*Original Article*

# COMPARISON OF PATIENTS QUALITY OF LIFE TREATED WITH TWO DIFFERENT REGIMENS FOR ADVANCED GALLBLADDER CANCER

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**ABSTRACT**

***Objective:*** Still there is no standard regimen for the treatment of patients with advanced gallbladder malignancy who suffer from poor quality of life. Hence we wanted to evaluate the quality of life in patients with advanced gallbladder cancer treated with either 5-fluorouracil (5-Fu) and Folinic acid (FA) or with Gemcitabine (Gem) plus Cisplatin (Cis).

***Methodology:*** Records of all patients, including quality of life questionnaire were reviewed retrospectively. These patients with unresectable locally advanced or metastatic adenocarcinoma of gallbladder were seen in oncology clinic at Ziauddin Hospital and Baqai Institute of Oncology Karachi. Out of 40 patients, twenty received 5-FU with Folinic Acid (FA) (Group-1) and remaining twenty patients received Gem plus Cis (Group-2).

***Results:*** In Group-I, out of twenty patients, two (10%) were males and eighteen (90%) were females. Eleven (55%) patients showed relief in few symptoms for a mean duration of 5.9 (±3.3) months. There was no major impact of treatment on improving quality of life. In Group-II, out of twenty, three (15%) were males and seventeen (85%) were female patients who were treated with Gemcitabine plus Cisplatin.In this group sixteen (80%) patients showed a significant improvement in quality of life with relief of many symptoms for a mean duration of 6.2 (±3.4) months.

***Conclusions:*** Gemcitabine plus Cisplatin is effective in the management of patients with advanced gallbladder cancer and showed improvement in quality of life as compared to, 5-Fu with FA which does not result in improving the quality of life and is ineffective.

**Key Words:** Gall bladder cancer, Quality of life, 5-fluorouracil, Folinic acid, Gemcitabine, Cisplatin.

**Pak J Med Sci October - December (Part-I) 2007 Vol. 23 No. 5 703-707**

## INTRODUCTION

There is no effective treatment for the majority of patients with advanced gallbladder cancer who have bad prognosis with poor quality of life. The evaluation of quality of life assesses patient's well-being by taking into account physical, psychological and social conditions. Beside and beyond the physical and the metabolic effects of cancer, patients often suffer as well from psychological distress, including depression depending on the type of cancer and its treatment modality(either curative or palliative).[1] Increasingly more aggressive chemotherapy together with expected small differences between treatments with respect to objective endpoints has heightened awareness about the importance of addressing how patients experience and value the impact that treatment has had on their overall life situation.[2]

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* Received for Publication: June 8, 2007

* Accepted: July 5, 2007

Primary gallbladder carcinoma (GBC) is the fifth most common cancer of the gastrointestinal tract and is the most common malignant tumor of the biliary tract.[3] The higher frequency of gallbladder tumor in female is also notable and it has been reported as the second commonest malignancy of gastrointestinal origin in females.[4] The frequency increases with age.

In the United States gallbladder carcinoma is an uncommon tumor accounting for less than 2% of all cancer reported annually. It is the fourth leading cause of cancer deaths in Chili which is the highest in the world.[5] The frequency of the gallbladder tumor is also higher in Pakistan as compared to other countries.[6] This marked geographic differences seen in the frequency of gallbladder carcinoma suggest a possible environmental cause besides race and ethnicity.[7]

The risk of developing gallbladder cancer is significantly higher in patients with cholelithiasis, calcified or porcelain gallbladders, anomalous pancreatic duct-biliary duct junction and typhoid carriers.[8] Increased intake of total carbohydrates is associated with increased risk, while some acts as protective, and showed significant reduction in the risk with increased intake of some vitamin like B-6, E,C and dietary fibers.[9]

Gene mutation like tumors suppressor gene P53 (TP53), RAS mutations especially KRAS were noted in high grade hyperplasia, and causing carcinogenesis.[10]

Treatment of gallbladder cancer depends primarily on surgical excision and is the mainstay of curative intent treatment. However the role of aggressive surgery has remained controversial.[11] Chemotherapy has not shown its effectiveness so far. There is no standard regimen for patients with gallbladder cancer who present with either locally advanced or metastatic disease.[12]

Radiation therapy or combined chemoradiotherapy has not proved to be of substantial benefit.[13] A number of chemotherapeutic regimens have been developed to treat unresectable cancer of the gallbladder. These regimens have generally used 5-fluorouracil alone and in combination with a variety of other agents. But none appears to be more effective. Response rate to chemotherapy is low, duration of response is short and there is no improvement in overall survival. Combination chemotherapy is more toxic and no survival benefit is observed, but it may yield slightly higher response rate.[14]

In this study we evaluated the impact of chemotherapy (5-Fu with FA in group-I and Gemcitabine plus Cisplatin in group-II) on quality of life of patients with advanced (unresectable locally advanced or metastatic) carcinoma of gallbladder.

## PATIENTS AND METHODS

Record forms, flow sheets, toxicity cards and quality of life questionnaire of 40 patients with unresectable locally advanced or metastatic adenocarcinoma of gallbladder, were reviewed retrospectively. These patients completed a quality of life questionnaire before start of treatment and after every second treatment course. This study was done after approval from hospital ethics review committee. Twenty patients in Group-1, received 5-Fu with FA daily for five days and twenty patients in group-2, received Gem plus cis. These patients were seen at Ziauddin Hospital Karachi and Baqai Institute of Oncology Karachi, Clinical variables for quality of life assessed included weight loss, performance status, pain, nausea, vomiting and treatment toxicity.

## RESULTS

In Group-1 twenty patients (2 males and 18 females) with stage IV disease were enrolled according to the inclusion and exclusion criteria. The female to male ratio in this group was 9:1. The mean age of study patients was 52.8 years ± SD 8.4 (range 35-66). 10% of patients had ECOG performance status of 0; 15% of patients had performance status of one and 45% of patients had performance status of two and 30% of patients had performance status of three. One patient had a partial response and 10 had stable disease. Nine patients showed progressive disease.

There was no significant change in weight, performance status remained same in responder only and deteriorated in patients with progressive disease. Symptomatic relief in pain, nausea and vomiting were seen for duration of 5.9 (±3.3) months. There was no impact of chemotherapy in improving quality of life in this group.

In Group-2 twenty patients (3 males and 17 females) with stage IV disease were enrolled according to the inclusion and exclusion criteria. The female to male ratio in this group was 8.5:1.5

The mean age of study patients was 53.95 years ± SD 7.3 (range 35-75). Five percent of patients had ECOG performance status of 0; 10% of patients had performance status of one and 55% of patients had performance status of two and 30% of patients had performance status of three. Eleven (55%) patients had partial response and five (25%) had stable disease. Four (20%) patients showed progressive disease.

There was no significant change in weight. Performance status improved in 80% of patients who showed response (partial response and disease stabilization) and deteriorated in patients with progressive disease. Symptomatic relief in pain, nausea and vomiting were seen for duration of 6.2 (±3.4) months. There was significant impact of chemotherapy in improving quality of life in this group.

Table-I: Demographic features of the patients

| *No. of Patients* | *Group-1 (%)* | | *Group-2 (%)* | |
|---|---|---|---|---|
| Total | 20 (100) | | 20 (100) | |
| Male | 2 (10) | | 3 (15) | |
| Female | 18 (90) | | 17 (85) | |
| *Age (years)* | *Group-1* | | *Group-2* | |
| Mean ± SD | 52.80 ± 8.40 | | 53.95 ± 7.3 | |
| Range | 35-66 | | 35-75 | |
| *Performance status (ECOG)* | *0* | *1* | *2* | *3* |
| Group-1 | 2 | 3 | 9 | 6 |
| Group-2 | 1 | 2 | 11 | 6 |

## DISCUSSION

Improving quality of life (QOL) in oncology patients is an important therapeutic goal, and most treatment decisions are heavily influenced by their effect on QOL. Although measuring QOL has been a significant challenge because of a lack of consensus on the definition of QOL, research in this field has advanced rapidly. Numerous instruments now exist for measuring QOL and symptom burden, ranging from general health status measures to considerably more focused symptom measures. QOL measures have been routinely incorporated in clinical trials, and their use in clinical settings is strongly encouraged because their value in cancer patient management is now established. These measures also have a potential impact in the managed care environment because they provide information on patient satisfaction and quality of care provided.[15]

Accurate assessment of the quality of life (QOL) of patients can provide important clinical information to physicians, especially in the area of oncology. Changes in QOL are important indicators of the impact of a new cytotoxic therapy, can affect a patient's willingness to continue treatment, and may aid in defining response in the absence of quantifiable endpoints such as tumor regression. Because QOL is becoming an increasingly important aspect in the management of patients with malignant disease, it is vital that the instruments used to measure QOL are reliable and accurate. Assessment of QOL involves a multidimensional approach that includes physical, functional, social, and emotional well-being.[16] Cancer and its treatment result in severe biochemical and physiological alterations associated with a deterioration of QOL. These metabolic changes lead to decreased food intake and promote wasting. Cancer-related malnutrition can evolve to cancer cachexia due to complex interactions between pro-inflammatory cytokines and host metabolism. Beside and beyond the physical and the metabolic effects of cancer, patients often suffer as well from psychological distress, including depression.

Gallbladder cancer is an aggressive disease and carries extremely poor prognosis. It is

usually asymptomatic in the early stage, later the non specificity of symptoms is responsible for delayed diagnosis resulting in low curability of the disease. The laboratory findings are also non specific and the tumor markers carcinoembryogenic antigen (CEA) and CA 19-9 may be elevated but are not usually helpful in diagnosis. Ultrasonography is usually the first diagnostic modality.[17]

Surgery is the standard treatment for gallbladder cancer and complete tumor resection is the most important factor for better survival.[18] However, curative tumor resection is possible only in a small number of the patients. In these patients open procedure is indicated and laparoscopic cholecystectomy should be avoided. There is no role for cytoreductive surgery.[19] Despite recent advances, prognosis of patients with these cancers has not improved significantly and no progress has been made in the treatment of gallbladder cancer.

There are few trials reported in the literature utilizing systemic chemotherapy for the management of patients with gallbladder cancer. Most of these studies are based upon small number of patients and little data is available in literature for comparison of results. Most series include gallbladder cancer in biliary system along with bile duct cancers. Therefore direct comparison is difficult.[20]

5-fluorouracil has been widely used in the oncologic practice and it has been the most active single agent in gastrointestinal malignancy with a 10-20% response rate.[21] Gemcitabine has shown as a promising agent in recent trials. Approximately 30% response rate have been observed with Gemcitabine. Addition of Cisplatin may increase the response rate. These trials have shown better results as compared to previously used regimens in this type of malignancy.[22] Other agents with reported activity are Capecitabine, Oxaliplatin, Docetaxel, Mitomycin-C, Doxorubicin and Nitrosureas. Response rate of 47% to mitomycin-C was reported in a small series,[23] which could not be confirmed in a subsequent study.

These agents have been tried in too small a number of patients to be clinically meaningful. But currently none of the chemotherapy regimen is established as a standard of care for the treatment of gallbladder cancer. Patients have poor quality of life and short survival.

There was a correlation between objective responses, subjective responses, and improvements in quality of life, although discrepancies were noticed, particularly in patients with only slight symptoms.

## CONCLUSION

Thus we can conclude that in group-2 combination chemotherapy with Gemcitabine plus Cisplatin results in significant response and is effective in the management of patients with advanced gallbladder cancer. Relief of symptoms was observed, and there was significant improvement in quality of life. On the other hand, in group-1 patients who received 5-Fu with FA does not show response and remained ineffective in improving quality of life.

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