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Adjuvant intravesical instillation for primary intermediate and high-risk non-muscle invasive bladder cancer: BCG versus docetaxel

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Abstract

Background: BCG is the standard treatment for non-muscle invasive bladder cancer (NMIBC). However, the high recurrence rates and the significant local and systemic toxicity have led to increased interest in alternative intravesical therapies. Docetaxel has been shown to be a safe and effective intravesical therapy with no systemic absorption and minimal toxicity.

Objectives: To compare the efficacy and safety of intravesical BCG and docetaxel for intermediate and high-risk NMIBC.

Patients and methods: 82 patients with NMIBC were randomized into 2 groups; and treated with six weekly intravesical BCG (group I, 40 patients) and docetaxel (group II, 42 patients). Outcome measures were overall recurrence rate, progression rate, 1-year recurrence free and progression free survival. Treatment related toxicities were also evaluated.

Results: No difference between the 2 groups in recurrence rate (32.5% vs. 42.9%), progression rate (20% vs. 28.6%), 1-year recurrence free survival (72.5% vs. 61.9%), 1-year progression free survival (80% vs.71.4%). No difference for intermediate and high risk patients in BCG group and their counterparts of docetaxel group in recurrence rate (16.7% vs. 42.9%) and (39.3% vs. 42.9%), progression rate (16.7% vs. 14.3%) and (21.4% vs. 35.7%), 1-year recurrence free survival (83.3% vs. 76.9%) and (67.9% vs. 53.6%), 1-year progression free survival (83.3% vs. 84.6%) and (78.6% vs. 65.5). Age, grade and multiplicity were independent predictive factors for recurrence while grade was the independent factor for progression. The adverse events of BCG group were more marked.

Conclusions: Intravesical docetaxel demonstrate significant efficacy and minimal toxicity for the management of NMIBC. In comparison to BCG, there was no significant difference in terms of disease recurrence, progression or survival, and the decision to use either agent may be based on adverse events and cost. The results of this study support the role of intravesical docetaxel for intermediate risk patients and it can be of major concern for high risk patients, however, randomized multi-institutional trials should be considered.

Keywords: Bacillus Calmette-Guérin, docetaxel, intravesical therapy, NMIBC

Introduction

Non muscle-invasive bladder cancer (NMIBC) accounts for 60-80% of newly diagnosed bladder cancer. NMIBC is characterized by a tendency for recurrence and progression where the recurrence rate ranged from 50-80% and the progression rate is 10-45%, according to disease risk [1-2]. Based on the results of multiple randomized trials, intravesical BCG with or without maintenance is effective in treating intermediate and high-risk NMIBC; and it is superior to other intravesical agents to prevent recurrence and progression [3-8]. However, the recurrence rate is as high as 30% and the local and systemic toxicities were significant, so interest has been increased seeking for alternative intravesical therapies [9,10]. Intravesical chemotherapy has shown comparable efficacy to BCG in certain patients and the perioperative instillation of chemotherapy has become standard of care [10]. Taxoids are attractive agents for

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intravesical therapy due to their potency, high molecular weight and lipophilicity. They act by inhibiting the polymerization of microtubules by promoting intracellular bundling; resulting in M-phase cell cycle arrest and cell death [**10**]. Docetaxel has been shown to be effective with no systemic absorption and minimal toxicity. The aim of this study was to compare the efficacy and safety of intravesical instillation of BCG and docetaxel for primary intermediate and high-risk NMIBC.

Patients and methods

This was a prospective phase III trial carried out between September 2010 to August 2014. The study was conducted after obtaining institutional review board approval. Written informed consent was obtained from all patients. The study population consisted of 88 intermediate-and high-risk patients with NMIBC according to the EORTC(European Organization for Research and Treatment of Cancer) classification [**3**].

- Intermediate-risk NMIBC: multifocal or multi-recurrent Ta low -intermediate grade tumors,>3 cm.
- High -risk NMIBC: high grade Ta, T1 tumors.

Patients were randomized into 2 groups; 44 patients in both groups; I and II. However, 4 patients in group I and 2 patients in group II discontinued treatment. Patients were scheduled to undergo transurethral resection of the tumor (TURBT) at the department of Urology, South Egypt Cancer Institute and oncology department, Assiut University hospital.

Inclusion criteria

1. Men and women >18 years of age with primary NMIBC.
2. Normal upper tract study (IVP, CT) within 3 months of enrollment.
3. Hematologic-inclusion within 2 weeks of treatment: Absolute neutrophil count >1,500/mm3, Haemoglobin>8.0 g/dl, Platelet count >100,000/mm3.
4. Renal inclusion criteria within 2 weeks of treatment: creati nine clearance ≥60 mL/minute, serum creatinine ≤1.3 mg/dL
5. Hepatic-inclusion within 2 weeks of entry: Total Bilirubin must be within normal limits. SGOT and/or SGPT may be up to 2.5 x institutional upper limit of normal (ULN) if akaline phosphatase is <ULN.
6. Women of childbearing potential must have a negative pregnancy test.
7. No intravesical therapy within 6 weeks of study entry.

Exclusion criteria

1. Patients with muscle invasion (T2).
2. Previous systemic or radiation therapy for bladder cancer.
3. Concurrent treatment with chemotherapy.
4. Pregnant or lactating Women.
5. Prior treatment with docetaxel.
6. History of vesico-ureteral reflux or an indwelling urinary stent.

Treatment and follow-up

The pre study clinical evaluation comprised history, general physical examination, electrocardiogram, computed tomography-urography scan, chest radiograph and haematological, renal and hepatic evaluation. Patients started treatment 4–6 weeks after TUR. One week before each treatment day, all patients had a CBC that should fulfill the hematopoietic inclusion criteria. Additionally, three doses of dexamethasone 4 mg were administered; 12 hours before, 1 hour before, and 8 hours after each treatment cycle. Group I patients received weekly intravesical instillations of BCG (Pasteur strain) 150 mg in 50 ml saline. Group II received intravesical instillations of 75 mg of docetaxel diluted in 100 mL Patients retained the drug in the bladder for 2 hours before voiding. All patients were administered 6 weekly intravesical instillations. 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 [**11**]. Side-effects were checked after each instillation and recorded in the database. Serum studies and cystoscopy with bladder biopsies under anesthesia were performed four weeks after completing the treatment, to evaluate safety and efficacy. During the treatment, urine analysis and urine culture was carried out weekly. Cytological analysis of voided urine and cystoscopy were performed at 3-month intervals. Intravenous urography or computed tomography-urography was performed annually.

Outcome measures

Recurrence was determined by detection of lesions at cystoscopy and pathologically confirmed. Positive cytology was not considered a recurrence unless bladder mapping was performed for pathological confirmation of the tumor. Time to recurrence was defined as the time from TUR to the date of the first recurrence. Progression was defined as an increase in tumor stage and grade. Time to progression was defined as the time between TUR and first progression. The recurrence and the progression rate were defined as the percentage of recurring or progressing patients at 1-year follow-up. 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. 1-year progression free survival was defined as the time from the date of TUR to the date of progression or last follow-up among patients who achieved a CR at 1-year follow-up.

Statistical analyses

Descriptive analysis (e.g., mean, median, standard deviation, frequencies, percentage) were calculated and analyses was performed using the student's t-test and Fisher Exact T-Test. Mann-Whitney U-tests were used when appropriate to compare continuous data between groups non-parametrically. All reported P values were two-sided, and $P<0.05$ was considered statistically significant. The survival curves were made using the Kaplan-Meier method and comparison was with the log rank test. Independent predictors of tumor recurrence were determined using Cox regression modeling. 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 Excel (Realmond, W.A, USA) software.

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Results

Patient characteristics

The median age of patients of group I was 56 years (range 37-75 years) while it was 60years (range 39-79 years) for group II. No significant differences were noted between the 2 groups in terms of age, sex, tumor number, growth pattern, or histological grade of tumor. On stratification of the patients according to risk, 12 patients (30%) in group I were of intermediate risk and 28 (70%) were of high-risk, while 14 patients (33.3%) of group II were of intermediate risk and 28 patients (66.7%) were of high –risk with no significant difference (p=0.746) as shown in **Table 1**.

Disease recurrence

The minimum period of follow up was 12 months, while the maximum period was 36 months for both groups and the median period of follow up was 18and 12 months for group I and II respectively. In Group I, 13/40 (32.5%) patients developed disease recurrence versus 18/42 (42.9%) in Group II (p =0.334). The minimum period of time to recurrence was 6 and 3 months and the mean time to recurrence was 14±5.3 and 13.6±6.7 months for group I and II respectively with no significant statistical difference (p=0.382). When patients were stratified according to risk, It was found that for *intermediate risk patients*, the recurrence rate was 16.7% (2/12 patients) and 42.9% (6/14 patients) for group I and II respectively with no statistical significance (p=0.309). The minimum period of time to recurrence was 6 and 3 months and the mean time to recurrence was 15.8±5.4 and 16.3±6.8 months for group I and II respectively with no statistical significance (p=0.151). For *high risk patients*, the recurrence rate was 39.3% (11/28 patients) for group I and 42.9% (12/28 patients) for group II with no significant statistical difference (p=0.786). The minimum period of time to recurrence was 6 and 3 months while the mean time to recurrence was 14.4±5.3 and 12.4±6.3 months for group I and II respectively with no statistical significance (p=0.533).

Kaplan-Meier curves showed that the l-year recurrence free survival rate was 72.5% and 61.9% and the mean recurrence free survival was 19.9 and 17.6 months for group I and II respectively with no statistical significance (p=0.308) (**Figure 1**).

For the *intermediate risk* patients, the1-year recurrence free survival rate was 83.3% and 76.9% and the mean recurrence free survival was 21.3 and 20.5 months for group I and II respectively with no significant statistical difference (p=0.237) (**Figure 2**).

For *high risk* patients, the 1-year recurrence free survival rate was 67.9% and 53.6% and the mean recurrence free survival was 19.3 and 16.3 months for group I and II respectively with no significant statistical difference (p=0.237) (**Figure 2**).

Table 1. Patients characteristics of the 2 groups.

	Group 1 BCG (n= 40)		Group II Docetaxel (n=42)		P-value
	No.	%	No.	%	
Sex					
Male	38	95.0	38	90.5	0.717
Female	2	5.0	4	9.5	
Age: (years)					
Mean ± SD	55.80 ± 11.33		58.90 ± 11.44		0.294
Median (Range)	56.0 (37.0-75.0)		60.0 (39.0- 79.0)		
Grade:					
Grade I	7	17.5	12	28.6	0.193
Grade II	6	15.0	2	4.8	
Grade III	27	67.5	28	66.7	
Multiplicity:					
Yes	5	12.5	10	23.8	0.185
No	35	87.5	32	76.2	
Risk					
Intermediate	12	30.0	14	33.3	0.746
High	28	70.0	28	66.7	
Site:					
Anterior wall	6	15.0	10	23.8	0.314
Posterior wall	24	60.0	22	52.4	0.860
Left wall	7	17.5	6	14.3	0.690
Right wall	3	7.5	0	0.0	0.223
Posterior & Right wall	0	0.0	2	4.8	0.496
Posterior & Ant wall	0	0.0	2	4.8	0.496
Shape:					
Papillary	35	87.5	36	85.7	0.746
Non-papillary	5	12.5	6	14.3	

Disease progression of recurrent tumors

Disease progression was defined as recurrent tumor with muscular invasion, progression of grade to G3, or distant metastasis. No patients displayed recurrence involving distant metastasis. Recurrent G3 cancer was detected in 4 of all 82 patients comprising 1/40 of group I and 3/42 of group II patients. Recurrent

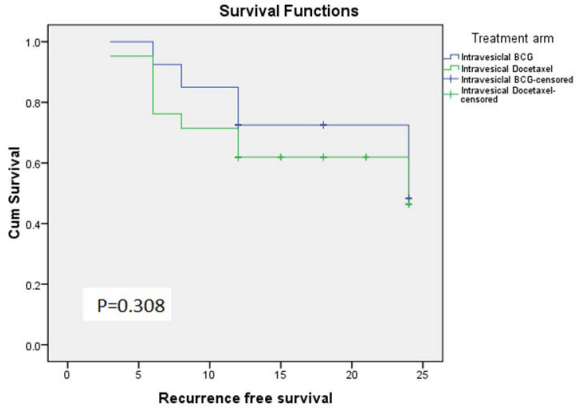

Figure 1. The recurrence free survival of the 2 groups. Kaplan–Meier curves showing a non-significant difference in recurrence free survival between patients with NMIBC treated with intravesical BCG (group I) and patients who received docetaxel (group II).

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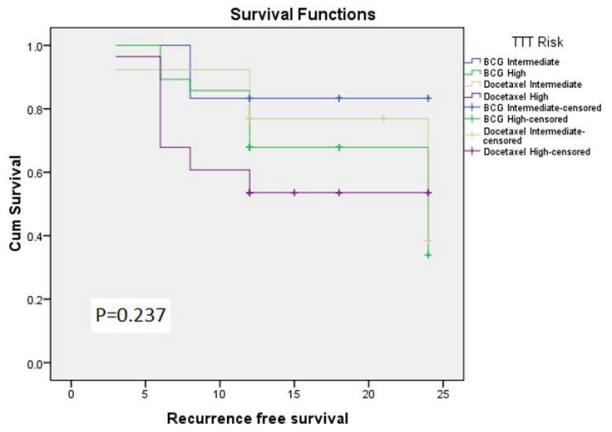

Figure 2. The recurrence free survival of the 2 risk subgroups of both groups.
Kaplan–Meier curves showing a non-significant difference in recurrence free survival between patients of intermediate risk treated with intravesical BCG (group I) and patients who received docetaxel (group II) or those of high risk patients of the 2 groups.

cancer with muscular invasion was detected in 16 patients; 7/40 in group I and 9/42 in group II patients. The progression rate was 20% (8/40 patients) and 28.6% (12/42 patients) for group I and II respectively with no significant statistical difference (p=0.366). The minimum period of time to progression was 6 months for both groups while the mean time to progression was 16.9±8.2 and 16.1±8.3 for group I and II respectively with no significant statistical difference (p=0.643). For *intermediate risk patients*; the progression rate was 16.7% (2/12 patients) and14.3% (2/14 patients) for group I and II respectively with no statistical significance (p=0.867). The minimum period of time to progression was 6 and 13 months while the mean time to progression was 15.8±5.4 and 19.8±8.5 months for group I and II respectively with no significant statistical difference (p=0.060). For *high risk* patients, the progression rate was 21.4% (6/28 patients) for group I and 35.7% (10/28 patients) for group II with no significant statistical difference (p=0.237). The minimum period of time to progression was 6 months for both groups while the mean time to progression was 17.4±9.2 and 14.4±7.9 months for group I and II respectively with no significant statistical difference (p=0.727).

Kaplan-Meier curves showed that the l-year Progression free survival rate was 80% and 71.4% and the mean progression free survival was 30.4 and 27.8 months for group I and II respectively, with no statistical significance (p=0.340) (**Figure 3**). For *intermediate risk* patients, the l-year Progression free survival rate was 83.3% and 84.6% and the mean progression free survival was 21.3 and 32.3 months for group I and II respectively, with no statistical significance (p=0.350) (**Figure 4**). For *high risk* patients, the l-year Progression free survival rate was 78.6% and 65.5% and the mean progression free survival was 30.07 and 25.7 months for group I and II respectively, with no statistical significance (p=0.350) (**Figure 4**).

Predictors of tumor recurrence and progression

A Cox regression model was used to isolate independent prognostic factors among sex, age, tumor grade, tumor multiplicity, tumor size and treatment protocol (BCG versus docetaxel). Age, tumor grade and multiplicity were proved to represent independent prognostic factors for local recurrence (**Table 2**). For progression; grade was proved to represent the single independent prognostic factor for progression (**Table 3**).

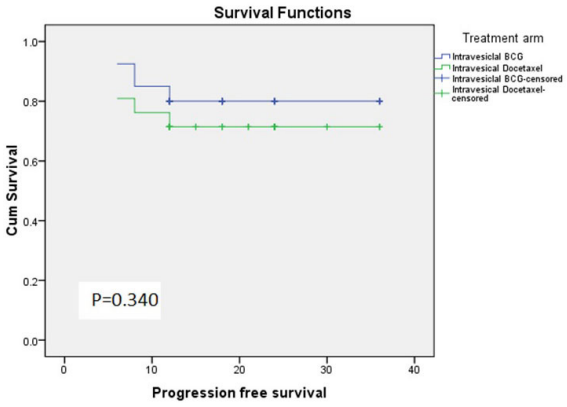

Figure 3. The progression free survival of the 2groups.
Kaplan–Meier curves showing a non-significant difference in progression free survival between patients with NMIBC treated with intravesical BCG (group I) and patients who received docetaxel (group II).

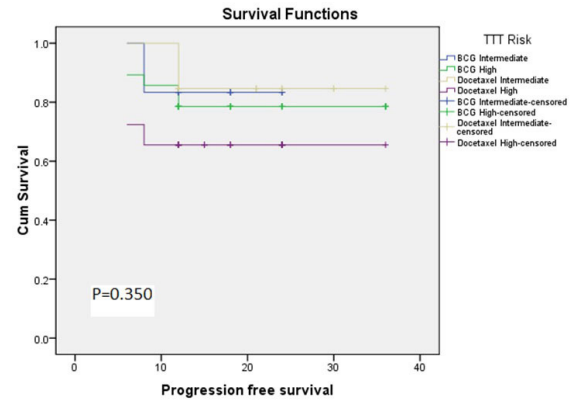

Figure 4. The progression free survival of the 2 risk subgroups of both groups.
Kaplan–Meier curves showing a non-significant difference in progression free survival between patients of intermediate risk treated with intravesical BCG (group I) and patients who received docetaxel (group II) or those of high risk patients of the 2 groups.

Adverse effects

Urinary symptoms represented the main adverse events in both

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groups. Intravesical administration of docetaxel was generally well tolerated. 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 both groups ; constituting 30% (12 patients) in group I ,with grade 3 occurred in 3 patients (7.5%), while it constituted 19% (8 patients) in group II with only 1 patient had grade 3(2.4%) and the difference was statistically insignificant (p=0.248). Haematurea was the next most frequent side effect constituting 15% (6 patients) in group I while it was 9.5% in group II (4 patients) with grade 3 occurred in 1 patient in each group and the difference was not statistically significant (p=0.675). Urinary frequency was another local complaint, described by 5% (2 patients) in group I and 7.1% (3 patients) in group II and the difference was not statistically significant (p=0.685). As regards the systemic side effects, fever was the main side effect occurring in 2 patients in group I; (**Table 4**, **Figure 5**).

Table 2. Cox regression analysis for recurrence in 82 patients.

	HR	P-value	95.0% CI	
			Lower	Upper
Line of treatment (BCG vs. docetaxel)	0.674	0. 321	0.309	1.468
Age (≥65 vs. <65)	3.080	0.025*	1.148	8.263
Sex (male vs. female)	0.372	0.270	0.064	2.158
Grade (high vs. low)	11.798	0.008*	1.907	72.981
Multiplicity (multiple vs. single)	2.710	0.041*	1.040	7.060
Size (≥3 cm vs. <3 cm)	1.178	0.682	0.539	2.575

Table 3. Cox regression analysis for progression in 82 patients.

	HR	P-value	95.0% CI	
			Lower	Upper
Line of treatment (BCG vs. docetaxel)	0.584	0. 289	0.216	1.578
Age (≥65 vs. <65)	3.833	0.088	0.821	17.905
Sex (male vs. female)	4.264	0.080	0.889	7.990
Grade (high vs. low)	14.203	0.048*	1.028	196.161
Multiplicity (multiple vs. single)	2.974	0. 071	0.911	9.710
Size (≥3 cm vs. <3 cm)	0.482	0. 203	0.157	1.483

Discussion

Controversies still exist as regard the indication, type and agents of intravesical therapy for NMIBC [**12**]. Despite the established role of BCG, it is difficult to achieve long-term recurrence-free and progression-free survival [**13**]. Intravesical chemotherapy plays an important role in the dilemma of NMIBC treatment [**1**]. Docetaxel has been considered to be a safe and effective intravesical agent with no systemic absorption and minimal toxicity. This study compares the efficacy and safety of intravesical instillation of BCG and docetaxel for primary intermediate and high-risk NMIBC. Several studies and meta-analyses have shown that both intravesical chemotherapy and BCG reduce the recurrence rate in comparison to TUR alone [**4**,**14**]. Also chemotherapy has been considered to be the preferred intravesical agent for intermediate-risk NMIBC, having fewer side-effects than BCG. However, high-risk NMIBC is the greatest challenge where patients have high incidence of recurrence and a

Table 4. Toxicity of the 2 groups.

	Group 1BCG (n= 40)		Group II Docetaxel (n= 42)		P-value
	No.	%	No.	%	
Dysurea:	12	30.0	8	19.0	0.248
Grade I	7	17.5	5	11.9	0.474
Grade II	2	5.0	2	4.8	0.960
Grade III	3	7.5	1	2.4	0.574
Haematurea:	6	15.0	4	9.5	0.675
Grade I	4	10.0	2	4.8	0.627
Grade II	1	2.5	1	2.4	0.972
Grade III	1	2.5	1	2.4	0.972
Frequency:	2	5.0	3	7.1	0.685
Grade I	2	5.0	3	7.1	0.685
Grade II	0	0.0	0	0.0	--
Grade III	0	0.0	0	0.0	--
Fever	2	5.0	0	0.0	0.453

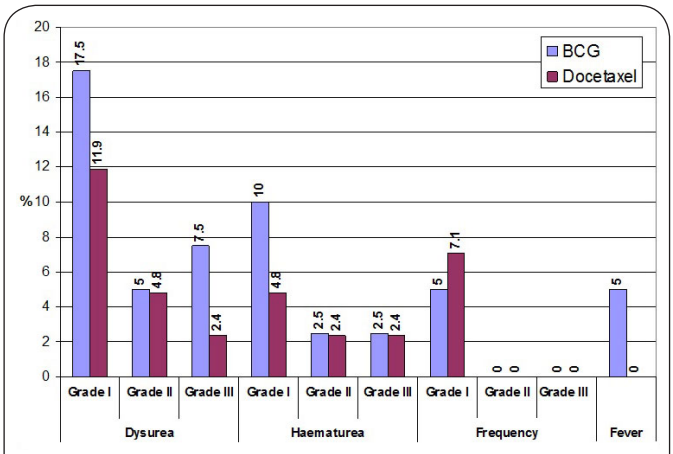

Figure 5. Treatment toxicity of the 2 groups.

considerable capacity for progression. BCG with maintenance therapy is the standard treatment for this group [15].

In the present study, the recurrence rate and the recurrence free survival of the docetaxel group were comparable to that of BCG; in addition, with subgroup analysis; the recurrence rate and the recurrence free survival of patients of intermediate risk and high risk of the docetaxel group were comparable to their counterparts of the BCG group. These results are parallel to the results of the studies that have shown reduction of recurrence rates by approximately 32% and prolongation of the median time to recurrence to 2-4 years with intravesical BCG [16]. However, intravesical chemotherapy have reduced the risk of recurrence for intermediate-risk patients in the short term, but in the long term, it has only a modest effect [15].

While reducing recurrence is an important issue, an even more important aim of treatment is the prevention of progression. Two large meta-analyses have demonstrated a 27% reduction of disease progression with intravesical BCG [5,7]. However, the value of BCG relative to chemotherapy is controversial for intermediate-risk patients who have a probability of recurrence of 50% and a probability of progression of only about a 10% [3]. Meta-analyses of EORTC and medical research council data revealed that chemotherapy prevents recurrence but not progression [14,15]. Other meta-analyses have demonstrated that chemotherapy delays the time to first recurrence; however it has no influence on the time to progression, or progression free survival [17]. However, in the present study, the progression rate and the progression free survival of the docetaxel group were comparable to that of BCG; in addition with subgroup analysis; the progression rate and the progression free survival of patients of intermediate risk and high risk were comparable to their counterparts of the other group.

In the previous published series, docetaxel exhibited significant efficacy in BCG refractory patients, where 55% of patients had a complete response (CR) in a phase I trial of Laudano et al; [18]. Long-term follow-up, confirmed disease free survival (DFS) in 22.2% and progression in 11.1% of the patients. In a study of Barlow; 61% of patients were found to have CR and 1-year and 2-year DFS was 45% and 32% [19]. Another study of intermediate- and high-risk BCG refractory patients, the CR rate was 76.9% and the DFS was 46.2% [20]. Follow-up revealed that 1 year and 3 years DFS was 40% and 25% respectively [21]. Intravesical nab-paclitaxel (Paclitaxel bound to albumin) has minimal toxicity and a 35.7% response rate in BCG refractory patients [22].

Comparing BCG with other chemotherapeutics proved conflicting results. Most studies comparing mitomycin C(MMC) with BCG has shown equivalent or superior results in favor of BCG. However; the meta-analysis of Malmstrom concluded that BCG with maintenance was superior to MMC in preventing recurrence, where there was a 32% reduction in risk of recurrence, while the risk reduction was 28% in patients receiving BCG without maintenance. On the other hand, disease progression did not differ significantly for either BCG or MMC [23]. The meta-analyses of Shelley et al, indicate that recurrence was significantly reduced with BCG compared to MMC in high risk patients, however, there was no difference in terms of disease progression or survival [24].

Comparing BCG with gemcitabine; in Bendary study of intermediate risk patients, recurrence rate was similar (25% gemcitabine, 30% BCG), and there was no difference in the progression rate [25]. The Porena study revealed that gemcitabine was significantly inferior to BCG in patients with primary high risk disease [26]. However, in the study of Lorenzo gemcitabine was significantly superior to BCG in BCG refractory patients where it significantly reduced the recurrence rate [27]. In Abd-Alrahim and Essa study there was no significant difference of the overall recurrence rate(33.3% vs. 25%),or the progression rate (6.7% vs. 6.2%) in patients of intermediate risk of recurrence, however in high risk patients gemcitabine was significantly inferior to BCG [28].

Comparing BCG with epirubicin, intravesical BCG had significantly fewer recurrence rates than epirubicin but there were no significant differences in disease progression or overall survival [29]. In the study of Shang et al, the recurrence rate of BCG was (35.5%) while it was (51.4%) for epirubicin [30].

In this study, the adverse events of the BCG were more marked than that of the docetaxel group but with no significance. Intravesical docetaxel was generally well tolerated and the local toxicity was minimal and generally described as self-resolving. The previous studies confirm the good tolerability with minimal local and systemic toxicity of docetaxel in contrary to BCG that have significant local and systemic toxicity. McKiernan et al reported that 44% of their patients experienced grade 1 or 2 toxicities, with dysuria being the most common [31]. Barlow et al reported 36% of patients had grade 1 or 2 local toxicities with no grade 3 or 4 toxicities [19].

Patients with NMIBC have a high probability of recurrence and progression, thus it is important to find out the risk factors predictive of recurrence and progression, so that post-operative follow-up might be adjusted in time for better treatment. In this study, it was found that age, grade and multiplicity were independent predictive factors for recurrence; while grade was the single predictive factor for progression. The most important prognostic factors for recurrence in the published series are the number of tumors, their size, and the prior recurrence rate. Also, the most important prognostic factors for progression are the T category, grade, and the presence of CIS; factors representing the biological aggressiveness [3,32-34]. Patients in older age groups are at increased risk for high grade of superficial bladder cancer, which predict the aggressive clinical course [35].

Conclusions

Intravesical docetaxel demonstrate significant efficacy and minimal toxicity for the management of NMIBC. In comparison to BCG, there was no significant difference in terms of disease recurrence, progression or survival, and the decision to use either agent may be based on adverse events and cost. The

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results of this study support the role of intravesical docetaxel for intermediate risk patients and it can be of major concern for high risk patients, however, randomized multi-institutional trials should be considered.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors shared in research design and conduction and analysis of data. The corresponding author (Essa HH) wrote the paper and had primary responsibility for final content. All authors read and approved the final manuscript.

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