

METRONOMIC CHEMOTHERAPY IN INOPERABLE CARCINOMA GALL BLADDER: OUR EXPERIENCEVijai Prakash Srivastava¹, Jagadamba Sharan², R. C. Kesarwani³, Tanmay Prasad⁴**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: Gallbladder cancer is an aggressive malignancy and carries an extremely poor prognosis. The most consistently implicated etiologic factor in the development of gallbladder cancer is cholelithiasis and chronic inflammation. Surgery is indicated in only very selected cases because often the disease presents at an advanced stage. The poor prognosis corresponds to the high proportion of patients presenting with advanced disease. There are no proven effective options for adjuvant radiation or chemotherapy for patients with gallbladder cancer in terms of survival. To improve the quality of life of these terminally ill patients without significant toxic side effects at a significantly lower cost, metronomic chemotherapy appears to be a promising option. We studied metronomic chemotherapy in advanced inoperable carcinoma of gall bladder using 5 FU and Cisplatin with promising results.

KEYWORDS: Metronomic, chemotherapy, Gall bladder, cancer.

INTRODUCTION: Cancer chemotherapy in advanced cancer cases, often fails, to improve the outcome of the patient, as well as, if given at maximum tolerated dose, it may severely impair the quality of life of these terminally ill patients. Thus, new targets and new strategies to fight cancer are essential to improve treatment.⁽¹⁾ Research on tumor angiogenesis was initiated by the pioneering work of Judah Folkman.⁽²⁾ Over the past 40 years, angiogenesis has gained the status of a key driver in the local and distant growth of cancer.⁽³⁾ Nevertheless, both intrinsic and acquired resistance to anti-angiogenic drugs are emerging as clinically relevant issues.^(4,5) An alternative to these angiogenesis inhibitors that is generating clinical interest is metronomic chemotherapy.^(6,7) Kerbel suggested that anti-cancer agents may be able to target tumor vasculature because many of the endothelial cells that compose the wall of tumor blood vessels are immature and constantly proliferating.⁽⁸⁾ 10 years later, Klement et al.⁽⁹⁾ and Browder et al.⁽¹⁰⁾ published two provocative pioneering articles showing that mice bearing subcutaneous tumors could respond to frequent repeated low doses of chemotherapy, even when they displayed acquired drug resistance to the same agents given in a conventional way. Hanahan et al.⁽¹¹⁾ coined the term metronomic to describe this type of treatment. Metronomic chemotherapy was then defined as the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses, and with no prolonged drug-free breaks. It is thought this type of chemotherapy inhibits tumor growth primarily through anti-angiogenic mechanisms while significantly reducing undesirable toxic side-effects. Further in vitro and in vivo data strengthened the rationale for using metronomic chemotherapy in practice.^(6,7,12) Subsequent clinical trials were undertaken in adults and in children with various tumor types using different drugs, drug combinations, doses and schedules of administration.

India has a very high number of cancer cases. Many of these patients present at an advanced stage. In Rohilkhand region (Western UP) carcinoma gall bladder is the commonest gastrointestinal

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malignancy as observed in clinical practice. The reasons for this observation are difficult to pinpoint, however cholelithiasis (large stone >3cm) is probably the most common risk factor involved. Most of these patients are often having chronic cholecystitis with cholelithiasis but refuse to undergo surgery due to fear, ignorance and financial reasons. By the time these patients present to the treating physicians they develop advanced disease. Treatment of these patients is a challenge as they are often inoperable, having chemotherapy only as a treatment option. The financial as well as toxic burden imposed by conventional chemotherapy at times cannot be tolerated by many of these patients. Metronomic chemotherapy may prove beneficial to these patients as other measures fail to improve the outcome as well as quality of life of such patients. Various drugs have been tried for various malignancies in India using metronomic chemotherapy.^(13,14,15,16,17)

Based on the promising results shown by metronomic chemotherapy, a search for its application in advanced gall bladder cancer was made thoroughly, however no such trial could be found. Few trials on metronomic treatment of cholangiocarcinoma using 5 Fluorouracil (5 FU) or gemcitabine with a platinum salt.^(18,19) were found. Based on these evidences a protocol was devised and metronomic chemotherapy in advanced inoperable carcinoma gall bladder was done using 5 Fluorouracil and Cisplatin.

MATERIAL AND METHODS: 12 Patients with inoperable carcinoma gall bladder observed during past 3 years (2011 – 2014) with or without obstructive jaundice presenting with palpable mass in the right hypochondrium were included in this study. Presence of multiple peritoneal or liver metastases, distant metastases, extensive involvement of hepatoduodenal ligament, encasement or occlusion of major vessels and poor performance status were considered contraindications for surgical resection.⁽²⁰⁾ All patients were thoroughly counselled and a detailed consent regarding the treatment being offered was taken. Thorough radiological evaluation (USG abdomen, CECT abdomen and MRCP – in patients with obstructive jaundice), Liver function tests, renal function tests and routine hemogram was done in all the patients. Staging was done using AJCC guidelines. All patients had stage four disease.

PROCEDURE: Weekly 500 mg of 5 FU in 500 ml of normal saline was infused slowly in 4 hours for 1 month and then once a month for 3 months along with Cisplatin 20mg per meter square dissolved in 500 ml of normal saline infused slowly over 4 hours once a month was given. 4 patients with obstructive jaundice underwent endoscopic stenting to relieve the obstructive jaundice after undergoing vitamin K supplementation.

OBSERVATION AND RESULTS: We studied 12 patients having inoperable gall bladder cancer (10 female, 2 male) who consented to the metronomic treatment being offered. The average age at presentation was 48 yrs. (Range 45-60 yrs.) 4 patients had obstructive jaundice with deranged liver function tests. All the patients had palpable, hard, immobile lump in right hypochondrium. After first dose of metronomic chemotherapy clinical improvement, suggested by, improved appetite, and a sense of wellbeing was noted among all the cases. Patients who had jaundice showed a decreasing trend of serum bilirubin and liver enzymes on repeated testing over 1 month, however this trend was inconsistent in subsequent months with 2 patients showing further improvement and other 2 failed to improve further. In none of the patient complete disappearance of jaundice was seen. After

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completion of 4 months of chemotherapy, 8 patients showed radiological improvement on repeated CT scanning (Reduction in liver metastasis, decrease in lymph nodes), in other 4 patients no improvement was noted radiological. In general, all the patients noted an improved quality of life, which was very significant considering their condition. No significant toxicity was noted in any of the patients. 8 patients had occasional nausea and vomiting, one patient had mild diarrhea which was treated conservatively. The patients were kept on regular monthly follow up.

DISCUSSION: The incidence of carcinoma gall bladder in India ranges from 1.01 per 100000 for males to 10.1 per 100000 for females.⁽²¹⁾ but the actual number may be much more in the endemic zones of Western Bihar and Eastern Uttar Pradesh where it is the third commonest malignancy of the alimentary tract.⁽²²⁾ Chronic cholecystitis and gallstones, choledochal cysts, female gender, age and exposure to carcinogens are some of the factors implicated in the causation of gall bladder cancer but a definite cause - effect relationship has yet to be established for any of these factors.⁽²³⁾ The stage at presentation is the most important prognostic determinant. Presently, the overall survival in carcinoma gallbladder is extremely discouraging. Hension et al.⁽²⁴⁾ have shown 2 year survival is 45% for stage I, 15% for stage II, 4% for stage III and 2% for stage IV. Median survival is 19, 7, 4 and 2 months for stage I, II, III and IV disease respectively. Most of the cases present with advanced disease. In early carcinoma of the gallbladder sign and symptoms mimic benign disease. Based on these observations it can be stated that surgery is the only curative treatment for gallbladder cancer, other modalities of treatment including chemotherapy and radiotherapy are being tried with variable results depending on the stage of presentation. With emergence of metronomic chemotherapy a new concept for treatment of advanced malignancies is being tried with variable success.

Our study clearly suggests improvement in the quality of life of patients with advanced, inoperable gall bladder carcinoma with or without obstructive jaundice with metronomic chemotherapy using 5 FU and Cisplatin. Since no study had been conducted for such patients, our selection of drugs was based on previous studies done on cholangio carcinoma, low toxicity and cost effectiveness. Endoscopic biliary diversion if possible or bilioenteric diversion improves jaundice.⁽²⁵⁾ whereas metronomic chemotherapy contributes to overall improvement in quality of life of patients with minimal toxic effects. Since small number of cases have been included in the study, further studies are required to assess the efficacy of metronomic chemotherapy in carcinoma gall bladder.

CONCLUSION: Metronomic chemotherapy may be offered to those cancer patients who cannot tolerate the toxicity of conventional doses and are either unfit to undergo definitive or palliative surgery. In developing countries like India the role of metronomic chemotherapy may prove of great benefit to a very significant number of patients, as advanced disease at presentation is often seen. Carcinoma gall bladder invariably has a poor prognosis in advanced cases. For these patients conventional chemotherapy is a treatment option with variable results and significant toxicity and cost. Improvement in quality of life with minimal toxicity can be achieved at a reduced cost by metronomic chemotherapy in these patients. More studies are required to provide further evidences in this field to establish a more detailed protocol for the benefit of cancer patients.

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