Bacillus Calmette-Guérin versus Gemcitabine for Intravesical Therapy in Intermediate and High-Risk Superficial Bladder Cancer

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Abstract: Bacillus Calmette Guerin (BCG) has been the mainstay of intravesical treatment, however, its clinical effectiveness is accompanied by a wide range of adverse events. Gemcitabine has a good safety profile with promising features for the use against intermediate risk non-muscle invasive bladder cancer (NMIBC). It can be a potential chemotherapeutic drug for high- risk patients. The aim of this study was to evaluate the safety and efficacy of adjuvant intravesical gemcitabine versus BCG in the treatment of intermediate and high -risk NMIBC. Patients and methods: Between May 2006 and April 2008, a total of 57 patients were randomized into 2 groups; group I: 28 patients, were treated with six weekly intravesical instillation of BCG and group II: 29 patients, received six weekly intravesical grmcitabine. Patients were evaluated for response, at 8 weeks, then every 3 months. Outcome measures were response rate, overall recurrence rate, progression rate, median recurrence free period, median progression free period and 1-year recurrence free survival. Treatment related complications were also evaluated. Results: For intermediate risk patients, there was no significant difference between the two groups in the complete response (CR) rate (93.3% vs. 87.5%), the overall recurrence rate (33.3%vs.25%), the progression rate (6.7% vs. 6.2%), and the median progression free period (13 vs. 16 months). However, the median recurrence free period was longer for group I compared to group II (18.5 vs. 15 months) and the difference was statistically significant. Kaplan-Meier curve showed that there was no significant difference between the two groups in the 1-year recurrence free survival (95.3% vs. 98.7%) and the median recurrence free survival (22 vs.18 months). For high risk patients there was no significant difference between the 2groups in CR rate (61.5% vs. 76.9%), the progression rate (15.4% for both groups) the median recurrence free period (15 vs. 14 months) and the median progression free period (17 vs. 15 months). However, the overall recurrence rate of group I was lower than that of group II (7.7% vs. 30.8%) and the difference was statistically significant. Kaplan-Meier curve showed that there was no significant difference between the two groups in the 1-year recurrence free survival (76.9% vs. 69.2%) and the median recurrence free survival (18 vs.15 months). The adverse events of group I were more marked than that of group II. Conclusion: Gemcitabine is active and well tolerated for intravesical instillation.It is considered to be an efficient treatment for intermediate risk NMIBC. However, for high- risk group, it is inferior to BCG, but owing to its favorable toxicity profile, it may be useful for patients intolerant to BCG.

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1. Introduction

Transitional cell carcinoma (TCC) is the second most common urologic malignancy, and 70% of patients present with superficial, or non-muscle invasive disease (NMIBC)[1]. The probability of recurrence is about 60% within one year and 80% within five years. Risk of tumour progression to muscle invasion is about 17% to 45% in one to five years respectively [2]. ../Administrator/My Documents/Downloads/paper0/article.asp.htm -ref1Chemotherapy and immunotherapy with bacillus Calmette-Gue´rin (BCG); are the main forms of intravesical instillation therapy following transurethral resection (TURBT)[3]. The goals of intravesical therapy are to avoid post-TURB implantation of tumour cells, eradicate residual disease, prevent tumour recurrence, and delay or reduce tumour progression[4]. Chemotherapy reduces recurrence frequency and, therefore, further resection requirements, and BCG treatment is reported to delay the progression of high-risk tumours[5].

The intermediate-risk disease can be treated with either immunotherapy with BCG or chemotherapy, and BCG is now the treatment of choice for high-risk tumours[6]. Unfortunately, approximately 20% of patients discontinue BCG due to local and systemic toxicity and more than 30% show evidence of recurrence; this has led to increased interest in alternate chemotherapeutic agents. Induction intravesical chemotherapy has shown comparable efficacy to BCG in select patients and the immediate perioperative instillation of chemotherapeutic agents has become standard of

care[1].

Gemcitabine is a novel deoxycytidine analogue with a broad spectrum of anti-tumour activity. Its pharmacokinetic properties also make gemcitabine an ideal candidate for regional therapy. Gemcitabine seems to have fulfilled the requirements to be a promising new candidate for standard intravesical therapy in NMIBC[7].

2. PATIENTS AND METHODS

Inclusion and exclusion criteria:

Patients with NMIBC scheduled to undergo curative resection by TURBT at the department of Urology, South Egypt Cancer Institute and oncology department, Assiut University hospital were enrolled into this prospective study. Between May 2006 to April 2008 a total of 69 patients were involved in this study.The cutoff date of the analysis of the outcome was April 2008 ,corresponding to 1 year of follow up for the last patient enrolled in the study.Patients were randomized into 2 groups;35 patients in group I and 34 patients in group II. However, 7 patients in group I discontued treatment primarily because of marked treatment toxicity and 5 patients in group II discontued treatment;1 patient due to severe haematurea and the other 4 patients were missed due to unknown causes. Eligible patients were those with intermediate and high-risk NMIBC, based on the European Organization for Research and Treatment of Cancer scoring system(EORTC) [2]. Intermediate risk patients included: multiple grade 1 stage T1 tumours, grade 2 stage Ta tumours and a single grade 2 stage T1 tumours. High risk patients included: multiple grade 2 stage T1 tumours, grade 3 stages Ta and T1 tumours, and carcinoma in situ. Informed consent, a WHO performance status of 0–2, WBC > 3000, PLT > 100.000, Hb_> 10 g/dl, renal and hepatic function values not exceeding 2 times the upper normal value were also required for study entry. Patients were excluded from the study if they were considered to have low-risk NMIBC i.e. single grade 1,2 stage Ta tumour , or had any other severe illness. Concomitant or recurrent urinary tract infections and the presence of significant urological disease interfering with intravesical therapy constituted exclusion criteria. Patients were enrolled consecutively to the study and randomized to either group I or group II. The pre-treatment assessments included a full medical history and examination, plain chest X ray, urine culture, full blood count, and liver and kidney function.

Treatment schedule and toxicity monitoring:

Group I patients received six weekly intravesical instillations of BCG (Pasteur strain) 150 mg in 50 ml saline. Group II received intravesical instillations of 2000 mg of gemcitabine in 50 ml of normal saline (0.9%) with a final concentration of 40 mg/ ml. The pH of the reconstituted solution varied between 2 and 3 and no buffering was adopted. The patients were asked to avoid urinating for 1 hour after the instillation. Protocol therapy consisted of 6 weekly instillations to be started within 15 days of the TUR. Urine cytology, urine culture, full blood count, and liver and renal function were assessed.

Toxicity was assessed with the use of the Common Toxicity Criteria version 3.0 Table (4-a) [8]. Grade 3 side-effects resulted in patients' exclusion from the study. In case of grade 2 toxicity, the treatment was delayed for 1 wk and repeated. If toxicity relapsed at grade 2, the treatment was stopped. Side-effects were checked after each instillation and recorded in the database.

Evaluation:

Outcome measures were response status, recurrence status and overall recurrence rate, progression status and overall progression rate, median recurrence free period and progression free period. 1-year recurrence free survival,median recurrence free survival and treatment related complications were also evaluated. Patients' response status was defined at cystoscopy as complete responders (CRs; i.e., absence of any macroscopic residual lesion, confirmed by negative histology and cytology) and non responders (NRs; i.e., presence of any residual lesion). Recurrence was determined by lesions that were detected at cystoscopy and pathologically confirmed after TUR, and Progression was defined as an increase in tumour stage and grade. The recurrence and the progression rate was defined as the percentage of recurring or progressing patients at 1-year follow-up. Recurrence free period was defined as the time from TUR to the date of the first recurrence and the progression free period was defined as the time between TUR and first progression. 1-year recurrence free survival was defined as the time from the date of TUR to the date of recurrence or last follow-up among patients who achieved a CR at 1-year follow-up.

Statistical analysis:

Data were recorded on specialized forms and all statistical tests were performed using SPSS version 16 for windows (SPSS Inc, Chicago, IL, USA) and Microsoft Excell (Realmond, W.A, USA) software. Descriptive analysis (e.g., mean, median, standard deviation, frequencies, percentage) were calculated and analysis was performed using the student's t-test and Fisher ExactT- Test, P value <0.05 was considered significant. The survival curves were made using the Kaplan-Meier method

and comparison was with the log rank test.

3. Results

Patients characteristics: table (1)

The median age of patients of group I was 60 years range (45-82 years) while it was 57 years (range 30 – 78 years) for group II. There were 21 men (75%) and 7 women (25%) in group I with male: female ratio of 3:1, while there were 24 men (82.8%) and 5 women (17.2%) in group II with male: Female ratio of 4.8:1 for group II. On stratification of the patients according to risk, 15 patients (53.6%) in group I were of intermediate risk and 13 (46.4%) were of high-risk, while 16 patients (55.2%) of group II were of intermediate risk and 13 patients (44.8%) were of high –risk as shown in table(1).

Outcome:

The minimum period for follow up was 12 months for both groups,while the maximum period was 30 and 29 months and the median period of follow up was 17.5 and 16 months for group I and II respectively. Twenty two patients (78.6%) of group I achieved CR, while 24 patients (82.8%) of group II had CR, with no significant statistical difference (p=0.47). The overall recurrence rate of group I was 21.4% (6 patients), while it was 27.6% (8 patients) for group II, with no significant statistical difference (p=0.7). The progression rate was 10.7% and 10.3% for group I and II respectively (3 patients for both groups) with no significant statistical difference (p=0.5).The minimum period of time to recurrence was 10 and 3 months and the maximum period was 30 and 29 months for group I and II respectively. The median recurrence free period was 14 and 15 months for group I and II respectively with no significant statistical difference (p=0.2).The minimum period of time to progression was 3 months for both groups while the maximum period was 30 and 29 months for group I and II respectively. The median progression free period was 18 and 16 months for group I and II respectively with no significant statistical difference (p= 0.9) as shown in table (2).

Kaplan-Meier curves showed that the l-year recurrence free survival rate was 88.1% and 96.6% and the median recurrence free survival was 19 and 16 months for group I and II respectively, with no statistical significance (p= 0.7) (Fig. 1).

When patients were stratified according to risk, It was found that for intermediate risk patients, the CR rate was 93.3% and 87.5% (14 patients for both groups) for group I and II respectively with no statistical significance (p= 0.5). The overall recurrence rate was slightly higher in group I (33.3%; 5 patients) compared with group II (25%; 4 patients) but this difference was not statistically significant (p=0.3). The minimum period of time to recurrence was 12 and 3months and the maximum period was 25 and 18 months for group I and II respectively.The median recurrence free period was longer for intermediate risk patients of group I (18.5 months) compared with those of group II (15 months), and this difference was statistically significant (p=0.005). The progression rate was nearly similar (6.7% and 6.2%) for group I and II respectively (1 patient for both groups) with no significant statistical difference (p= 0.6). The minimum period of time to progression was 10 and 6 months while the maximum period was 25 and 26 months for group I and II respectively.The median progression free period was 13 and 16 months for group I and II respectively with no significant statistical difference (p= 0.8) as shown in table (3).

Kaplan-Meier curves showed that the 1-year recurrence free survival rate was nearly similar for the intermediate risk patients of both groups (95.3% and 98.7%) and the median recurrence free survival was 22 and 18 months for group I and II respectively with no significant statistical difference (p=0.6) (Fig. 2).

For high risk patients, the CR rate was 61.5% (8 patients) for group I and 76.9% (10 patients) for group II with no significant statistical difference (p= 0.3). The overall recurrence rate was 7.7% (1 patient) in group I, while it was 30.8% (4 patients) in group II and this difference was statistically significant (p=0.04). The minimum period of time to recurrence was 12 and 3months and the maximum period was 30 and 28 months for group I and II respectively. The median recurrence free period was 15 and 14 months for group I and II respectively with no significant statistical difference (p=0.1). The progression rate was 15.4% (2 patients) for both groups with no significant statistical difference (p= 0.5). The minimum period of time to progression was 3 months for both groups while the maximum period of time to progression was 30 and 28 months for group I and II respectively. The median progression free period was longer for group I (17 months) compared with that of group II (15 months) but the difference was statistically not significant (p= 0.7) as shown in table (3).

Kaplan-Meier curves showed that the 1-year recurrence free survival rate was 76.9% for high risk patients of group I, while it was 69.2% for group II, and the median recurrence free survival was 18 and 15 months for both groups respectively and the difference was statistically not significant (p= 0.08) Fig. (3).

Comparison of the local side effects showed overall, few severe (grade 3) adverse events in the 2 treatment groups. Dysurea was the most frequent

local side effect in group I constituting 46.4% (13 patients) with grade 3 occurred in 3 patients, while it constituted 6.9% (2 patients) in group II with only 1 patient had grade 3 and the difference was statistically significant (p=0.001). Haematurea was the next most frequent side effect in group I constituting 32.1% (9 patients) with grade 3 occurred in 2 patients while it was 13.8% in group II (4 patients) and the difference was not statistically significant (p= 0.09). Urinary frequency was another local complaint, described by 7.1% (2 patients) in group I and 10.3% (3 patients) in group II and the difference was not statistically significant (p=0.5). As regards the systemic side effects, fever was the main side effect in group I constituting 17.9% (5 patients) with only 1 patient had grade 3, while there were no systemic side effects in group II. table (4-b), Fig. (4).

Table 1: Patient characteristics of the 57 patients:

		Group 1 Intravesical BCG (n=28)	Group 2 Intravesical gemcitabine (n = 29)	
Sex	Male	21(75.0%)	24(82.8%)	0.5*
	Female	7(25.0%)	5(17.2%)	
Age		60	57	0.02**
Multifocality		10(35.7%)	13(44.8%)	0.6*
Site	Ant.	1(3.6%)	2(6.9%)	N/A
	Post.	17(60.7%)	15 (51.7%)	
	Ant.& post.	2(7.1%)	7(24.1%)	
	Left	6(21.4%)	4(13.8%)	
	Right	1(3.6%)	0(0.0%)	
	Dome	1(3.6%)	0(0.0%)	
	Ant.& left	0(0.0%)	1(3.4%)	
Stage	Ta	9(32.1%)	7(24.1%)	0.4*
	T1	19(67.9%)	22(75.9%)	
Grade	G1	8(28.6%)	14(48.3%)	0.1*
	G2	7(25.0%)	2(6.9%)	
	G3	13(46.4%)	13(44.8%)	
Risk	Intermediate	15(53.6%)	16(55.2%)	0.6*
	High	13(46.4%)	13(44.8%)	

*Fisher Exact test & **Independent T-test

Table (2) : treatment outcome of the 2 groups:

	Group 1 Intravesical BCG (n=28)	Group 2 Intravesical gemcitabine (n=29)	p-value`
CR	22(78.6%)	24(82.8%)	0.5*
Recurrence	6(21.4%)	8(27.6%)	0.7*
Progression	3(10.7%)	3(10.3%)	0.5*
Median recurrence free period (months)	14	15	0.2**
Median progression free period(months)	18	16	0.9**

*Fisher Exact test & **Independent T-test

Table (3): treatment outcome of the 57 patients according to risk groups:

Variables		Group 1 Intravesical BCG (n=15)	Group 2 intravesical gemcitabine (n = 16)	p-value
Intermediate Risk	CR	14(93.3%)	14(87.5%)	0.5*
	Recurrence	5(33.3%)	4(25.0%)	0.3*
	Progression`	1(6.7%)	1(6.2%)	0.6*
	Median recurrence free period (months)	18.5	15	0.005**
	Median progression free period (months)	13	16	0.8**
High Risk (n=13)	CR	8(61.5%)	10(76.9%)	0.3*
	Recurrence	1(7.7%)	4(30.8%)	0.04*
	Progression`	2(15.4%)	2(15.4%)	0.5*
	Median recurrence free period (months)	15	14	0.1**
	Median progression free period(months)	17	15	0.7**

*Fisher Exact Test & ** Independent T-test

Table (4-a): Toxicity grades according to Common Toxicity Criteria version 3.0:

	Grade 1	Grade 2	Grade 3	Grade 4
Dysurea	Asymptomatic	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain medications; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated
Heamaturea	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Life-threatening consequences; major urgent intervention indicated
Frequency	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase>2 x normal but<hourly	≥1 x/hr; urgency; catheter indicated	—
Fever	38.0 – 39.0°C	>39.0 – 40.0°C	>40.0°C for ≤24 hrs	>40.0°C for >24 hrs

Table (4 -b): treatment toxicity of the 2 groups:

	Group 1 Intravesical BCG (n=28)	Group 2 Intravesical gemcitabine (n=29)	P-value*
Dysurea	13(46.4%)	2(6.9%)	0.001
Grade 1	-	-	
Grade 2	10	1	
Grade 3	3	1	
Grade 4	-	-	
Heamaturea	9(32.1%)	4(13.8%)	0.09
Grade 1	-	1	
Grade 2	7	3	
Grade 3	2	-	
Grade 4	-	-	
Frequency	2(7.1%)	3(10.3%)	0.5
Grade 1	2	1	
Grade 2	-	2	
Grade 3	-	-	
Grade 4	-	-	
Fever	5(17.9%)	0(0%)	0.001
Grade 1	1	-	
Grade 2	3	-	
Grade 3	1	-	
Grade 4	-	-	

*Fisher Exact test

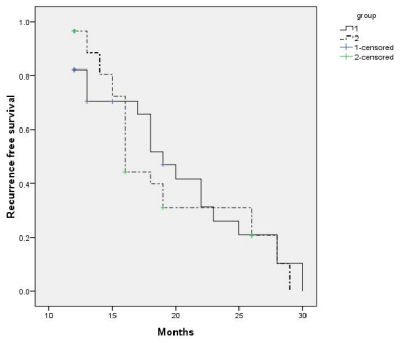

Figure (1): The recurrence free survival of the 2 groups of patients: Kaplan–Meier curves showing a non-significant difference in recurrence free survival between patients with NMIBC treated with intravesical BCG (group I) and patients who received gemcitabine (group II).

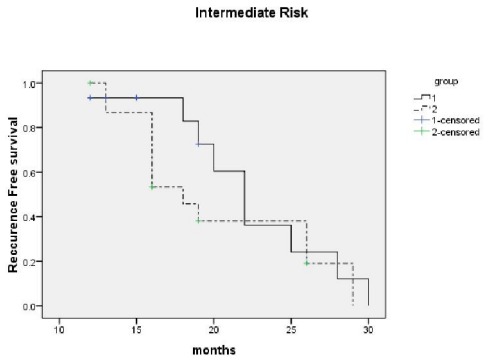

Figure (3): The recurrence free survival of the high risk group: Kaplan–Meier curves showing a non significant difference in recurrence free survival between patients with intermediate risk NMIBC treated with intravesical BCG (group I) and patients who received gemcitabine (group II)

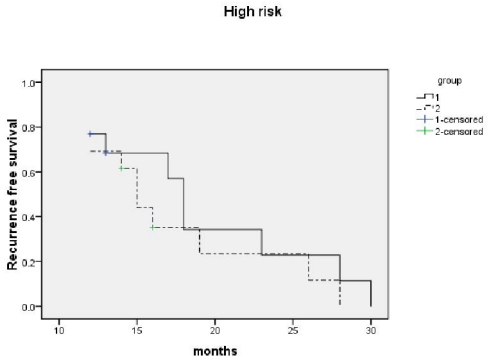

Figure (3): The recurrence free survival of the high risk group: Kaplan–Meier curves showing a non significant difference in recurrence free survival between patients with intermediate risk NMIBC treated with intravesical BCG (group I) and patients who received gemcitabine (group II)

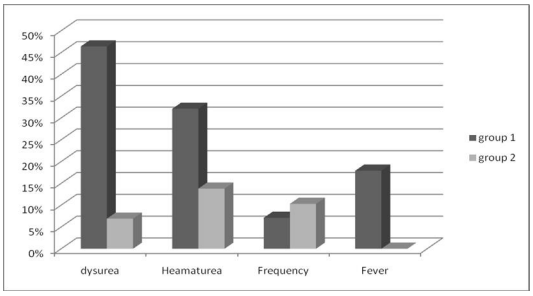

Figure (4): treatment toxicity of the 2 groups

4. Discussion

The advent of effective and safe intravesical therapies has improved the management of NMIBC, however, there is still clear need for novel or improved adjuvant treatment modalities [9].

There are limitations in the efficacy of intravesical treatment for intermediate and high-risk NMIBC. Though intravesical adjuvant therapy with BCG is superior to any other immunotherapeutic/chemotherapeutic agent in reducing tumour recurrence and disease progression, its real efficacy remains controversial as one-third of the patients will be non-responders. Also, following conventional intravesical chemotherapy, the short term recurrence rate of intermediate risk NMIBC cannot be reduced by more than 15-20% and long term risk of recurrence by 6% [10]. Hence, there is increasing interest in alternative first-line drugs for the treatment of the intermediate and high-risk NMIBC[11,4].The aim of this study was to evaluate the safety and efficacy of adjuvant intravesical gemcitabine versus BCG in the treatment of intermediate and high-risk NMIBC.

Intravesical gemcitabine has been tested in several phase II studies that explored its clinical utility for intermediate and high-risk NMIBC. Activity against marker lesions and primary and previous refractory tumours has been demonstrated in multiple trials.

In the present study, the CR rate of gemcitabine arm is comparable to that of the BCG arm but higher than that reported by others. Phase II studies have showed CR in up to 60% of cases of marker lesions in intermediate risk and few attempts have been made to test the activity of intravesical gemcitabine in high risk group [12, 13, 11, 14]. Dalbagni et al., tested the efficacy of intravesical gemcitabine in patients with BCG refractory, high risk NMIBC in a phase II prospective trial. Results showed that 50% of patients had a CR and 21% were free of disease at one year [15].

The CR rate of BCG arm is comparable if not better than that reported in previous similar studies where it ranged from 35% to 84% [16,17,18,19]and for high risk group the CR ranged from 64% to 84% [20,21,22,23]. The variation between this study and the other series can be explained by the presence of large numbers of patients with lower risk tumours and by variation of regimens and dosages used where most of those regimens include maintenance.

In the present study,The recurrence rate of the gemcitabine arm is comparable to that of BCG arm, however, there is a significant reduction in recurrence in favor of BCG in the subgroup analysis involving patients with high risk group. The recurrence rate of gemcitabine arm is comparable to that of Bartoletti et al., where they reported a recurrence rate of 25.4% while the 1- year recurrence free survival was 74.6% [24]. In the study of El-Koushy, intravesical gemcitabine was tested in patients refractory to BCG, recurrence rate was 28.6% [25].

The recurrence rate of BCG arm is lower than that of Elmallah, (29.6%) Lamm, (31%), Lundholm (51%), Bohel et al., (40%), Kim et al., (26.7%) and Cho et al., (33%) [26, 27, 28, 29, 3,5].conversely, it is higher than that of librenjack et al., (12%).[30].

With regard to disease progression, the results of BCG versus chemotherapy are less clear [31]. It has been proved that BCG decreases the progression of superficial bladder cancer, however a meta-analysis of EORTC and medical research council data demonstrated that chemotherapy prevents recurrence but not progression [32,33]. Another meta-analyses showed that chemotherapy delays the time to first recurrence, however it has not been shown to influence either the time to progression to muscle invasive disease, duration of survival or progression free survival [31]. In our study, the progression rate of the gemcitabine arm is

comparable to that of BCG arm. This result is parallel to that of Lundholm et al., and Krege et al., on their comparative study between BCG and MMC, where tumour progression was similar in both groups (13% and 4.2% respectively) [34,35].

Conversely a meta-analysis by Sylvester et al., and Bohle and Bock showed reduced progression rate in favor of BCG compared to chemotherapy [36, 37]. These trials showed risk reduction in progression of disease only on maintenance BCG therapy.

For intermediate risk patients, intravesical chemotherapy is currently administered with the prophylactic intent of reducing recurrence rate. The risk of progression for this category is generally low and it is not taken as a primary end point. In the present study, on subgroup analysis, there was no significant difference in the recurrence rate between BCG and gemcitabine and this result is comparable to that of two meta-analyses focusing on intermediate risk group where there was no difference in recurrence rate between intravesical chemotherapy and immunotherapy in this risk group [38,39]. So, according to 2009 guidlines from European Association of Urology (EAU), the treatment of choise for intermediate risk group is either chemotherapy or immunotherapy and both types of treatment are accepted as standard in this subgroup [40].

In the present study, although, there was no significant difference in recurrence rate between BCG and gemcitabine in the intermediate risk group, there was a significant difference in the median recurrence free period in favor of BCG. This result is parallel to the finding that intravesical chemotherapy can clearly reduce the risk of recurrence of intermediate risk patients in the short term, however, in the long term, it has only a modest effect on the risk of recurrence [10, 33].

High risk group remains a challenge for the urologist. This study had shown a significantly lower recurrence rate with intravesical BCG compared to gemcitabine. However, there was no difference in progression rate or recurrence free survival between the two treatment groups. The result of our study is confirmed by a study of porena et al., where they evaluated the efficacy of BCG versus gemcitabine in high risk groups, the recurrence rate of BCG arm was significantly lower than that of gemcitabine (28.1 vs. 53.1) and there was no disease progression in both groups [41].

The recurrence rate of the high risk patients of BCG arm is comparable to that of Yumura et al., (21.1%), but higher than that of Gunlusoy et al., (6.1%) and lower than that of Brake et al., (11%), Kulkarni and Gupta (35%), Margel et al., (35%) Peyromoure et al., (42.1%),Lerner et al.,(50%),and Shahin et al.,(70%)[42,43,44,45,46,47,48,49].

In contrary to BCG, few studies have assessed the activity of intravesical gemcitabine in high risk patients. In phase II study of Bartoletti, et al., the recurrence rate of high risk patients treated with intravesical gemcitabine was higher than that of our study (77%) [24].

However, for high risk patients in whom BCG fails gemcitabine might represent a safe and effective option. In a study of Di Lorenzo comparing between gencitabine and BCG in those patients, recurrence rate was 52.6% vs. 87.5% for both groups respectively [50]. In another single arm study of Perdonà et al., the recurrence rate of the patients who received gemcitabine was 55% [51].

The progression rate of high risk patients of BCG arm is comparable to that of Yumura et al., (15.8%) but it is higher than that of Shahin et al., (3.3%), Kulkarni and Gupta, (12%) and Brake et al., (13%) and lower than that of,Margel et al., (18%),Gunlusoy et al.,(21.7%) and Peyromaure et al., (22.8%)[42,49,45,44,46,43,47].

The adverse events of the BCG were more marked than that of the gemcitabline arm. Intravesical gemcitabine was generally well tolerated and the local toxicity was minimal and generally described as rapidly self resolving. The published reports confirm the good tolerability with minimal local and systemic toxicity of gemcitabine in contrary to BCG which have frequent local and systemic adverse effects [52,5].On the otherhand, chemotherapeutic agents, such as MMC and doxorubicin, despite the low probability of systemic side effects, can give rise to severe forms of chemical cystitis. The molecular weigh of gemcitabine, 299.66 Da, is less than that of currently used intravesical drugs, yet is high enough to make significant systemic absorption unlikely (in an intact bladder) whilst being low enough for improved penetration of the bladder mucosa. The safety of intravesical administration of up to 2000 mg gemcitabine in 50 ml saline is substantiated by the evidence of how little gemcitabine is actually absorbed into the systemic circulation [53].

Some peculiarities of the present study are to be pointed out. Although a significant initial CR was achieved in high risk group of patients receiving gemcitabine, the majority of patients experienced recurrence within 12 months. This is not unexpected given the mechanism of cytotoxicity for chemotherapy and the brief duration of therapy in this study where there was no maintenance treatment. Conversely, immunotherapy is felt to induce a host response, against the tumour. This may be a potential reason that BCG is superior to chemotherapy

approaches in general.

One consideration to improve durability of response to gemcitabine is to consider maintenance therapy, although the role of maintenance therapy for intravesical agents is controversial [54,55]. In a meta-analyses of 11 randomized trials, Huncharek, suggested that chemotherapy for 2 years had the greatest effect on decreasing the recurrence rates [56]. This would not be unexpected given the log-cell kill obtained with chemotherapy agents, provided that chemoresistance does not develop.

A second consideration is that multiple-agent chemotherapy may be more successful than just using a single agent. Single agent chemotherapy is extremely limited in curing systemic disease, and the best results have been achieved with multiple agents. However, using two different chemotherapeutic agents, taking advantage of their synergistic effect, has not been attempted in intravesical approaches [15].In vitro studies have demonstrated a marked synergism between gemcitabine and MMc, the most commonly used intravesical chemotherapeutic agent [57]. Intravesical docetaxel was well tolerated in phase I trial, making a combination of docetaxel and gemcitabine a viable option [58,15].Several studies have shown that the efficacy of intravesical therapy can be increased by sequential administration of BCG and chemotherapy as MMc and gemcitabine. Intravesical chemotherapy and BCG have different mechanisms of action and may thus have a potentiating anti-tumour effect [59,60,5].

So, the early significant CR with intravesical gemcitabine and the high recurrence rate warrants investigating the role of maintenance therapy in high risk group in the future trials. Because of the low and transient adverse events and excellent cytotoxic effect of gemcitabine, more intense treatment schedules are now being contemplated [61].

Conclusion:

Gemcitabine is active and well tolerated for intravesical instillation.It is considered to be an efficient treatment for intermediate risk NMIBC. However, for high- risk group, it is inferior to BCG, but owing to its favorable toxicity profile, it may be useful for patients intolerant to BCG. Further studies are necessary to accumulate a larger amount of consistent data.

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