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Gemcitabine and Cisplatin In Metastatic Carcinoma Gallbladder. A Single Institution Retrospective Analysis

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Abstract: *Background- Metastatic gall bladder cancer (GBC) is an aggressive disease and is often prone to delayed diagnosis. Chemotherapy is the modality most often employed to prolong survival and is superior to best supportive care alone.*
Aim- *The aim of this study was to analyse the effect of gemcitabine and cisplatin (G+C) based chemotherapy in metastatic GBC.*
Design- *Retrospective single institution analysis.*
Material and methods- Medical records of patients with a histopathologic proven diagnosis of metastatic GBC presenting from January 2014 to July 2015 to the department were reviewed, and data were collected from the departmental case files.
Results- Total number of patients analysed was 25. The median overall survival was 36 weeks (range 3.4-95 weeks). The median time to progression was 20.6 weeks (range 1-82 weeks). 7/25 (28%) patients achieved a complete response, 8/25 (32%) patients had stable disease while 10/25 (40%) patients had progressive disease. The toxicities encountered were chiefly ototoxicity (7.5%), neuropathy (7.5%), anaemia (4.33%) and nausea-vomiting (3.5%).
Conclusion- *G+C appears to be a safe and effective regimen for advanced GBC in the subset of patients presenting to our institute. The results achieved by us are comparable to literature.*
Keywords: *Cisplatin, Gemcitabine, metastatic gall bladder cancer, survival, toxicity.*

I. INTRODUCTION

Biliary tract cancers (BTC) include cancers of the biliary tract, gallbladder cancer (GBC), cholangiocarcinoma of intrahepatic and extrahepatic bile ducts and cancers of the ampulla and papilla of Vater [1]. The incidence varies widely in different geographic regions, with the lowest incidence rates seen in Western countries, and the highest in Asia and Latin America [2]. GBC are the most common type of BTC. It is a common cancer in the northern/ north eastern states of India [3] and ranks among the first 10 cancers in the Indian council of medical research registries (2006-2008) of Delhi, Dibrugarh, Kolkata, Bhopal and Mumbai [3]. Surgery is presently the only curative modality but the 5-year survival rate for surgically resected patients remains a dismal 5% [3]. Majority patients of with GBC present in advanced stages as the symptoms are nonspecific and many present after cholecystectomy with GBC diagnosed on histopathology. Clinical findings of jaundice, cachexia, anorexia, ascites, left supraclavicular lymphadenopathy and hard lump in right hypochondrium are usually seen in advanced GBC [4]. Although surgery still remains the only curative treatment, chemotherapy (CT) has been reported to prolong survival in advanced BTC when compared to best supportive care alone [5, 6]. There is still discrepancy with respect to a standard CT regimen addressing the BTC. Valle J et al [7] in a large multicentric phase III trial have shown a significant survival advantage with gemcitabine and cisplatin (G+C) as compared to gemcitabine alone in the management of BTC and the subgroup analysis showed that combination therapy can also prolong the survival of GBC patients. GBC differs from the other BTC at the molecular and clinical level and has been reported to show a better response rate, but a shorter overall survival than cholangiocarcinomas [8]. Several gemcitabine based combination therapies (gemcitabine-oxaliplatin as well as combinations involving targeted therapies) have been reported in the management of BTC, with the most substantial evidence reported for G+C. The aim of the present study was to assess the tolerability and efficacy of G+C combination in advanced GBC presenting to our institution.

II. MATERIAL AND METHODS

Twenty five patients with metastatic GBC treated with G+C during the period January 2014 to July 2015 were retrospectively analysed. Case files were evaluated for the patient characteristics, performance status, history of weight loss, duration of symptoms and tumour characteristics. Patients between the age of 18 to 80 years with histologically confirmed, metastatic GBC, who had not received prior CT or radiotherapy, had a good performance status with no central nervous system metastases, no uncontrolled infection, and a life expectancy

of >3 months, adequate hematological parameters (neutrophils ≥4000/mm^3, platelets ≥100,000/mm^3), and adequate renal and liver functions were included. All the patients received G+C regimen that comprised of injection Gemcitabine @ 1000mg/m^2 on days 1, 8 and injection Cisplatin 70mg/m^2 on day 1. The primary end point was the treatment efficacy of CT in terms of overall survival (OS). Secondary endpoints were assessment of progression free survival (PFS) and toxicity of the G+C therapy. OS was defined as the time from the first CT to death from all causes. PFS was defined as the time from the first CT to the earliest date of disease progression (local, regional, distant and/or second cancer), death (from all causes) or data cut-off (from all causes).

Standard tumor measurements were used in keeping with the following definitions: Complete response (CR) was defined as a complete disappearance of the tumor for at least 4 weeks after time documentation ;Partial response (PR) was defined as more than a 50% decrease in the sum of the products of the two largest perpendicular diameters of all measurable lesions, as determined 4 weeks apart, consecutively; stable disease (SD) was defined as not only no CR or PR, but also no objective progression; progressive disease (PD) was defined as a 25% or greater increase in the size of any measurable lesion or the appearance of new lesions or ascites.

Time to progression was calculated from the first treatment day to the identification date of PD or death. Duration of response was measured from the date of response notation to the first record of disease progression or death, and survival was measured from the first day of treatment to death.

III. RESULTS

All patients were assessable for toxicity from the time of the first CT dose. All patients who underwent two or more treatment cycles were assessable for a response. Of 25 assessable cases, there were 4 males and 21 females. The median age was 60 years (range 31–69 years), and median Karnofsky performance status 80% (range 60–90%). Seven cases (28%) achieved PR, 8 SD (33%), and 10 cases did not respond to chemotherapy (PD) (40%). Toxicity was mild to moderate (Table 2), ototoxicity was observed in 7.5% cases, mild to moderate nausea and vomiting were seen in all cases despite prophylactic antiemetics. Anemia grade 3 was seen in 4.33%, neutropenia grade 3 in 1.73% and thrombocytopenia grade 3 in 2.38% of cases.

IV. FIGURES AND TABLES

Patient's baseline characteristics - Table 1.

CHARACTERISTIC	N (PERCENTAGE)
TOTAL PATIENTS	25 (100)
MALES	04 (16)
FEMALES	21 (84)
MEAN AGE	60 (range 40-75)
KARNOFSKY PERFORMANCE SCORE	80 (range 60-90)

Patient's response characteristics - Table 2.

RESPONSE

CHARACTERISTIC	N(PERCENTAGE)	MEDIAN (RANGE IN WEEKS)
PARTIAL REPONSE	7 (28)	
STABLE DISEASE	8 (32)	
PROGRESSIVE DISEASE	10 (40)	
TIME TO PROGRESSION		20.6 (1-82)
RESPONSE DURATION		25.7 (8-65)
SURVIVAL		36.0 (3.4-95)

Patient's toxicity characteristics - Table 3.

TOXICITY	PERCENTAGE
Anemia grade III/IV	4.33/1
Neutropenia grade III/IV	1.73/2
Thrombocytopenia grade III/IV	2.38/0.59
Nephrotoxicity (increased creatinine) grade I	1.19
Ototoxicity grade II	7.5
Neuropathy grade II	7.5
Rash grade I/II	7.14/0.59
Nausea/vomiting grade II	3.57

V. DISCUSSION

No standard CT regimen has been established for advanced GBC. Clinical trials on CT for GBC have not been actively pursued because it is rare in the West, the difficulties of obtaining an adequate biopsy specimen, and high incidences of complications, such as, cholangiohepatitis and jaundice. A pooled analysis of

clinical trials showed that the mean number of GBC patients per clinical trial was only 16.7 [9]. However, drug activity in these cancers appears to be similar to that in adenocarcinoma, of the pancreas and GBC. Historically, 5-fluorouracil (FU) has been the most active single agent, although response rates are only in the order of 10–15% [10]. Other agents that have been reported as active in biliary tract cancer are mitomycin, doxorubicin, oxaloplatin, capecitabine, cisplatin and gemcitabine A phase III ABC-02 trial including 410 patients demonstrated overall survival superiority of G+C combination over gemcitabine alone, establishing a new standard in front-line CT for BTC (11.7 vs. 8.2 months, HR 0.64; 95%CI, 0.52 to 0.80; P < 0.001). The PFS was 8.0 months in the G+C arm versus 5.0 months in the control arm (P < 0.001). Adverse events were similar in both groups, with the exception of more neutropenia in the combination arm [11]. Since the randomized multicentric phase III ABC-02 trial, G+C combination is considered as the standard first-line CT in advanced BTC [9]. However, Gemox CT is frequently preferred as first-line CT in many cancer institutions and is frequently used in recent clinical trials in association with biotherapies in exploratory studies and as the comparative arms [12, 13]. In clinical practice, Gemox and G+C are frequently used as first-line therapy in advanced BTC but they have never been compared. In the present study, we enrolled 25 GBC patients, which is a relatively good number. G+C resulted in a tumour PR of 28% and stable disease in 33%.Median time to progression and OS were 5.3 and 6.8 months, respectively. Five phase II trials have been conducted exclusively in GBC to determine the activities of palliative CT [14, 15, 16] and compared with those of present study. The regimens used in these studies were single gemcitabine, 5 FU-cisplatin, or gemcitabine plus platinum agents. The five studies and the present study, RRs ranged from 21.2% to 64% and median OS from 5 to 7.5 months. However, because none of these studies had a control group, it is difficult to determine the merits and demerits of the regimens used. Hematologic and nonhematologic toxicity of grade 3 or 4 occurred more frequently during gemcitabine-cisplatin than gemcitabine-oxaliplatin studies. In a study by Valle et al [7] although results were obtained by subgroup analysis of heterogenous biliary cancers rather than by analysis of an exclusive GBC population, gemcitabine-cisplatin was found to be superior to gemcitabine alone in GBC patients, especially when PS was good.

VI. Conclusion

The results obtained in the present study for a gemcitabine-cisplatin based combination therapy, and in the previous studies, suggest that gemcitabine plus a platinum agent can be used to manage locally advanced or metastatic GBC. Summarizing, the present study shows that gemcitabine -cisplatin chemotherapy is feasible and safe in indian patients with advanced GBC.

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