EFFICACY OF COMBINATION CHEMOTHERAPY; GEMCITABINE AND DOCETAXEL, IN PATIENTS WITH ADVANCED URINARY BLADDER CARCINOMA

Sameed Hussain, Abdus Samad Syed, Fauzia Abdus Samad*, Nabeela Awan

Combined Military Hospital Rawalpindi, *Fauji Foundation Hospital Rawalpindi

ABSTRACT

Objective: To evaluate the efficacy of combination chemotherapy; gemcitabine and docetaxel, in terms of objective response, in advanced urothelial carcinoma of urinary bladder.

Study Design: Quasi-experimental study.

Place and Duration of Study: Oncology Department of Combined Military Hospital Rawalpindi, from Oct 2012 to July 2013.

Patients and Methods: Fifty one patients with histologically confirmed urothelialcarcionoma of the bladder were enrolled into this study. Patients were staged and their radiological features were documented before chemotherapy. Four cycles of gemcitabine and docetaxel; combination chemotherapy were administered to the patients. Response was evaluated after 4 courses. Patients with progressive disease were not given further chemotherapy. Patients who could not complete 4 courses were excluded from the study. Remaining patients were given 2 more courses of chemotherapy. Patients were followed up for a period of 1 year after being enrolled for the study to document median survival.

Results: Total 46 patients were included in the study out of which 2.2% patients had a complete response, 37% had a partial response, 28.3% patients had a stable disease while 32.6% patients had a progressive disease. The objective response rate was 39.2% while the median survival time was 42 weeks.

Conclusion: The results of our study have shown that combination of gemcitabine and docetaxel in patients with advanced urothelial carcinoma of the urinary bladder, has a good therapeutic index and stands as a reasonable first line option for such patients.

Keywords: Docetaxel, Gemcitabine, Urothelial carcinoma bladder

INTRODUCTION

Transitional cell carcinoma of the urinary bladder is the fourth most common cancer in men and ninth most common cancer in the females[1,2]. Male to female ratio is 3:12. Of patients with muscle invasive carcinoma of the bladder, about 50% develop pelvic recurrence or distant metastases[3]. Transitional cell carcinoma of the bladder is a chemosensitive neoplasm. The development of the MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimen marked a big step forward in the treatment of patients with advanced disease. Despite the good efficacy shown by this regimen, its short comings were noticed as regards its toxicity and recurrence after therapy[4,5]. The objective response rates with MVAC was 35-45% and median survival was 12 months in metastatic bladder carcinoma[6,7]. As a result, a combination of cisplatin and gemcitabine was developed with an aim of increasing median survival but its toxicity was also an issue[4]. Thus, newer agents were sought with both improved activity and tolerability. Among the most important of these newer agents are taxanes.

During the last decade, several new chemotherapeutic agents have shown activity against advanced transitional cell urinary bladder carcinoma, including docetaxel and gemcitabine. The mechanism of action of gemcitabine and docetaxel are different from cisplatin. Docetaxel is an anti microtubule agent and acts by high affinity binding to microtubules causing their polymerisation and thus inhibition of mitosis and cell division. Gemcitabine is an antimetabolite which kills tumor cells in S phase of cell cycle by incorporating in DNA as diphosphates and triphosphates[8]. These two agent act in a synergistic manner as Docetaxel acts in M

Correspondence: Dr Sameed Hussain, Oncology Dept, CMH Rawalpindi
Email: drsameed@gmail.com
Received: 07 Jul 2014; Accepted: 30 Oct 2014

phase while Gemcitabine acts in S phase; thus blocking the cell cycle at two different points in the cell cycle. Cisplatin which has been used previously is a nephrotoxic agent. A significant number of patients of bladder carcinoma have associated hydronephroureter, resulting in deranged renal profile. These patients cannot be given Cisplatin as first line agent. Docetaxel has no renal toxcicity and thus can replace Cisplatin in such circumstances.

For this reason the combination of these two agents i.e docetaxel and gemcitabine is thought to be more effective than standard regimens of M-VAC and gemcitabine and cisplatin[9]. A previous study measuring the effect of docetaxel therapy showed complete response in 7.4% of cases, partial response in 25.9%, stable disease in 18.5% and progressive disease in 40.7% of cases of advanced urothelial carcinoma[10]. This study is aimed at evaluating the efficacy of combination chemotherapy; gemcitabine and docetaxel, in terms of objective response, as an alternate to combination of gemcitabine and cisplatin in advanced bladder carcinoma.

PATIENTS AND METHODS

This quasi-experimental study was conducted at Oncology Department, CMH Rawalpindi. Eligible patients had histologically proven urothelial carcinoma of the bladder. A total of 51 patients were enrolled in this study. Patients had one of the following three features; a) inoperable T4 disease (tumor involving prostatic urethra, vagina, uterus, pelvic wall or abdominal wall), b) presence of LN in pelvis on imaging with size >1 cm in short axis diameter, c) radiologically confirmed metastatic disease. All patients had an ECOG performance status of < 2. Adequate bone marrow reserve was mandatory with TLC > 3000/mm^3, Hb> 10 g/dL and platelets > 75000/mm^3. Adequate renal and hepatic function was required as well with ALT and bilirubin within normal limits. Serum creatinine between 70-120 mmol/L and urea 3.8-6.2 mg/dL was required. No patient more than 75 years of age was included in the study. Patients who had prior chemotherapy or a previous malignancy other than urothelial carcinoma of the bladder were excluded from the study.

All eligible patients were subjected to maximal transurethral removal of bladder tumour (TURBT) before chemotherapy. CT scan of chest, abdomen and pelvis were done in all patients to document extent of primary disease, hepatic metastasis or pulmonary metastasis. Bidimentional measurement of tumor was documented at baseline. Non measurable lesions like skeletal metastasis were only mentioned as present or absent. Patient's name, height, weight, age, sex and contact number were recorded in all cases. Informed written consent was taken from all patients. All patients underwent blood complete picture, liver function tests, serum urea and creatinine before each course of chemotherapy.

All patients were started on 8mg of oral dexamethasone, twice daily, one day prior to start of each cycle. All patients were administered 8 mg of intravenous dexamethasone and 50 mg of ranitidine before administering chemotherapy on day-1. Gemcitabine 1250 mg/m^2 was given in 250 mL 0.9% N/S over 30 min and docetexal was given in dose of 80 mg/m^2 in 500mL 0.9% N/S over 1 hour on day-1. Gemcitabine was repeated on day-8 in same dose without any premedication. Only Blood complete picture was done before administration of gemcitabine on day-8. This cycle was repeated every 21 days for a total of 4-6 cycles.

Dose adjustment was considered when haematological, renal or hepatic tocxicity was encountered. Dose was delayed by a week in patients with absolute neutrophil count of < 1500/mm^3 or platelet count of < 50000/mm^3. Patients developing haematological toxicities were given prophylactic G-CSF with next course of chemotherapy. Patients with prolonged neutropenia or thrombocytopenia i.e, persisting for more than 2 weeks were withdrawn from the study. No dose reduction of gemcitabine was required for hepatic or renal profile derangement. Docetaxel was omitted. No dose reduction was required for docetaxel in face of renal profile derangement, however, no further docetaxel was given when bilirubin

level was above normal range or ALT was more than 1.5 times the upper limit.

Response evaluation was done with CT scan after administration of four courses of chemotherapy, using the RECIST criteria. Complete response was defined as total disappearance of all target lesions. Partial response was defined as at least 30% decrease in the tumor dimensions. Progressive disease was defined as a 20% increase in the dimension of the target lesion or appearance of new lesions. All above responses were measured after an interval of four weeks. First assessment was carried out after two courses of chemotherapy and second assessment was done after four courses. If progressive disease was seen after two or four courses, no further chemotherapy was given. If a complete or partial response or a stable disease was seen after administration of four courses of

Table-1: Showing demographic and study variables (n=46).

Variables	Frequency (%)
Male	37 (80.4)
Female	9 (19.6)
STAGE	
T4 N0 M0	23 (50)
Any T N1 M0	7 (15.2)
Lung mets	8 (17.4)
Liver mets	7 (15.2)
Others	1 (2.2)
AGE	
Range	42-74
Mean	64.57 (SD +6.514)
Performance Status	
ECOG 0	10 (21.7)
ECOG 1	21 (45.6)
ECOG 2	15 (32.6)
No of chemo cycles	
6	31 (67.4)
4	15 (32.6)
Response	
CR	1 (2.2)
PR	17 (37.0)
SD	13 (28.3)
PD	15 (32.6)
Objective Response (CR + PR)	18 (39.2)

Table-2: Showing comparison with other studies.

Study	Chemotherapy	Objective response	Median survival (months)
Witte. et al[11]	Ifosfamide	20%	
Lorruse. et al[12]	Gemcitabine	22.5%	
Albers et al[13]	Gemcitabine	11%	
McCaffery et al[14]	Docetaxel	13% PR	
Sternberg et al[15]	Gemcitabine/ Paclitaxel	60%	14.4
Gitlitz et al[10]	Gemcitabine/ Docetaxel	33.3%	12
Hussain et al (Current study)	Gemcitabine/ Docetaxel	39.2 %	9.5

chemotherapy, two further courses of chemotherapy were administered. An objective response included both complete and partial response.

Survival times were measured from date of enrollment into study to date of death or date at which patient was last known to be alive. Patients declining further treatment were contacted monthly to assess survival duration. The severity of adverse events were graded according to NCI-CTC version 3.0. Data was analyzed through SPSS version 16. Descriptive statistics were used to describe the results.

RESULTS

Fifty one patients (40 males and 11 females) of histologically proven urothelial carcinoma of bladder were enrolled into this study. Thirty one (60.8%) patients were administered all 6 cycles of chemotherapy. Fifteen (29.41%) patients were administered four cycles of chemotherapy. Two (3.9%) patients were administered two cycles of chemotherapy whereas 3 (5.9%) patients were given only one course (table-1). (Out of 3 patients who receivedone course of chemotherapy, 2 developed grade IV neutropenia which persisted for more than 2 weeks, so they were withdrawn from the study while one patient refused to undergo any further chemotherapy after administration of first course. One patient developed hepatic profile derangement, warranting withdrawl from study after administration of 2nd course of chemotherapy. Neutropenia and thrombocytopenia were seen as dose limiting toxicities in 3 and 1 patients respectively). Five patients, who could not complete four courses of chemotherapy were withdrawn from study.

Five patients developed renal impairment and required percutaneous nephrostomy for correction of renal derangement after chemotherapy was started. However this renal impairment was not due to chemotherapy and was due to already existing or developing hydronephroureter due to the location of primary tumor. This resulted in delay in administration of chemotherapy but these patients were not withdrawn from study.

Forty six evaluable patients who completed 4 courses of chemotherapy, underwent CT scan for response evaluation. Only 1 (2.2%) patient showed a complete response, 17 (37%) showed a partial response, 15 (32.6%) showed a progressive disease, 13 (28.3%) showed stable disease. The objective response (complete and partial response) rate was 39.2%.

Mean age at diagnosis was 64.8 years. All underwent CT scan of the pelvis, abdomen and chest for accurate staging. A T4a/b disease was labeled in 23 (45%) patients without involvement of pelvic lymph nodes (LN) or distant metastasis. Out of 46 patients, 7 (15.2%) had radiological LN involvement without evidence of distant metastasis. Eight (17.4%) patients had pulmonary metastases and 7 (15.2%) patients had hepatic metastases. One (2.2%) patient had skeletal metastasis which was confirmed by bone scan.

Median survival was 40 weeks. It ranged from 8 weeks to 52 weeks. Seven (15.2%) patients were alive at the end of follow up period of 52 weeks. They were not followed beyond 52 weeks as it did not affect the median survival.

DISCUSSION

Commonly used chemotherapeutic regimens like combination of gemcitabine and cisplatin or MVAC have a low therapeutic index i.e they are considerably toxic and the efficacy is only modest at best[6,7,10]. The efficacy of gemcitabine and docetaxel is also modest with a response rate of only 39.2% but the therapeutic index of this combination is better as demonstrated by this study. There were only four instances of hematological dose limiting toxicities. Only one patient developed dose limiting hepatic toxicity warranting discontinuation of chemotherapy. Results of some previous trials are shown in table-2 .

The combination of gemcitabine and paclitaxel showed a response rate of 60% which showed that combination chemotherapy can be more effective than single agents in cases of advanced bladder carcinoma[15]. Gitlitz et al used the same regimen as used in this study[10]. The response rate was slightly less than current

study but the survival rates were better by 3 months. Response rates with single agents are less as compared to combination chemotherapy with response rates reaching 20% on two instances[11-14].

Combination of gemcitabine and cisplatin is the standard of care in advanced bladder carcinoma[16]. This has been proven by a phase III study which compared gemcitabine and cisplatin with the traditionally used combination chemotherapy M-VAC[16]. However cisplatin is a nephrotoxic drug and thus, is of limited use in patients with renal profile derangement. Docetaxel can be a reasonable alternate to cisplatin in such cases. Current study was not aimed at proving superiority of docetaxel over cisplatin. However the response rate of around 35% makes docetaxel a reasonable option in advanced bladder carcinoma. The therapeutic index of gemcitabine and cisplatin is inferior to gemcitabine and docetaxel in such patients with increased urea and creatinine.

Future phase III trials comparing gemicitabine and docetaxel with gemcitabine and cisplatin would be required to demonstrate the superiority of one regimen over the other. Till then combination of gemcitabine and docetaxel cannot be recommended to be the only first line regimen in cases of advanced bladder carcinoma based on results of this trial. However results of this trial are encouraging with an objective response rate of 35%, and can form basis for future phase III trials. But it should be kept in mind that combination of gemcitabine and cisplatin does not remain an automatic first line choice as many patients have elevated serum urea and creatinine due to ureteric orifice involvement. In such a situation combination of gemcitabine and docetaxel can serve as an appropriate first line choice.

CONCLUSION

Results of our study have shown that combination of gemcitabine and docetaxel is a reasonable regimen for advanced urothelial carcinoma of the bladder with a good therapeutic index, mainly attributable to low toxicity of this regimen.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Yafi FA, North S, Kassouf W. First- and second-line therapy for metastatic urothelial carcinoma of the bladder. CurrOncol. 2011; 18: e25–e34.
2. Ismaili N, Amzerin M, Flechon A. Chemotherapy in advanced bladder cancer: current status and future. J HematolOncol. 2011; 4: 35.
3. So A. Perioperative chemotherapy: the case for adjuvant chemotherapy for muscle-invasive bladder cancer. Can UrolAssoc J. 2008; 2: 225–227.
4. deVos FYFL, de Wit R. Choosing chemotherapy in patients with advanced urothelial cell cancer who are unfit to receive cisplatin-based chemotherapy. TherAdv Med Oncol. 2010; 2: 381–8.
5. Tsukamoto T, Yonese J, Ohkubo Y, Fukui I.Phase I/II study of a combined gemcitabine, etoposide, and cisplatin chemotherapy regimen for metastatic urothelial carcinoma. Cancer2006; 106: 2363–8
6. Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, et al. Long term follow up of a Phase III intergroup study of cisplatin alone or in combination with methotrexate , vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J ClinOncol. 1997;15:2564-2570.
7. Stadler WM, Kuzel TM, Rahgavan D, Levine E, Vogelzang NJ, Roth B, et al. Metastatic bladder cancer : advances in therapy. Eur J Cancer. 1997;;33(Suppl 1):523-526.
8. Chu E, de Vita VT. Physicians' Cancer Chemotherapy Drug Manual. Sadbury, Massachusetts: Jones and Bartlet Publishers; 2008.
9. Dumez H, Martens M, Selleslach J, Guetens G, De Boeck G, Aerts R, et al. Docetaxel and gemcitabine combination therapy in advanced transitional cell carcinoma of the urothelium: results of a phase II and pharmacologic study. Anticancer Drug. 2007; 18:211-8.
10. Gitlitz BJ, Baker C, Chapman Y, Allen HJ, Bosserman LD, Patel R, et al. A phase II study of gemcitabine and docetaxel therapy in patients with advanced urothelial carcinoma. Cancer. 2003 ; 98: 1863–9.
11. Witte RS, Elson P, Bono B, Knop R, Richardson RR, Dreicer R, et al. Eastern Cooperative Oncology Group phase II trial of ifosfamide in treatment of previously treated advanced urothelial carcinoma. J ClinOncol. 1997;15:589-593
12. Lorusso V, Pollera CF, Antimi M, Luporini G, Gridelli C, Frassineti GL, et al. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treatedwith platinum. Eur J Cancer. 1998;34:1208-1212.
13. Albers P, Siener R, Hartlein M, Fallahi M, Haeutle D, Perabo FG, et al. Gemcitabine monotherapy as second line treatment in cisplatin refractory transitional cell carcinoma-prognostic factors for response and improvement of quality of life. Onkologie. 2002;25:47-52.
14. McCaffery JA, Hilton S, Mazumdar M, Sadan S, Kelly WK, ScherHI,et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J ClincOncol. 1997;15:1853-1857.
15. Sternberg CN, Calabro F, Pizzacaro G, Marini L, Schnetzer S, Sella A. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. Cancer. 2001;92:2993-2998.
16. Von der Masse H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer; results of a large , randomized, multinational, multicenter, Phase III study. J ClincOncol. 2000;18:3068-3077.