ORIGINAL ARTICLE ◄

Comparison between the radiosenstizing effect of cisplatin & gemcitabine in locally advanced non metastatic transitional cell carcinoma of the bladder

M. Farouk, MD[1], W. Arafat, MD[1], A. Gewil, MD[1], A. Hassan, MD[2]
(1) Clinical Oncology Department, Faculty of Medicine, Alexandria University
(2) Oncology Department, Medical Research Institute, Alexandria University

✉ *Corresponding Author: Dr Mohamed Farouk Mostafa, MD*
E-mail: mfarouk69m@yahoo.com

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Abstract

Introduction: Bladder cancer is one of the most common malignancies in Egypt. No curative treatment for locally advanced inoperable TCC of the bladder, with radiotherapy alone offering palliation. Cisplatin and gemcitabine are known by having a radiosenstizing effect. **Materials:** Fifty patients with locally advanced TCC of the bladder were randomized into two groups, 25 patients each. **Methods:** Group 1 received pelvic irradiation 60 GY concomitant with weekly gemcitabine 100 mg/m^2, while group 2 received the same radiotherapy course concomitant with weekly cisplatin 30 mg/m^2. Patients were followed up at least for 2 years. **Results:** all patients completed phase I, three patients in each group did not complete phase II. 68%of the patients in group 1 achieved CR in comparison to 64% in group 2, while 20% in group 1 achieved a PR in comparison to 28% in group 2.The most common grade 3 toxicities were diarrhea (24% vs. 12% for group 1 and 2 respectively), nausea (24% vs. 20%) and dysurea (24% vs. 28%). The mean time to disease progression for group 1 was 11.69 m compared to 12.67 m for group 2. At 2 years the overall survival was 68% for group 1 in comparison to 72% for group 2. **Conclusion:** Cisplatin and gemcitabine can be used safely and effectively as radiosentizers in patients with locally advanced TCC of the bladder with remarkable and maintained response rate.

Introduction

Urinary bladder cancer is one of the most common cancers worldwide, with the highest incidence seen in industrialized countries (30 per 100,000 per normal population). In Egypt, the incidence of bladder cancer is much higher in males than in females and till the year 2005, it was ranked as the first malignancy in males, representing 16.2% of all male cancers [1].

The histopathological profile of bladder cancer in Egypt has changed significantly over the past 26 years. Historically, squamous cell carcinoma was the predominant form of bladder cancer in Egypt; however transitional cell carcinoma (TCC) has become the most frequent type [2].

Among Egyptian patients diagnosed as having bladder cancer nearly 25% have inoperable tumors (Locally advanced non-metastatic unresectable) [1]. These patients can only be palliated with definitive radiotherapy alone or followed by chemotherapy [3]. Results of radiotherapy alone for locally advanced unresectable bladder cancer are not satisfactory as the chance of tumor eradication using definitive irradiation may be as high as 66% for solitary T2 tumors but drops to around 9% in cases of advanced multiple tumors with hydronephrosis [3, 4]. Several attempts to improve the response rate to radiotherapy (and hopefully improve the DFS and OS were done, of which the most promising was the use of radio-sensitizers.

Cisplatin was used as a radiosensitizer in several phase II studies with higher response rates (especially CR), better pelvic control than radiotherapy alone, but no difference in the incidence of distant metastasis [5-7].

Also, gemcitabin was discovered to have a radiosensitizing effect. Several phase I and II studies evaluated its efficacy in bladder cancer with very promising results [8-12].

Aim of the study: The aim of the present study was to compare between the radiosenstizing effect of cisplatin and gemcitabine when given concomitant with pelvic irradiation in locally advanced inoperable bladder cancer as regards the response rate and time to disease progression; also two years survival data are included.

Materials

Between June 2005 and February 2007, a total of fifty patients with locally advanced unresectable TCC of the bladder with no distant metastasis (T3b-T4, any N, and M0) presented at the Clinical Oncology Department, Faculty of Medicine, Alexandria University and Damanhour Oncology Center entered the study. Patients gave their informed consent to the study, and the study had been accepted by the Ethical Committees of each participating hospital.

Eligibility criteria: Patients who offered to enter our protocol are patients with surgically inoperable locally advanced transitional cell carcinoma with no distant metastasis who fulfill the following criteria: age less than 70 years and more than 18 years, good performance status (70 - 100%) according to Karnofsky· s scale [13], no prior pelvic irradiation or chemotherapy and normal hematological, hepatic and renal functions. Grade one and two unilateral or

bilateral hydronephrosis were accepted in absence of elevated renal functions (no renal impairment).

N.B seven patient (four in group 1 and three in group 2 were medically inoperable)

Methods

Pre-treatment evaluation: Our patients were subjected to history taking, physical examination, complete laboratory investigations including complete blood count, liver function profile, renal function profile, urine analysis and cytology, chest x-ray, CT scan of the pelvis, abdomen and chest, isotopic bone scanning, cystoscopy and biopsy for histopathologic documentation.

Treatment protocol: All patients performed cystoscopy with transurethral resection of the bladder tumor (TUR) for pathologic examination, complete TUR was not a prerequisite to enter the study; actually none of our patients did complete TUR before entering the study. The patients were randomized to receive either weekly cisplatin or weekly gemcitabine concomitant with definitive pelvic irradiation. The results of the two treatment groups were compared as regards the complications, the response rate in addition to time to disease recurrence.

Chemotherapy: Concomitant chemo-radiotherapy was started 3-4 weeks after TUR. Patients were randomized to receive either gemcitabine (25 patients) in a dose of 100 mg/ m^2 starting on the middle of the first week of the radiotherapy course and every week thereafter (group 1) or cisplatin as a radiosestizer (25 patients) in a dose of 30 mg/m^2 weekly starting on the middle of the first week of the radiotherapy course and every week thereafter (group 2). No adjuvant chemotherapy was given to any of our patients.

Bladder irradiation: Whole pelvis external beam radiotherapy was used to a total tumor dose of 45Gy / 4.5 weeks (2G / fraction, 5 fractions / week). Radiation fields were directed to the entire bladder, perivesicular tissues, and adjacent lymph nodes using two fields (direct anterior and direct posterior opposing field technique). The upper border was at the level of LV5, lower border at the lower margin obturator foramen, lateral borders 1-2 cm beyond the widest bony margins of the pelvis.

After a period of 2 weeks rest, a boost dose of 20Gy/2weeks (2Gy/fraction, 5 fractions/ week) was given, using three fields technique one direct anterior and 2 lateral posterior oblique fields to the bladder with 1cm safety margin beyond margin of distended bladder to increase tumor dose up to 60Gy.

Localization of the bladder was done under the CT simulation after ascending cystogram with barium in the rectum.

Forty patients were treated using linear accelerator (10 MV) with an SSD of 100 cm, and dose calculation was done using the computer planning system (two dimensions), while the last ten patients who entered the study were treated using 3D conformal radiotherapy with the arrival of our new Elekta linear accelerator. During the course of concomitant chemo-radiotherapy treatment, all patients were monitored for the acute chemo- radiotherapy toxicity with weekly clinical examination, complete blood picture, renal and liver function tests, in addition to urine analysis. Any toxicity observed was recorded according to the NCI / NIH common toxicity criteria grading system. [14] Any patients developed grade III-IV toxicity was provided by supportive measures and radiotherapy was postponed treatment until recovery.

Follow up: All patients were followed up weekly during treatment and every three month after.

Assessment of the response: Assessment of the response was carried out to all patients four weeks after finishing the last radiotherapy session using RECIST criteria [15] by doing CT pelvis and abdomen, urine cytology and cystoscopy with a biopsy of any residual lesion.

Statistical analysis: In addition to the calculation of tumour response rate based on the patient's best response, Kaplan–Meier estimates were calculated for the distribution of time to PD, and the overall survival time.

Results

Patient's characteristics

From June 2005 till February 2007, a total of fifty patients with locally advanced unresectable transitional cell carcinomas of the bladder (TCC) entered the study. Table [1] summarizes the patients' characteristics at base line. The two groups were comparable as regards the clinic-pathologic criteria.

All fifty patients were Egyptians, the mean age for group 1 was 57.4 years as compared to 56.8 years for group 2. Males constituted the majority (70%) of the cases of the study as a whole. The majority of the patients (74%) had a performance status of 90% according to karnofsky scale [13].

The size of the tumor ranges between 2 and 8 CM with a mean size of 3.7 cm for group 1 as compared to 3.9 cm for group 2. The prevalence of smoking as a habit and schestozomiasis as an endemic disease was compararable between the two groups.

Tumors involving one site of the bladder only were seen in 36% of the cases in group 1 compared to 44% in group 2, a difference that was not significant. The right and left lateral walls in addition to the base of the bladder were the most common sites to be involved by the tumor in both groups.

Seventy two (72%) of the patients in group 1 had Non papillary infiltrative tumor as compared to 52% in group 2, a difference that was not statistically significant.

In the gemcitabine group, 68% were having tumors that were considered T3 lesions in comparison to 52% in the cisplatin group; on the other hand, T4 lesions were higher 48% in cisplatin group as compared to 32% only in the gemcitabine group.

Lymph node involvement were nearly comparable in both groups (36% in gemcitabine group as compared to 40% in cisplatin group). Both unilateral and bilateral hydronephrosis were comparable among both groups. Seventy six (76%) of the patients in group 1 had grade III tumors compared to 84% in group 2.

Response to treatment: [table 2]

The response rate (CR & PR) was 88% in the gemcitabine group (group 1) compared to 92% in the cisplatin group (group 2), a difference that is not statistically significant Table[2].

Complete responders were seen in 68% (17 patients) in the gemcitabine group compared to 64% (16 patients) in the cisplatin group, a difference that was not statistically significant.

Two patients progressed in the gemcitabine group in comparison to one patient only in the cisplatin group. When correlating the response rate to the different clinic-pathologic criteria, the size of the tumor, the grade of the tumor, the depth of tumor invasion and lymph node positivity where considered the most important prognostic factors, table [3]

Time to disease progression and two years survival

The time to disease progression was nearly identical among both groups; the mean time to disease progression was 11.69 months in group 1 compared to 12.69 months in group 2, a difference that was not statistically significant.

A minimum follow up of two years was done to all patients (two patients lost follow up in group one and one patient in group two), at two years 68% of the gemcitabine group were alive compared to 72% in the cisplatin group, again the difference was not statistically significant. [Table 4 and figure 1]

Toxicity

Symptoms of bladder irritability in the form of increased frequency and dysurea in addition of gastrointestinal symptoms in the form of nausea vomiting and proctatitis were encountered in all patients receiving the two protocols, and these symptoms were responsible for the discontinuation of the treatment after phase one radiotherapy in three patients in each of the treatment groups. On the other hand hematological toxicities were minimal.

The most common grade 3 toxicities encountered in group 1(gemcitabine) were nausea, diarrhea and dysurea occurring in nearly 24% of the patients each. While dysurea, nausea, vomiting and diarrhea were the most common toxicities occurring in group 2 (cisplatin) (28, 20, 12 and 12% respectively). [Table 5].

Discussion

The problem of dealing with locally advanced non-metastatic transitional cell carcinoma of the bladder in Egypt is of concern, as bladder cancer is ranked as first in incidence among male patients, of them, nearly 25% will have locally advanced non-metastatic disease [1].

This study was done following several reports demonstrating the radiosenstizing activity of cisplatin [4-7] and gemcitabine [8-12] in unresectable transitional cell carcinoma of the bladder.

In our study Seventeen patients (68%) in group 1 who received gemcitabine as radiosenstizer achieved complete response in comparison to sixteen patients (64%) in group 2 who received cisplatin as radiosensrizer, while five patients (20%) in group 1 achieved a partial response in comparison to seven patients (28%) in group 2, thus a response rate of 88% in group 1 was achieved in comparison to 92% in group 2, a difference which is not statistically significant.

Our response rates are comparable to the response rate obtained in the study done by patel et al. evaluating the a single institution experience with concurrent capecitabine and radiation therapy in weak and/or elderly patients with urothelial cancer in which a 77% complete response was achieved [16].

Hussain sa et al published in 2004 the results of synchronous mitomycin and fluorouracil in forty one patients with locally advanced bladder cancer with 71% of the patients achieving complete macroscopic response [17].

A complete response rate of 76,6% was achieved in patients with locally advanced bladder cancer treated by multimodality therapy (maximum TUR, chemotherapy and radiotherapy) in the study done by George et al. and published in urology 2004[18].

In our study, the mean time to disease progression was 11.69 months in group (1) receiving gemcitabine compared to 12.69 months in group (2) receiving cisplatin , a difference that was not statistically significant, in addition, at two years, 68% of the gemcitabine group were alive compared to 72% in the cisplatin group , again the difference was not statistically significant.

In the study done by Hussain et al[17]., at two years only 49% of the patients were alive , this poor survival rate could be explained by the more active sensitizing effect of both gemcitabine and cisplatin in comparison to mitomycin and fluorouracil, or may be explained by a better performance status of our patients.

In a retrospective analysis of patients with bladder cancer treated by definitive radiotherapy alone, the two years overall survival was nearly 40%[19], which is much inferior when compared to the use of concomitant chemo-radiotherapy.

In our study grade three diarrhea occurred in 24% of the patients receiving gemcitabine in comparison to only 12% in patients receiving cisplatin, this was comparable to 29% incidence of grade three diarrhea with the use of capecitabine in the study done by patel et al.[16] while the incidence of grade three diarrhea was only 10% in the study done by hussain et al[17].

While grade three dysurea was seen in 24 and 28% in group one and group two respectively, its incidence was only 2.5% in the study done by Hussain et al[17] and no one in patel´s study developed such grade three toxicity[16].

Fatigue was one of the most common side effects encountered in the study done by Patel et al[16] it was not seen in any of our patients or any of the patients in the study done by Hussain et al. [17]

Conclusions

The toxicity profiles of both gemcitabine in the dose of 100 mg/ m^2 and cisplatin in the dose of 30 mg/m^2 when used as a radiosenstizers are very tolerable with minimal dose limiting toxicities.

Definitive radiotherapy with either cisplatin or gemcitabine as radiosenstizers are considered reasonable and effective treatment modalities for the group of patients with locally advanced irresectable cancer bladder instead of either palliative radiotherapy alone or palliative chemotherapy alone as these radiosenstizing agents will afford a reasonable meaningful long term remissions for those who will achieve complete response.

Conflict of interest statement

No conflict of interest for any of the participating authors.

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Tables

Table 1: Comparison between the two studied groups regarding clinico-pathologic criteria.

	Group 1 Gemzar		Group 2 Cisplatin		P
	No.	%	No.	%	
Age					
< 50 years	6	24.0	6	24.0	
> 50 years	19	76.0	19	76.0	
Range	43 - 66		44 – 67		
Mean±S.D.	57.40±7.194		56.88±6.704		0.793
Sex					
Female	7	28.0	8	32.0	0.780
Male	18	72.0	17	68.0	
P. status					
80%	28%		24%		
90%	72%		76%		0.753
Size (cm)					
Range	2 - 8		2 – 8		
Mean± S.D.	3.64±1.598		3.88±1.833		0.624
BILH.	15	60.0	13	52.0	0.388
SMOK.	15	60.0	13	52.0	0.388
HEAM.	25	100.0	25	100.0	-
DYSUREA	20	80.0	18	72.0	0.371
NECROT.	5	20.0	12	48.0	0.036*
PATHOL.					
Non papill. Infiltrative	18	72.0	13	52.0	
Papillary	7	28.0	12	48.0	0.122
SITE					
Anterior wall	2	8.0%	0	0.0%	
Base	2	8.0%	5	20.0%	
Both lateral walls	4	16.0%	3	12.0%	
Lt lateral wall and base	6	24.0%	5	20.0%	43.33
Neck	1	4.0%	0	0.0%	0.0001*
Posterior wall	2	8.0%	1	4.0%	
Rt lateral wall and base	6	24.0%	7	28.0%	
Trigone	2	8.0%	4	16.0%	
Grade					
G2	6	24.0	4	16.0	0.363
G3	19	76.0	21	84.0	
Depth of invasion					
T3	17	68.0	13	52.0	0.193
T4	8	32.0	12	48.0	
Positive LN	9	36.0	10	40.0	0.50

Table 2: Response in the two studied groups.

	Gemzar		Cisplatin		P
	No.	%	No.	%	
CR	17	68.0	16	64.0	
PR	5	20.0	7	28.0	0.874
PD	2	8.0	1	4.0	
SD	1	4.0	1	4.0	

Table 3: Correlation between the response rate and the most important clinic-pathologic criteria.

	CR & PR "n=45"		SD & PD "n=5"		P
	No.	%	No.	%	
Age					
< 50 years	11	24.4	1	20.0	0.82
> 50 years	34	75.6	4	80.0	
Sex					
Male	14	31.1	4	80.0	0.03*
Female	31	68.9	1	20.0	
P. status					
Range	80 - 90		80 - 90		0.36
Mean±S.D.	87.33±4.47		88.0±4.47		
Size (cm)					
Range	2 - 8		4 - 8		0.0105*
Mean±S.D.	3.59±1.54		6.0±1.41		
Grade					
G2	5	11.1	5	100.0	0.00041*
G 3	40	88.9	0	0.0	
T stage					
T3	30	66.7	0	0.0	0.0031*
T4	15	33.3	5	100.0	
L.N					
Positive	14	31.1	5	100.0	0.002*
Negative	31	68.9	0	0.0	

Table 4: Comparison between the two studied groups regarding time to disease progression.

Time to disease progression	Gemzar	Cisplatin	P
Range	3 - 20	2 – 20	0.316
Mean	11.69±4.64	12.67±5.37	
S.D.			
Survive at 2 years	17/25 68.0%	18/25 72.0%	0.352

Table 5: The most common grade three toxicity in both groups.

	Gemcitabine		Cisplatin		P
	No.	%	No.	%	
Nausea (G3)	6	24.0	5	20.0	0.75
Vomiting (G3)	3	12.0	3	12.0	1.0
Diarrhea (G3)	6	24.0	3	12.0	0.232
Proctatitis (G3)	1	4.0	0	0.0	0.312
Dysurea (G3)	6	24.0	7	28.0	0.75
Frequency (G3)	3	12.0	2	8.0	0.637
R. Dermatitis (G3)	4	16.0	0	0.0	0.024*
(G4)	1	4.0	0	0.0	
Leucopenea (G3)	2	8.0	2	8.0	1.0
Thrombocytopenea (G3)	2	8.0	1	4.0	0.55

Figures

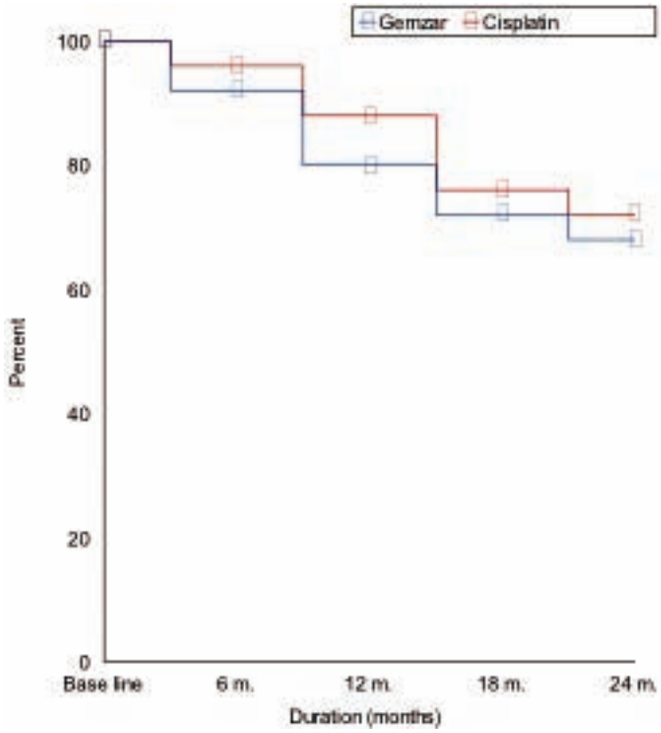

Fig 1: Kaplan-Meier survival curve for 2 years.