

Impact of Gemcitabine and Cisplatin with Radiotherapy in locally Advanced or Metastatic Transitional Cell Carcinoma of Urinary Bladder

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Abstract

Objective: The primary object of this study is to evaluate the efficacy and safety of Gemcitabine and Cisplatin along with radiotherapy in transitional cell carcinoma of urinary bladder.

Patients and Methods: Twenty patients with locally advanced or metastatic TCC of urinary bladder were enrolled during the 22-months period from January, 1999 to October, 2000 and followed up till March 2002. Three patients received 4 cycles, five patients received 5 cycles and twelve patients received 6 cycles of Gemcitabine 1250mg / m² on day 1 and day 8 and Cisplatin 80mg / m² on day 1; administered every 3 weeks. No patient received prior chemotherapy, radiotherapy or surgery. However, four patients received prior intravesical chemotherapy. All patients received radiotherapy after completion of chemotherapy regimen.

Results: Nineteen patients achieved complete response at the end of the treatment. The complete response rate was 95%. The confidence interval was at 95%, level of confidence ranged from 85% to 100%. Median duration of clinical benefit was 21 months. Six patients (30%) were documented neutropenia, three patients (15%) documented thrombocytopenia. No life threatening toxicity was observed.

Conclusion: Gemcitabine and Cisplatin along with radiotherapy in locally or metastatic Transitional cell carcinoma of urinary bladder, exhibited pronounced response rate among all the patients. The toxicity profile remained extremely low and disease free survival enhanced. The above investigation may further be continued at a larger scale encompassing a wide band of subjects (JPMA 53:547;2003).

Introduction

World wide, the vast majority of bladder cancer (90 to 95%) is transitional cell carcinoma.¹ Transitional cell carcinoma (TCC) of bladder has proved to be a chemosensitive disease with response rate for single agent chemotherapy of 20 to 30% in larger studies.¹ Platinum based regimens had a favourable impact on prognosis in all settings. New active agents, which have shown good activity include, gemcitabine, taxanes, gallium nitrate. However, combination chemotherapy is considered to be the standard care for locally advanced or metastatic bladder cancer. Response rate from 50 to 70% have been

documented in patients receiving cisplatin- based regimens and median survival is approximately one year.¹

Gemcitabine is pyrimidines nucleoside antimetabolites which has been studied in variety of solid tumors.² Gemcitabine (2', 2' difluorodeoxycytidine) is a novel antimetabolite that has a number of advantages over its analogues (such as cytosine arabinoside) with respect to intracellular uptake, prolonged intracellular retention and antitumor effects in preclinical human cancer model.³

Several phase II clinical trials were conducted investigating single agent gemcitabine in patients with locally advanced or metastatic bladder cancer.⁴⁻⁶ In these

studies gemcitabine was administrated in a dose of 1200mg/m² weekly for three weeks followed by one-week rest. Another phase II study in 35 previously platinum treated patients, 4 CRs and 3 PRs were observed in 31 assessable patients resulting in an overall RR of 23% (95% CI, 8 to 37%). The overall median survival time for all patients was 5 months (range 2 to 21+ months).⁴ Toxicities included WHO Grade 3 to 4 leukocyte toxicity (4 patients), neutropenia (7 patients), thrombocytopenia (5 patients) and anemia (5 patients).

Elevated liver enzymes occurred in a small percentage of patients. No grade 4 symptomatic toxicity was reported and grade 3 symptomatic toxicity include allergy, fever, flu-like symptoms, nausea/vomiting, constipation and pulmonary symptoms.

Several phase II and III trials of gemcitabine and cisplatin showed similar response rate to those of MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) and CMV (cisplatin, methotrexate, vinblastine) but showed better tolerability.

Combined modality organ-sparing treatment has become the standard of care for many malignancies, including anal cancer, laryngeal cancer, and soft tissue sarcoma, among others. Therefore, the question has arisen as to whether primary cystectomy in invasive bladder tumor could also be replaced by an organ-sparing treatment. When used alone, neither transurethral resection of bladder tumor (TURBT), chemotherapy, and radiotherapy results in significant local control. Many groups have reported the value of combined modality treatment, including TURBT, systemic chemotherapy and radiotherapy.⁷⁻¹⁴ With these programs, cystectomy has been reserved for the patients with incomplete response or local failure after combined modality treatment, and survival has not been compromised. However, the optimal regimen of delivering chemotherapy and radiotherapy sequentially or concurrently to be established. Multimodality therapy, including TURBT, induction chemotherapy and radiation therapy provides excellent local control and results in overall long term survival, comparable to immediate cystectomy ('classic RTOG') an approach of evaluating induction chemo-RT after maximal TURBT.¹⁵

In this study, we decided to test the same combination of gemcitabine and cisplatin, in different schedules to find an active and well tolerated regimen. We added radiotherapy to further enhance the disease free survival. We have designed this study to judge the response rate, toxicity and disease free survival with combined modality chemotherapy and radical radiotherapy.

Patients and Methods

Between January 1999 to October 2000, twenty patients entered in this study. Duration of follow-up for each patient was 22 months till March 2002. All of them gave their informed consent, and the study was conducted according to ethical principles laid in the latest version of the Declaration of Helsinki and the guidelines for good clinical practice.

Eligibility Criteria

Before entering the study, all of the patients had to meet following criteria: a histologic or cytologic diagnosis of TCC of urinary bladder, clinical stage III or IV according to the American Joint Committee of Cancer; grade II or above. No previous chemotherapy, surgery or radiotherapy was allowed. Only relaxation was given to those who had received previous intravesical chemotherapy. No second malignancy; absence of cerebral and meningeal metastasis on CT scan (computed tomography) or MRI (magnetic resonance imaging). Karnofsky performance status at least 70. Adequate bone marrow function (leukocyte = 4000/mm³; platelets = 100,000/mm³; haemoglobin >100g/L); adequate renal function; adequate liver function (without hepatic metastasis: bilirubin=1.25 times the normal value, transaminases = 2.5 times the normal value, cholinesterase >1200 U/L, alkaline phosphates <2.5 times the normal value) with hepatic metastasis: (bilirubin = 1.5 times the normal value, transaminase = 5 times the normal value, cholinesterase >1200 U/L, alkaline phosphatase <2.5 times the normal value); a negative pregnancy test and adequate contraception for women of childbearing age; written informed consent; ability to comply with the protocol follow-up.

Treatment Schedule

Gemcitabine 1250mg/m² intravenously (i.v.) over 30 minutes was administrated on days 1 and 8. Cisplatin 80mg/m² intravenously (i.v.) over 3 hours was administrated on day 1. The cycles were repeated after every 28 days from day 1. Premedication with ondasteron was given to prevent the chemotherapy-related emesis.

In the event of complete response the chemotherapy was given for further two cycles. Subsequently radiotherapy was given with the interval of at least 3 weeks. In case of CR, the total dose of 55 Gy was given to whole bladder and total dose of 45 Gy to the pelvic lymph nodes. The boost to tumor was prescribed to 60-66 Gy in 33 fractions. In case of partial response or stable disease, chemotherapy could be administered for total of six courses. Toxicity was assessed after the end of each administration, and the chemotherapy had to be discontinued in the presence of any grade 4 toxicity or two consecutive episodes of grade 3 toxicity (Treatment Protocol and Figures 1-6).

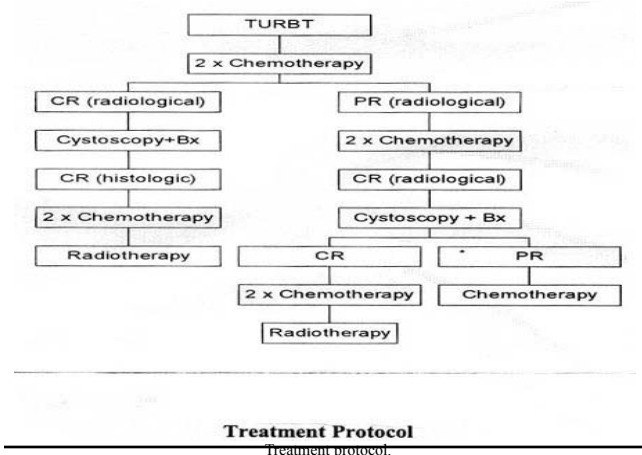


Figure 1. CT scan showing presence of tumor before treatment.

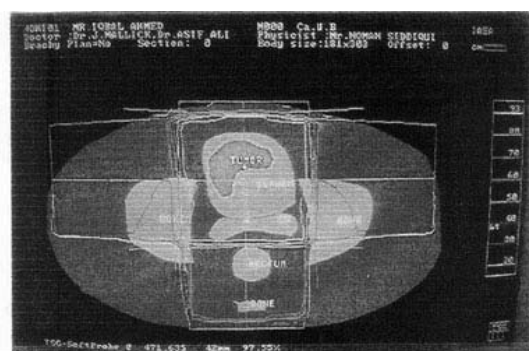


Fig-2 Radiotherapy Planning: Isocenter with 90-95% isodose lines for 8 MV, 4-fields

Figure 2. Radiotherapy planning. Isocenter with 90-95% isodose lines for 8 MV, 4-fields.

Baseline Data and Follow-up Assessment

Before enrolment, the patient's history and the results of physical examination, body weight, and measurement of indicator lesion were recorded. In addition, the following assessments were required: blood chemistry and blood cell counts, chest X-rays and CT scan abdomen & pelvis, bone scan and CT scan brain. MRI brain was

performed only if necessary when CT scan was unhelpful to rule out cerebral or meningeal metastasis.

Cystoscopy and biopsy was performed after 2 courses of chemotherapy or after every 2-4 months of completion of treatment.

Response and Toxicity Criteria

Response was evaluated according to World Health Organisation criteria. A complete response (CR) required the disappearance of all known lesions observed on 2 different occasions separated by at least 4 weeks, and no appearance of new lesion. A partial response (PR) required a greater than 50% reduction in the sum of the products of the longest perpendicular dimensions of all measurable lesions. All toxicities were evaluated according to National Cancer Institute Common Toxicity Criteria.

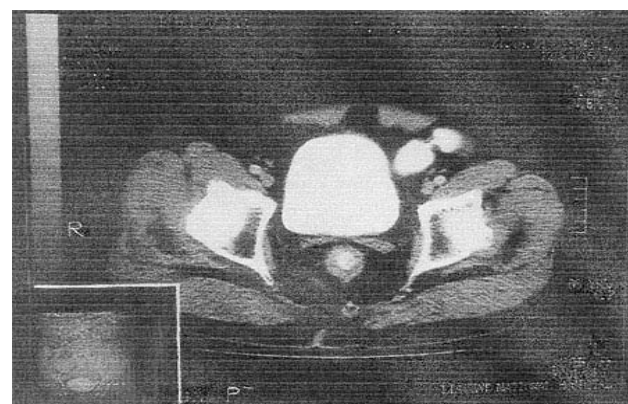


Figure 3. No evidence of tumor was observed after 16 months follow-up.

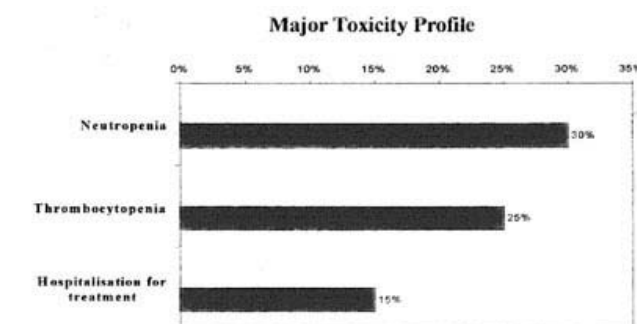


Figure 4.

Statistical Analysis

Data was collected through specifically designed Clinical Report Forms (CRF). Data analysis was done on SPSS (statistical package for social sciences). Disease stages and grades and their demographic characteristics classified patients. A total of 20 patients were enrolled for the study. Efficacy of the treatment was estimated by computing the proportion of those patients who showed complete response at the end of the study. 95% confidence

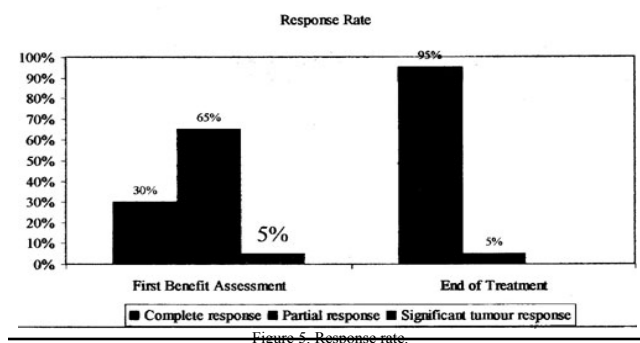


Figure 5. Response rate.

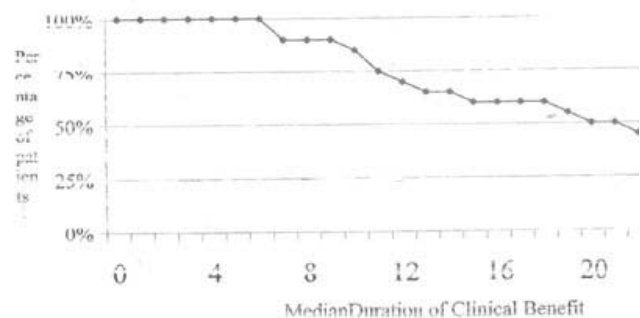


Figure 6. Median duration of clinical benefit.

interval for the estimated complete response rate was constructed by using standard statistical techniques. Median duration of clinical benefit was computed instead of mean duration because median is not sensitive to extreme observations. Sensitivity of the treatment was evaluated by computing the percentages of adverse events.

Width of confidence interval depends on the value of "p" (proportion of success). If a study is being done for the first time and any estimate of success is not available in literature, we assume $p = 0.5$ (50%). However, at $p = 0.5$ we get the maximum width of the confidence interval. On the other hand, smaller the width of the confidence interval, better would be the estimate of efficacy. In present study, $n = 20$ and if we assume $p = 0.5$ then the width of the confidence interval for all rates will be around 18%. This means that your estimates of overall response rate, complete response rate and partial response rate are as shown below:

Overall response rate: $76.7\% \pm 18\%$ i.e., from 58.7% to 94.7%. Complete response rate: $26.7\% \pm 18\%$ i.e., from 8.7% to 44.7%. Partial response rate: $50\% \pm 18\%$ i.e., from 32% to 68%. However, if from previous studies we have some estimates of overall response, complete response and partial response we can reduce the width of these confidence intervals from 18% to a lower number.

For example if overall response rate in previous studies is around 72% then width of the confidence interval will reduce to 14% from 18%. Similarly if previous studies show that complete response rates was around 20% then the

width of confidence interval will reduce to 11% from 18% which means that our estimates will be more precise.

Results

Twenty patients with locally advanced TCC of urinary bladder were enrolled in the study. Most patients (95%) had stage III, one with stage IV (5%) disease. All the patients were evaluable for toxicity; 20 were evaluable for

Table 1. Patients characteristics (n=20).

Characteristics	No of patients
Age	45 to 80 years
Range	60.5 years
Median age	
Sex	
Male	13 (65%)
Female	7 (35%)
Stage	
III	19 (95%)
IV	1 (5%)
Grade	
II	2 (10%)
III	17 (85%)
IV	1 (5%)
Intravesical chemotherapy	4 (20%)
Karnofsky performance status	
70	5 (25%)
80	5 (25%)

Table 2. Toxicity using National Cancer Institute Common Toxicity Criteria.

Symptoms	Grade 1-2		Grade 3		Grade 4	
	n	%	n	%	n	%
Nausea/vomiting	8	40	2	10	-	-
Alopecia	2	10	-	-	-	-
Neutropenia	4	20	2	10	-	-
Thrombocytopenia	4	20	1	5	-	-
Anemia	3	15	-	-	-	-
Mucositis	-	-	1	5	1	5
Flue-like syndrome	1	5	-	-	-	-
Hearing loss	-	-	-	-	-	-
Skin rash	-	-	-	-	-	-
Liver toxicity	-	-	-	-	-	-

response. None of the patients was lost to follow-up. The median duration of clinical benefit was 21 months. The complete response (CR) was 95%. The confidence interval (CI) was 95%; level of confidence interval ranged from 85% to 100%. Grade 3 to 4 neutropenia, thrombocytopenia was observed in 30% and 15% of patients respectively. 25% patients required hospitalisation for diarrhea, nausea/vomiting and dehydration. Three patients received 4 cycles; five received 5 cycles and twelve received 6 cycles of above mentioned chemotherapy regimen. Those who exhibited CR were shifted to radiotherapy, except one patient who had stage IV disease (Tables 1 and 2).

Discussion

Transitional cell carcinoma of urinary bladder is a chemosensitive tumor as demonstrated by over-all response rate 35-70% with the M-VAC.^{16,17} However, the toxicity of this regimen is significant and the median survival of all treated patients does not exceed twelve months.^{18,19}

Encouraging results have been obtained using new combination such as gemcitabine - cisplatin, paclitaxel, docetaxel. In vitro evidence suggests that cisplatin and gemcitabine have a synergistic activity.²⁰ Studies also showed that gemcitabine radiosensitizes a wide variety of rodent and human tumor cell culture. Maximum radiosensitization occurs in a cell that demonstrates concurrent redistribution into 'S' phase and d-adenosine triphosphate pool depletion. Although the mechanism of sensitization is not yet clear, recent evidence suggests that gemcitabine lowers the threshold for radiation induced apoptosis.²¹ Several phase II and III trials compared gemcitabine-cisplatin with M-VAC in patients with advanced bladder cancer. No significant difference in response rate, time to disease progression or median survival between the two arms was noted.

Comparable efficacy but better tolerability; gemcitabine-cisplatin offers an alternative to M-VAC in treatment of TCC.²² Single agent gemcitabine may be useful in older patients or those with poor renal function or as second line therapy.^{23,24}

In this study, we evaluated the activity and toxicity of gemcitabine as a first line treatment in locally advanced or metastatic bladder cancer; without cystectomy. Our secondary objective was to find the impact of adjuvant radiotherapy on disease free survival and bladder preservation.

The results with respects to response rate and disease free survival were encouraging in our study: the response rate was relatively higher to that obtained using cisplatin-containing regimens, and the median survival has enhanced possibly because we added radiotherapy. In fact the phase II

and III trials used 1000mg/m² of gemcitabine on days 1, 8 and 15 and cisplatin 75mg/m² on day 1; in contrast to our study which comprises gemcitabine 1250mg/m² on day 1 and 8 and cisplatin 75mg/m² after every 4 weeks from day one. Radiotherapy was delivered followed by chemotherapy with the gap of at least 3 weeks.

In our experience the combination of gemcitabine and cisplatin followed by radiotherapy was very well tolerated. Disease free survival was also enhanced; further studies are required on large scale using the same protocol, especially to evaluate the dose time and fractions of radiotherapy. This will help in future; to further modify the standard treatment of locally advanced or metastatic bladder cancer; without cystectomy.

In conclusion, combined chemotherapy with gemcitabine and cisplatin followed by radical radiotherapy is feasible and well tolerated. The proposed schedule and doses may be of interest for further trials, including a randomised study comparing it with other cisplatin-based regimens and role of cystectomy.

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