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Research Article

# Comparison of Hematological Toxicity Between Cisplatin-5-Fluorouracil and Gemcitabine-cisplatin used in Treatment of Gallbladder Cancer

**Mohd Daud Ali*, Hemant Sharma, Mohd Asif, Farhat Yasmin, Md. Sarfaraz Alam**
Mahavir Cancer Institute and Research Centre Phulwari Sharif Patna, Bihar, India

## Abstract

The occurrence of gallbladder cancer rare in United States and other western countries is increases. In fact, more than half of those patients die. Many patients do not receive palliative chemotherapy or adequate therapy. The question of whether a combined chemotherapy is better than a single drug-like gemcitabine. The objective of this prospective study was to compare the haematological toxicity between cisplatin-5-fluorouracil and gemcitabine-cisplatin used in treatment of gallbladder cancer at Mahavir Cancer Institute and Research Centre Phulwari Sharif Patna, Bihar. Toxicities were graded as per the National Cancer Institute Common Toxicity Criteria (NCI-CTC), grade I, II, III and IV. Anaemia of grade III-IV was observed 11% and 7% respectively of cycles of chemotherapy in cisplatin-5-fluorouracil, while in cisplatin-gemcitabine observe 13% and 4% respectively. Grade III-IV thrombocytopenia was more frequently in the cisplatin-5-fluorouracil chemotherapy cycle (2% & 1.3% respectively) compared with the cisplatin-gemcitabine (2.6% and 0% respectively). Grade III-IV neutropenia also occurred more frequently in cisplatin-5-fluorouracil (5.3% and 5.3% respectively) than in the cisplatin-gemcitabine respectively. However, the lack of statistical significance results in the present study may be due to inadequate sample size (8 in each Arm). As far as safety is concerned, cisplatin-5-fluorouracil seems to be safer than cisplatin-gemcitabine.

**Keywords:** Ketorolac Tromethamine, Solid Dispersion, Surfactants and Carriers.

***Corresponding Author: Md. Daud Ali, M Pharmacy,** Department of Pharmacy Practice National Institute of Pharmaceutical Education & Research, Hajipur India. **Email-**dali.niper@gmail.com

## 1. Introduction

Even though gallbladder cancer is a rare disease, it is estimated that close to 7,000 new cases occur annually in the United States [1]. Gallbladder cancer is an aggressive tumor with a poor prognosis. It is uncommon in the western world, with approximately 5,000 cases of gallbladder carcinoma annually in the USA [1,2]. Worldwide, the highest prevalence of gallbladder cancer is seen in Israel, Mexico, Chile, Japan, and among Native American women, particularly those living in New Mexico [2,3,6,9]. In Indian scenario a study conducted by the International Hepato-Pancreato Biliary

Association in association with Mumbai-based International Institute of Population Sciences on 22,000 people across 60 villages in the Gangetic plains of Uttar Pradesh and Bihar revealed second largest incidence of gall bladder cancer in the world, after Chile. The study found incidence of gall bladder cancer in the Gangetic regions of Vaishali, rural Patna and Varanasi to be around 20 to 25 per one lakh population, which was among the highest in the world. Compared to this, the rate in Bangalore was just 0.5/100,000 population and 12.5/100,000 in Delhi [2,3,4].

While surgical resection of the primary tumor and the areas of local extension remain the most effective therapy, <25% of patients will be respectable at presentation [4,5,7]. The remaining 75% will receive palliative therapy, with a median survival of ∼6 months. In addition, those undergoing potentially curative resections experience high rates of relapse and are generally incurable at recurrence.

Published chemotherapy studies in general have been limited by the small numbers of patients with biliary cancer, and by the inclusion of tumours from other, more common, primary sites such as hepato cellular and pancreatic cancers. Combinations including 5-fluorouracil (5-FU) have not demonstrated a clear superiority over single-agent 5-FU, but result in added toxicity [2,8].

A study performed by Glimelius et al [3,4]. suggested there was a benefit to chemotherapy in biliary tract cancer. They compared 5-FU or 5-FU/Etoposide with best supportive care in pancreatic and biliary cancers. The median survival time in the subset of 37 biliary patients was 6.5 months for the chemotherapy group (either regimen) and 2.5 months for the best supportive care group, but did not reach statistical significance in this subgroup analysis. The quality of life analysis showed a statistical difference favouring the use of chemotherapy [3,6,7,9].

**2. Materials and Methods:**

The study was conducted in outside patient department and inside patient department at Mahavir Cancer Institute and Research Centre Phulwari Sharif Patna, Bihar. The Institutional Ethical Committee of Mahavir cancer Sansthan, Phulwari Sharif Patna, approved the study. It was a prospective follow-up study conducted in a cohort of gallbladder cancer patients being treated with two regimens namely Cisplatin-Gemcitabine and Cisplatin-5-Fluorouracil with an aim to evaluate toxicity of two treatment regimens. First group of patients receiving Cisplatin-Gemcitabine was considered as Arm–A, and second group of patients receiving Cisplatin-5-Fluorouracil was considered as Arm– B. This study was conducted over a period of six months from December 2008 to May 2009. Data relevant to study were collected from the records of gallbladder patient available in medical record room and nursing station of inpatient department. Considering logistics and financial constraints of the study thirty patients in each group, Arm-A and Arm-B, were selected randomly. Inclusion criteria for patients was Histological or cytological confirmed or metastatic Adenocarcinoma of the Gall bladder carcinoma, age between 18 to 70 years of either sex with at least completed 2 cycles of chemotherapy. Patients were exclused from study if suffer from organ failure, HIV/Hbs Ag +ve, severe bone marrow suppression, pregnant and lactating women, allergic or anaphylactic like reaction. After enrolment of patients, before the starting of chemotherapy, baseline status of complete blood count, renal function test and liver function test were performed, and results of the entire hematological test were recorded. Likewise all the hematological test were also performed before starting next cycle of chemotherapy ,this results allow whether the next cycle of chemotherapy should be allow or not and result of all these test were also recorded.

Pre-treatment evaluation included complete medical history, physical examination, and evaluation of performance status, chest radiograph, and diagnostic studies for disease assessment such as ultrasound of the abdomen or CT scan. The treatment plan involved

administration of Gemcitabine 1g/m2 as a 30-minute intravenous infusion on days 1 and 8.When used, Cisplatin 75 mg/m2 was given intravenously over 30 minutes on day 1.Standard hydration and antiemetic protocols were followed.

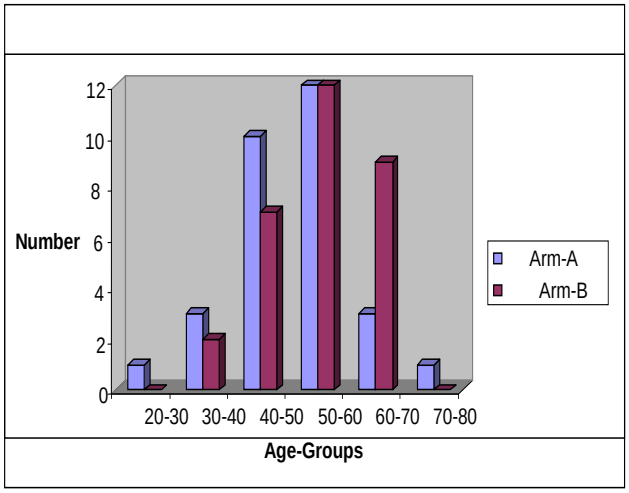
Treatment cycles were repeated every 21 days provided the patient had recovered from any drug-related toxicity associated with the previous course. Following a treatment course, toxicity grades were reviewed and dosage for the next cycle was modified according to the following schedule:-Dose of Gemcitabine was reduced by 20% for grade IV neutropenia associated with fever or infection or lasting more than 7 days, absolute neutrophil count of less than 1,000/mm3 lasting beyond day 21 of the treatment course, platelet nadir of less than 25,000/mm3 or any grade III-IV visual toxicity other than nausea and vomiting. Cisplatin dose was adjusted according to the serum creatinine value. If a patient had any toxicity that required a delay in the next treatment course, dosage in the subsequent cycle was decreased by 20%.Patients were continued on therapy until complete response or disease progression was documented or until unacceptable toxicity occurred. Patients were withdrawn from treatment if there was greater than 2 weeks delay in treatment because of toxicity. Growth factors were not routinely used. Anti motility drugs were used for diarrheal as needed.

Records of the enrolled patients were entered into computer using Epi-info ver3.2. The data were checked for accuracy and completeness. The databases were converted to MS Excel sheet for comparing safety, efficacy and toxicity between Arm-A and Arm-B. All the continuous variables were checked for normality by comparing mean, median and mode. Non-parametric tests were used for non-normal variables, and parametric tests for normal data. Values were expressed as Mean ± Standard deviation or as percentages. Within the group comparisons were done using Wilcoxon sign ranked test for non-normal data, and paired-t test for normal data.

Between-group comparisons were done using Mann-Whitney rank test for non-normal data and t-test for comparing means of two independent samples. Chi-square and Fisher exact test were used for comparing efficacy and non haematological toxicity. For all statistical analysis SPSS Ver15 was used.

**3. Results and Discussion:**

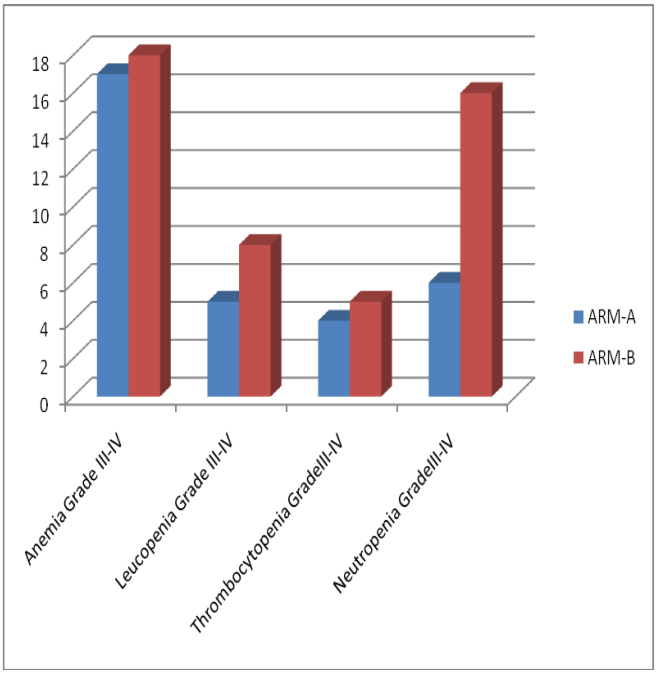
Haematological toxicities such as anaemia, neutropenia, thrombocytopenia and leucopoenia are presented (Table-1). Toxicities were graded as per the National Cancer Institute Common Toxicity Criteria (NCI-CTC), grade I, II, III and IV. Occurrences of toxicities grade III and IV are considered clinically severe as these require further management such as cessation of treatment or additional treatments. Hence grade III and IV toxicities observed in patients of both groups are combined together for the comparison between two arms. Bone marrow suppression (anaemia, neutropenia, thrombocytopenia, and leucopoenia) was comparatively higher among the patients in Arm-B than in Arm-A group.




Age-distribution: Age-distribution of patients in both arms A and B respectively is presented in figure-1

Fig: 1: In arm-A, 4 (13.33%) patients were male and 26 (86.66%) were female; whereas in arm-B, 3(10%) patients were male and 27(90%) were female.

| **Types of Toxicity** | **Group-A n=150(%)** | **Group-B n=150(%)** | **P-Value** |
|---|---|---|---|
| Anemia(Grade III,IV) | 17(11.2) | 18(11.9) | >0.05 |
| Grade I | 52(34) | 69(46) | <0.05 |
| Grade II | 11(7.3) | 26(17.3) | <0.05 |
| Grade III | 13(8.6) | 11(7.3) | >0.05 |
| Grade IV | 4(2.6) | 7(4.6) | <0.05 |
| Leucopoenia(Grade III,IV) | 5(3.2) | 8(5.2) | >0.05 |
| Grade I | 3(2) | 11(7.3) | <0.05 |
| Grade II | 7(4.6) | 8(5.3) | <0.05 |
| Grade III | 4(2.6) | 4(2.6) | <0.05 |
| Grade IV | 1(0.6) | 4(2.6) | <0.05 |
| Thrombocytopenia(Grade III,IV) | 4(2.6) | 5(3.3) | >0.05 |
| Grade I | 13(8.6) | 9(6) | >0.05 |
| Grade II | 10(6.6) | 8(5.3) | >0.05 |
| Grade III | 4(2.6) | 2(1.3) | >0.05 |
| Grade IV | 0 | 3(2) | <0.05 |
| Neutropenia(Grade III,IV) | 6(3.9) | 16(10.6) | <0.05 |
| Grade I | 2(1.3) | 7(4.6) | <0.05 |
| Grade II | 17(11.3) | 14(9.3) | >0.05 |
| Grade III | 5(3.3) | 8(5.3) | >0.05 |
| Grade IV | 1(0.6) | 8(5.3) | <0.05 |




Anaemia of grade III-IV was observed 11% and 7% respectively of cycles of chemotherapy in arm-B, while in Arm-A observe 13% and 4% respectively. The entire grade III-IV types of anaemic patients were received blood transfusion. Grade III-IV thrombocytopenia was more frequently in the Arm-B chemotherapy cycle (2% & 1.3%respectively) compared with the Arm-A (2.6% and 0% respectively). Grade III-IV neutropenia also occurred more frequently in Arm-B patients (5.3% & 5.3%% respectively) than in the Arm-A respectively).Grade III-IV Leucopoenia in Arm-B patients were reported 2.6% and 0.6% respectively while in Arm-A patients reported 2.6% & 2.6% respectively.

Discussion

Timely it is well documented that the gemcitabine and 5-fluorouracil and cisplatin is highly toxic and also fetal [10-14].

Toxicity was observed more frequently in patients receiving gemcitabine-cisplatin as compared to patients receiving Cisplatin-5-Fluorouracil. Previous study [1,2,5,6,9] also supported that gemcitabine-cisplatin is more toxic than Cisplatin-5-Fluorouracil. The incidence of anaemia with grade III-IV was 11% in those patients receiving gemcitabine-cisplatin in comparison to 18% receiving cisplatin-5fluorouracil. The incidence of thrombocytopenia with grade III-IV was 3.3% in patients taking 5-Fluorouracil-Cisplatin while in patients receiving gemcitabine-cisplatin it was 2.6%. Thrombocytopenia is the most common adverse events experienced on day 15, which needs dose reduction or omission of gemcitabine. On day 15, nearly one half of the patients needed gemcitabine dose reduction and two thirds of the patients needed gemcitabine dose omission due to thrombocytopenia. Such reduction/omission dictated by thrombocytopenia has not been seen with single agent gemcitabine. Leucopoenia with grade III-IV toxicities (5.2 %) were found more common in patients taking 5-flurouracil-cisplatin in comparison to patients receiving gemcitabine-cisplatin (3.2 %).

The main limitation of the study was inadequate sample size which was not adequate enough to detect clinical significance in response rate between two arms. To get power of 90% for having a clinical significance of response rate we need to have nearly 512 total subjects in two arms. The power to detect clinical significance of response rate between two regimens is very low for making any valid conclusion about finding in the present study.

Since the study was not a properly planned randomized trial, there could be high scope of influence of confounding variables on the outcome of the study. Since this is not a proper clinical trial, the two groups may not be comparable with respect to many variables which may act as confounder to response rate.

**Conclusion:**

The present research work was a prospective cohort study to assess the efficacy, safety, and toxicity of gemcitabine-cisplatin in comparison to 5-fluorouracil-cisplatin in the treatment of gallbladder cancer. The lack of statistical significance results in the present study may be due to inadequate sample size (8 in each Arm). As far as safety is concerned, Cisplatin-5-Fluorouracil seems to be safer than cisplatin-gemcitabine

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