagnosed as well as accounts for 33% of cases of cancer death.[3] Biliary tract carcinoma consists of cancer of the gallbladder, the bile duct & ampulla of Vater. Gall bladder cancer is the most common cancer of the biliary tract & accounts for two-thirds of these cancer patients, whereas bile duct cancer accounts for the remaining one-third. Cholangiocarcinoma is the term used to describe cancers arising from the epithelial cells of the bile duct which includes an intrahepatic, perihilar, and distal extrahepatic biliary tree. Biliary tract cancers are highly aggressive malignancy that is difficult to diagnose. Most patients present with locally advanced or metastatic disease in a very advanced stage at the time of initial diagnosis. Only a minority of patients with this aggressive tumor present with a respectable stage. Among them who undergo surgery eventually present with recurrent disease. So, patients with advanced biliary tract cancers typically have a poor prognosis, with an average five years survival rate of 5%.[4,5] According to GLOBOCAN, 22,717 new cases were diagnosed in the low Human development region and 316,753 new cases were found in the very high Human development regions. 74.5% of the new cases were in Asia. Age-standardized incidences rates are about twice as high for men and from 2.6 in Southern Africa to in Eastern Asia for women. Though Bangladesh has a lacking of definite population-based statistics for cancer. There are a few hospital-based statistics. According to the Hospital-based cancer Registry Report 2014 of the National Institute of Cancer Research and Hospital (NICRH), biliary tract cancer is the 10th most common cancer and the 5th most common cancer among females. Primary site of biliary tract cancer incidence rate: in Gall bladder, male 7.1% and female 18.4% (total 11.2%); in Ampulla of Vater, male 0.1% and female 0.3% (total 0.2%). Although BTC often occurs sporadically, there are some well-defined risk factors including gallstone and chronic infestation with liver flukes. HIV, HBV (chronic) HCV, congenital biliary cyst, environmental carcinogen, drugs, or toxin. Approximately 90% of all BTC are adenocarcinoma. Other varieties are well-differentiated, pleomorphic, giant cell,

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adenosquamous, oat cell, colloid cell, squamous cell, sarcoma, small cell, carcinosarcoma, carcinoids, melanoma, and lymphoma.[4,5,6] Molecular pathogenesis of biliary tract cancer including gall bladder carcinoma (GBC) arising in the presence of an Anomalous pancreaticobiliary junction (APBJ) consistently demonstrates KRAS mutations and also p53 mutations. The most frequently identified mutations in cholangiocarcinoma (CCA) include TP53, KRAS, NRAS, IDH ½, and chromatin remodeling genes BAP1, ARID1 A, and PBRM1, FGFR2. The former is characterized by the activation of oncogenic receptor tyrosine kinase signaling pathways, including MET, EGFR, HER-2, ERBB-3, and RAS-MAPK. The second subclass is distinguished by the activation of cytokine-related pathways and the constitutive activation of STAT3. There are two primary types of genetic association studies; candidate gene and genome-wide. All lymphatic drainage of the biliary tree system is distributed into two pathways: superiorly with lymph nodes along the cystic duct, hepatic artery, and celiac axis. Inferiorly with lymph nodes along the cystic duct, the anterolateral aspect of the portal vein, the posterior pancreas, and between the aorta and vena cava. Staging of Biliary tract cancer done by the American Joint Committee on Cancer (AJCC) staging system is used, which categorizes BTC in I-IV stage groups. But for management purposes, BTC is often divided into three clinical stages as follows: Early-stage-AJCC stage I-II. Locally advanced stage-AJCC stage III-IVA Metastatic stage-AJCC stage IVB. There are limited therapeutic options for advanced biliary cancers (ABCs) as outlined by guidelines of the National Comprehensive Cancers Network (NCCN). Surgical resection with a negative resection margin is a potential option for patients with locally advanced, non-metastatic biliary tract cancers. This may be followed by adjuvant chemotherapy or radiation. Moreover >70% of Biliary tract cancer patients who underwent surgery eventually had the recurrent disease.[6] Because of its late clinical manifestation and frequent recurrence after curative surgery, 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. Fluorouracil (5-FU) combined with platinum or an anthracycline agent has traditionally been the backbone of systemic chemotherapy.[1] The choice of treatment for advanced biliary tract cancer (ABTC) depends on the stage of the disease, tumor volume, histology, probability of lymph node involvement, age, and performance status of the patient. For advanced biliary tract cancer, systemic chemotherapy is the mainstay of treatment. Palliative chemotherapy prolongs survival and improves the quality of life to a greater extent.[7,8,9]

## Objective

### General objective:

To compare the efficacy and toxicities of the Gemcitabine-Oxaliplatin with Gemcitabine-Cisplatin regimen in the treatment of advanced biliary tract cancer.

### Specific objectives:

- To assess the efficacy in terms of reduction of tumor size by imaging which will be assessed according to RECIST criteria.

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- To compare the acute toxicity in terms of gradation of gastrointestinal, hematological, renal, and neurological complications (common toxicity criteria v 5.0)
- To measure the basic demographic characteristics of patients

## MATERIAL AND METHODS

This was a quasi-experimental study conducted combinedly in the Department of Oncology, Bangabandhu Sheikh Mujib Medical University, and the Department of Radiation Oncology, National Institute of Cancer Research and Hospital, from the period of January 2019 to June 2020. Patients with advanced biliary tract carcinoma, attending the Out-Patient Department, and admitted patients in the oncology ward of BSMMU & NICRH between January 2019 to June 2020 were enrolled in this study.

**Inclusion criteria:**

Clinically diagnosed and histopathologically proven locally advanced or metastatic adenocarcinoma of biliary tract cancer with advanced diseases with involvement of peritoneum, liver & cytologically proven pleural effusion & distant metastasis.

**Exclusion criteria:**

- Age below 20 years and above 70 years.
- Eastern Cooperative Oncology Group (ECOG) performance status of >2.
- Patients with a history of prior chemotherapy or radiotherapy.
- Initial surgery (excluding diagnostic biopsy) of the primary site.
- Patients with double primaries.
- Pregnant or lactating woman.
- Serious concomitant medical illness includes severe heart disease, uncontrolled diabetes mellitus, hypertension, or renal diseases.
- Patient with uncontrolled infection.

A total of 80 patients were selected from the Outpatient Department (OPD) and admitted patients in the oncology ward of the concerned hospital mentioned above during the period January 2019 to June 2020. After selecting patients, written informed consent was taken from each patient before his/her participation in the study. Clinical examination and necessary investigations were done.

**Patients were divided equally into two arms to receive -**

- Arm A - Gemcitabine (1000 mg/m2) and Cisplatin (25 mg/m2) on day 1 and day 8, every 3 weeks for 6 cycles.[7]
- Arm B - Gemcitabine (1000 mg/m2) on day 1 and Oxaliplatin (100 mg/m2) on day 2 every 2 weeks for 6 cycles.[7]

Data were analyzed as per the requirements 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, Fisher's exact test, and T-test, where applicable. The p-value, less than 0.05, was taken significantly.

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## RESULTS

**Table 1:** Comparison of age between two groups

| Category | Mean (± SD) Years | t- value | p- value |
|---|---|---|---|
| Arm A | 54 (± 8.13) | 0.374 | 0.354 |
| Arm B | 53 (± 8.60) | | |

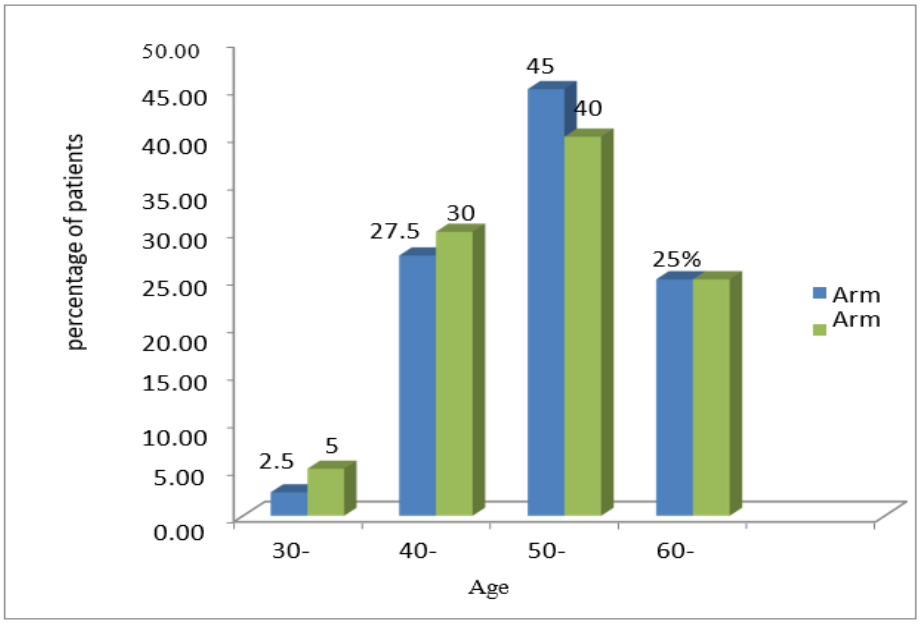


**Figure 1:** Patients Age Group Distribution

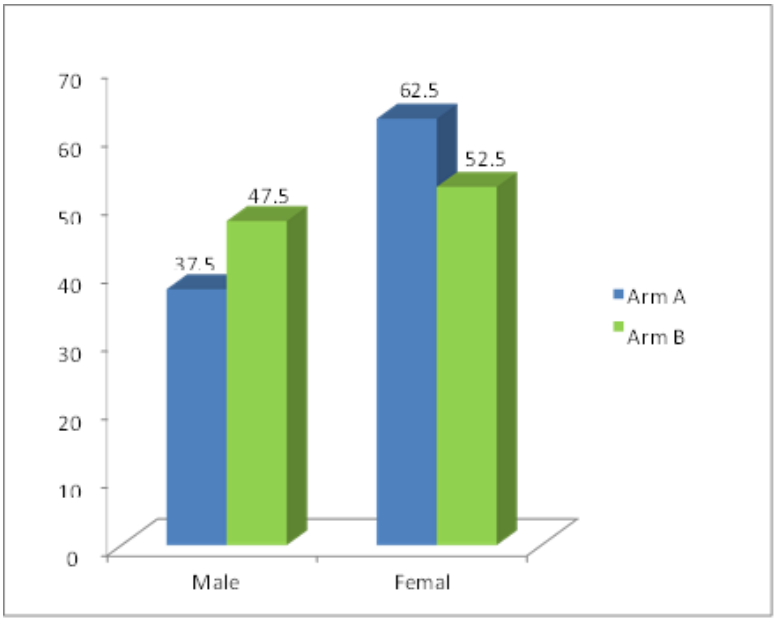


**Figure 2:** Distribution of the patients according to the sex

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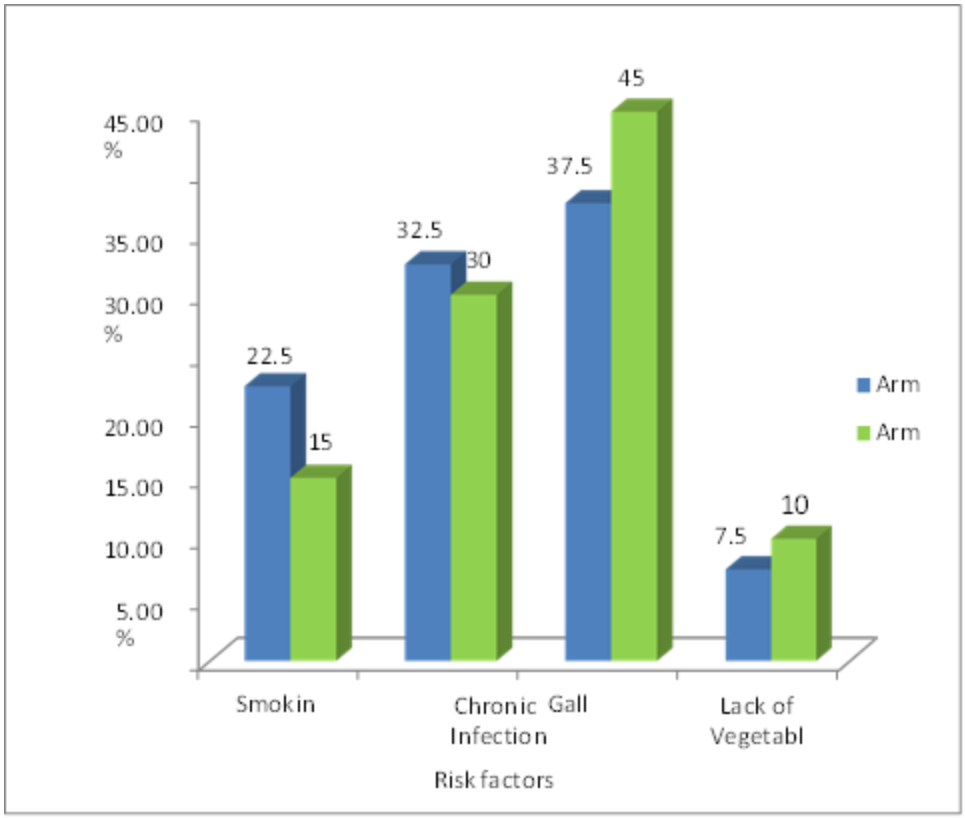


**Figure 3:** Distribution of the patients according to Risk Factor

**Table 2:** Treatment response assessment after 2nd cycle of CT

| Response | Arm A (n=40) | | Arm B (n=40) | | P-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Partial Response | 6 | 15.0 | 2 | 12.5 | 0.745 |
| Stable Disease | 34 | 85.0 | 35 | 87.5 | |

**Table 3:** Treatment response assessment after 4th cycle of CT

| Response | Arm A (n=40) | | Arm B (n=40) | | P-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Partial Response | 12 | 30.0 | 15 | 37.5 | 0.478 |
| Stable Disease | 28 | 70.0 | 25 | 62.5 | |

**Table 4:** Response assessment after 6 weeks of completion of 6 cycles of CT

| Response | Arm A (n=40) | | Arm B (n=40) | | P-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Partial Response | 15 | 37.5 | 18 | 45.0 | 0.792 |
| Stable Disease | 18 | 45.0 | 16 | 40.0 | |
| Progressive Disease | 7 | 17.5 | 6 | 15.0 | |

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**Table 5:** Distribution of the patients on the basis of development of Anemia during treatment

| Anaemia Grade | Arm A (n=40) | | Arm B (n=40) | | Total (n=80) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| No Toxicity | 2 | 5.0 | 14 | 35.0 | 16 | 20.0 |
| Grade 1 | 14 | 35.0 | 17 | 42.5 | 31 | 38.8 |
| Grade 2 | 18 | 45.0 | 7 | 17.5 | 25 | 31.2 |
| Grade 3 | 6 | 15.0 | 2 | 5.0 | 8 | 10.0 |
| Chi-Square test | 16.13 | | | | | |
| p-value | 0.001 | | | | | |

**Table 6:** Distribution of patients on the basis of development of Neutropenia during treatment\

| Neutropenia Grade | Arm A (n=40) | | Arm B (n=40) | | Total (n=80) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| No Toxicity | 6 | 15.0 | 16 | 40.0 | 22 | 27.5 |
| Grade 1 | 14 | 35.0 | 14 | 35.0 | 28 | 35.0 |
| Grade 2 | 14 | 35.0 | 8 | 20.0 | 22 | 27.5 |
| Grade 3 | 6 | 15.0 | 2 | 5.0 | 8 | 10.0 |
| Chi-Square test | 8.18 | | | | | |
| p-value | 0.042 | | | | | |

**Table 7:** Distribution of the patients on the basis of development of Thrombocytopenia during treatment

| Thrombocytopenia Grade | Arm A (n=40) | | Arm B (n=40) | | Total (n=80) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| No Toxicity | 8 | 20.0 | 19 | 47.5 | 27 | 33.7 |
| Grade 1 | 14 | 35.0 | 15 | 37.5 | 29 | 36.2 |
| Grade 2 | 14 | 35.0 | 5 | 12.5 | 19 | 23.8 |
| Grade 3 | 4 | 10.0 | 1 | 2.5 | 5 | 6.3 |
| Chi-Square test | 10.58 | | | | | |
| p-value | 0.014 | | | | | |

**Table 8:** Distribution of patients on the basis of development of Nausea during treatment

| Nausea Grade | Arm A (n=40) | | Arm B (n=40) | | Total (n=80) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| No Toxicity | 10 | 25.0 | 13 | 32.5 | 23 | 28.8 |
| Grade 1 | 20 | 50.0 | 15 | 37.5 | 35 | 43.7 |
| Grade 2 | 6 | 15.0 | 10 | 25.0 | 16 | 20.0 |
| Grade 3 | 4 | 10.0 | 2 | 5.0 | 6 | 7.5 |
| Chi-Square test | 2.77 | | | | | |
| p-value | 0.428 | | | | | |

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**Table 9:** Distribution of the patients on the basis of Vomiting during treatment (N=80)

| Vomiting Grade | Arm A (n=40) | | Arm B (n=40) | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| No Toxicity | 9 | 22.5 | 14 | 35.0 | 23 | 28.7 |
| Grade 1 | 19 | 47.5 | 16 | 40.0 | 35 | 43.7 |
| Grade 2 | 10 | 25.0 | 9 | 22.5 | 19 | 23.8 |
| Grade 3 | 2 | 5.0 | 1 | 2.5 | 3 | 3.8 |
| Chi-Square test | 1.73 | | | | | |
| p-value | 0.630 | | | | | |

**Table 10:** Distribution of patients according to Diarrhea during treatment (N=80)

| Diarrhea Grade | Arm A (n=40) | | Arm B (n=40) | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| No Toxicity | 20 | 50.0 | 24 | 60.0 | 44 | 55.0 |
| Grade 1 | 17 | 42.5 | 12 | 30.0 | 29 | 36.3 |
| Grade 2 | 3 | 7.5 | 4 | 10.0 | 7 | 8.7 |
| Grade 3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Chi-Square test | 1.37 | | | | | |
| p-value | 0.504 | | | | | |

**Table 11:** Distribution of patients on the basis of Fatigue during treatment (N=80)

| Fatigue Grade | Arm A (n=40) | | Arm B (n=40) | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| No Toxicity | 20 | 50.0 | 24 | 60.0 | 44 | 55.0 |
| Grade 1 | 16 | 40.0 | 12 | 30.0 | 28 | 35.0 |
| Grade 2 | 4 | 10.0 | 4 | 10.0 | 8 | 10.0 |
| Grade 3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Chi-Square test | 1.13 | | | | | |
| p-value | 0.254 | | | | | |

**Table 12:** Distribution of the patients on the basis of Anorexia during treatment (N=80)

| Anorexia Grade | Arm A (n=40) | | Arm B (n=40) | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| No Toxicity | 1 | 2.5 | 3 | 7.5 | 4 | 5.0 |
| Grade 1 | 25 | 62.5 | 21 | 52.5 | 46 | 57.5 |
| Grade 2 | 13 | 32.5 | 15 | 37.5 | 28 | 35.0 |
| Grade 3 | 1 | 2.5 | 1 | 2.5 | 2 | 2.5 |
| Chi-Square test | 1.49 | | | | | |
| p-value | 0.474 | | | | | |

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**Table 13:** Distribution of the patients on the basis of Renal Toxicity during treatment (N=80)

| Renal Grade | Arm A (n=40) | | Arm B (n=40) | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| No Toxicity | 19 | 47.5 | 39 | 97.5 | 58 | 72.5 |
| Grade 1 | 21 | 52.5 | 1 | 2.5 | 22 | 27.5 |
| Chi-Square test | 47.06 | | | | | |
| p-value | 0.0001 | | | | | |

**Table 14:** Distribution of the patients on the basis of Peripheral Neuropathy during treatment (N=80)

| Peripheral Neuropathy Grade | Arm A (n=40) | | Arm B (n=40) | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Grade 0 | 27 | 67.5 | 10 | 25.0 | 37 | 46.3 |
| Grade 1 | 13 | 32.5 | 24 | 60.0 | 37 | 46.3 |
| Grade 2 | 0 | 0.0 | 6 | 15.0 | 6 | 7.4 |
| Chi-Square test | 15.4 | | | | | |
| p-value | 0.0001 | | | | | |

## DISCUSSION

The aggressive pattern of BTC and its advanced presentation at diagnosis is documented Unfortunately, only a minority of patients have been diagnosed at an early respectable stage and disease recurrence rates are high despite curative-intent surgery. Chemotherapy is a palliative treatment option for patients with advanced biliary tract disease. Different drugs have demonstrated activity in BTC, including fluoropyrimidines, gemcitabine, cisplatin, and oxaliplatin. Gemcitabine combined with platinum compounds has been established as the standard of chemotherapy in advanced biliary tract cancer.[8] The Gemcitabine-Cisplatin regimen has become a standard of care in first-line treatment since the ABC-02 trial. However, the GEMOX regimen is a well-established regimen since Sharma's study. These two regimens have never been compared. So, the primary objective of the study was to compare the efficacy and treatment-related toxicities of these two platinum compounds. In this study, the mean age of the patients at diagnosis was 53±1 years, and the P value= was 0.354. The youngest patient was 37 years old and the oldest one was 70 years. Most of the patients were in the 50-59 years age group. In this study, female patients were predominant (62.5% in Arm A and 52.5% in Arm B) whereas male patients were 37.5% in Arm A and 47.5% in Arm B with a male-female ratio of 1.5:1 which correlates with GLOBOCAN 2018. Gallstone is the leading cause of Gallbladder carcinoma worldwide. In this study, 37.6% of ARM A and 45% of ARM B patients had gallstones. Chronic infection liver flukes and chronic HIV were the second cause (32.5% in Arm A and 30% in Arm B) of biliary cancer. Smoking was another because it accounts for 22% in Arm A and 15% in Arm B. Common site for primary carcinoma was gall bladder in both arms (52.5% in arm A and 45% in arm B) then cholangiocarcinoma (30% and 32.5% in arm A and B respectively). The rest of the patients had periampullary carcinoma 17.5% in Arm A and 22.5% in arm B.

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Most of the patients had liver metastasis. The second most common (27.5% and 32.5%) metastatic sites in arms A and B were peritoneal. The lunging was the 3rd most common metastatic site for biliary carcinoma with 7.5% and 5% cases in Arm A and Arm B respectively. Three assessments were done during and after the treatment was given. and 62.5% of patients from Arm A and Arm B showed SD. No patients showed disease progression. Pearson's Chi-Square test was used to calculate ate p-value which was insignificant. On the 3rd. Assessments, 37of .5% of patients in Arm A and 45% of patients in Arm B showed PR. 45% and 40% of patients from Arm A and B showed SD respectively. 17.5% vs 15% (seven patients in Arm A, six patients in Arm B) showed PD. Pearson's Chi-square Test was needed to determine the p-value. P-value was 0.792 which was nonsignificant. During treatment, the most prevalent toxicities of both arms were nausea, vomiting, diarrhea, anorexia, fatigue and peripheral neuropathy, and hematological and renal toxicities. It was implied that most of the patients in Arm A suffered from Grade1 and 2 anemia. It was 35% in Arm A and 42.5% in Arm B. Grade 2 anemia was experienced by 45% of Arms A and 17.5% of the Arm B patients. Grade 3 anemia was experienced by 15% of the Arm A patients. 5% of the Arm A and 35% of the Arm B patients did not have anemia during the treatment period. In respect of neutropenia, 27.5% of the patients in both arms did not suffer from any neutropenia. If considered separately, in Arm A it was 15% and in Arm B it was 40%. 35% of patients in both Arms experienced Grade1 neutropenia. And also 35% and 20% of patients in Arm A and B experienced Grade 2 neutropenia. Only 6 patients in Arm A and 3 patients in arm B suffered from Grade 3 Neutropenia. No patient in both Arms had Grade 4 Neutropenia. Most (47.5%) of the patients of Arm B did not have any thrombocytopenia at all. It was 20% for the patients of Arms A. In Arm, A 35% of patients had Grade 1 and 37.5% of arm B patients had Grade 1 thrombocytopenia. 12.5% of patients of Arm B and 35% of patients of Arms A suffered from Grade 2 thrombocytopenia. Only 1 patient from Arm B and 4 patients from Arm A had grade 3 thrombocytopenia. In terms of nausea, the majority of the patients from both arms suffered from Grade 1 nausea. 50% of patients from Arm A and 37.5% of patients from Arm B had Grade 1 nausea. 15% of patients from Arm A and 25% of patients from Arm B had Grade 2 nausea. Only 4 patients from Arm A and 2 patients from Arm B suffered from Grade 3 nausea. Around 28% of patients from both arms did not have any nausea. Most of the patients from both arms suffered from Grade 1 vomiting, 47.5% in Arm A and 40% in Arm B. On the other hand, 25% from Arm A and 22.2% from Arm B suffered from Grade 2 vomiting. Only 2 patients in Arm A and 1 patient in Arm B had Grade 3 vomiting. Around 28% of patients from both Arms did not have any occurrence of vomiting. According to Lee et al. 2015, in grades 3 and 4 Vomiting was in the Gemcitabine-Cisplatin (GP) at 3.3% and in Gemcitabine-Oxaliplatin Arm at 1.6%. In respect of diarrhea, it was revealed that the majority of the patients from both arms did not suffer from diarrhea. And most of the patients in both Arms suffered from Grade 1 diarrhea. If the arms are considered separately, then the number was 42.5% in Arm A and 30% in Arm B. both the Arms. No patient from both arms suffered from Grade 2, 3 diarrheas. It was pointed out that, most of the patients in Arm A

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did not have Peripheral Neuropathy. In Arm, A 32.5% of patients, and in Arm B 60% of patients developed Grade 1 neuropathy during treatment. Grade 2 toxicity after 6 cycles of chemotherapy completion was observed in Arm B which is about 15%. There was no grade 3, or 4 toxicities in arm A and Arm B. According to 9, grade 3 and 4 asthenia, peripheral neuropathy developed in the GEMOX arm (16% and 11% respectively). 65% of the patients in both Arms did not have any paresthesia. 20.51% of patients from Arm A and 28.21% of patients from Arm B had Grade 1, 15.39% of patients from Arm A and 5.12% of patients from Arm B had grade 2 paresthesia, no patient suffered from Grade 3 and Grade 4 paresthesia in both the Arms. According to the data, the majority of the patients from both Arms suffered from anorexia. Grade 1 anorexia is experienced by 64.10% and 53.85% of patients in Arm A and B respectively. 33.8% of patients in Arm A and 38.46% of Arm B had Grade 2 anorexia. Meanwhile, no patient from both Arms had Grade 3 and Grade 4 anorexia. It was seen that 5% of patients from both arms did not have anorexia. 64.10% of patients from Arm A and 58.98% of patients from Arm B did not suffer from fatigue. 25.64% and 10.26 % of patients from Arm A suffered from Grade 1 and Grade 2 fatigue respectively. On the other hand, 30.76 % and 10.25% of 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 GEMOX chemotherapy was well tolerated. There was less unexpected toxic effect in the GEMOX Arm. Patient treated with Gem-Cis compared with patients treated with GEMOX more likely to experience anemia (15% vs 8%, p=0.001), thrombocytopenia (10% vs 2.5%, p=0.014), neutropenia (15% vs 5%, p=0.042), renal toxicity (7.5% vs 0%, p=0.0001), nausea (10% vs 5%, p=0.428), vomiting (5% vs 2.5%, p=0.630). The occurrence of peripheral neuropathy was more in the GEMOX arm (0% vs 15%, p=0.0001). No patient from both Arms discontinued treatment due to toxicity. No treatment-related death and grade 3,4 toxicity occurred. No patient developed febrile neutropenia during the treatment period. All the toxicities were duly managed. The toxic events were more in the Gem-Cis Arm in terms of myelosuppression and renal toxicities which is statistically significant. On the other in the GEMOX arm, the patient experienced more peripheral neuropathy which also showed a statistically significant difference with the Gem-Cis regimen. Most of these findings correlate with the findings.[1] After careful analysis, it can be said that the GEMOX regimen is as active as the standard Gem-Cis regimen in the treatment of ABTC. It will also help to reduce the patient load in the hospitals to some extent and more patients will get the chance of indoor treatment. The interim analysis of the randomized BINGO study comparing to GEMOX plus Cetuximab showed 4-months PFS of 44% and 66% respectively. This combination with targeted therapies would be more logical to replace GEMOX in patients with BTC. Hence the available evidence suggests that Gemcitabine-Oxaliplatin can be a standard option for the treatment of ABTC with less toxicity.

**Limitations of the study**

Although optimum care had been taken in every step of the study, there were still some limitations:

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- The patients could only be monitored up to their PFS.
- A Large number of patients is required to assess the possible difference between the two drugs.
- The study was conducted among the patients of two hospitals in Dhaka city only. So entire situation of biliary carcinoma in Bangladesh could not be estimated.

## CONCLUSIONS

Gemcitabine combined with platinum compounds is a standard treatment option for patients of advanced BTC. Gemcitabine-Oxaliplatin regimen is widely used in routine practice. To conclude, treatment with the Gemcitabine-Oxaliplatin regimen is an excellent combination with fewer toxicities and more convenient in loco regional control of advanced inoperable biliary tract cancer.

**Recommendations of the Study:**

As Gemcitabine-Oxaliplatin is effective for the locoregional control of advanced inoperable biliary tract carcinoma, large-scale multi-institutional studies with more sample sizes are needed. A longer duration of the study to see the late toxicities of treatment and analyze progression-free survival & overall survival is recommended.

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