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OUTCOMES OF IMMUNOTHERAPY BY INTRAVESICAL BCG VACCINE INSTILLATION ON TUMOR RECURRENCE OF NON-MUSCLE-INVASIVE UROTHELIAL BLADDER CANCER

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ABSTRACT

Background: In 1976 Morales et al were the first to prove the effectiveness of intravesical BCG on the bladder cancer and reported a remarkable decrease in the rates of recurrence of superficial bladder cancer. In 1990, BCG was approved by the Food and Drug Administration (FDA) as a primary treatment for the bladder carcinoma in situ (CIS) and as a preventive treatment for papillary tumors, thus BCG became essential in complementary treatment for NMIBC. **Objective:** This study aims to evaluate the effectiveness of the immunotherapy by intravesical BCG vaccine instillation in reducing recurrence rates in non-muscle-invasive urothelial bladder cancer patients (NMIBC). **Methods and materials:** Patients diagnosed with bladder transitional cell carcinoma by transurethral resection with no muscular invasion in pathology and who had a high or intermediate risk for tumor recurrence were included. BCG immunotherapy Onco TICE (CFU=2-8×10^8) was given as an induction course of 6 weekly instillations. Maintenance treatment 3 weekly instillations every 3 months for 1 year, was given as a single standard. The follow-up program included a cystoscopy every 3 months with biopsies from the site of the previous curettage or new recurrence. **Results:** Our study reported recurrence in 26 (43.7%) cases. Tumors ≥3 cm and T1 tumors were more common (73.1%) and (80.8%) in the recurrence group respectively, however there was no important significance ($p>0.05$). On the other hand: high grade tumors, multifocal tumors, tumors with previous recurrence and tumors without concomitant CIS, each was more common in the recurrence group with an important significance($p<0.05$) (88.5%,76.9%,92.3% and80.8%)respectively. **Conclusion:** We support the previous studys that intravesical BCG vaccine instillation reduces the recurrence rates in non-muscle-invasive urothelial bladder cancer ptients(NMIBC), especially when a maintenance treatment program is used. This study also supports the recommendation of using BCG as the frst-line supportive treatment in patients with high-risk NMIBC.

KEYWORDS: Non-muscle-invasive bladder cancer, BCG, Recurrence.

INTRODUCTION

Bladder cancer of the transitional cell carcinoma type (TCC) is one of the most common urinary tract malignancies**.** It is the seventh and seventeenth most common cancer in men and women respectively.[1] Bladder cancer is divided into superficial cancer and muscle invasive cancer. The first one does not involve deeper than the subepithelial tissue, in other words it does not reach to the detrusor muscle.[2]

At presentation 70% of patients with transitional cell carcinomas will have superficial tumors (50% Ta and 20% T1), 25% have muscle invasive tumors and the remaining 5% will have carcinoma in situ (CIS). When a patient is newly diagnosed with a superficial bladder tumor, the possibility to has a multifocal tumor, recurrence and stage progression to muscle invasive or metastatic disease is 30%, 60-70% and 10-20% respectively.[3]

The treatment of bladder cancer in general depends on numerous factors, including tumor's stage and grade, patient's age, and their co-morbidity. The standard treatment of superficial bladder cancer is a transurethral resection, which usually removes the tumor but it is known that they have a great tendency for recurrence after it.[2]

European Association of Urology divided patients with superficial bladder cancer into three groups: (1) Low-risk: primary, single, less than 3 cm, Ta, G1 (LG) and without CIS tumor. (2) Intermediate-risk: all tumors that

do not belong to the low-risk group or the High-risk group. (3) High-risk: Any of the following: T1 tumor or HG tumor (G3) or tumor with CIS, or a recurrent, multiple, larger than 3 cm and Ta G1/G2 tumor.[4][5]

In 1976 Morales et al were the first to prove the effectiveness of intravesical BCG in the bladder cancer.10 patients were received 120 mg BCG mixed in 50 ml of normal saline instilled into the bladder in conjunction with intradermal BCG weekly for six weeks.[6] They reported a remarkable decrease in the rates of recurrence of superficial bladder cancer in nine patients.

The fact about the prevention role of intravesical BCG goes back to several old studies, led by Brosman in 1982 and Morales in 1992. They reported a reduction in the recurrence rate about 30% using a six-injection program.[7],[8] Later in 2006 Han and Pan used a maintenance program and reported a significant reduction in the rate of tumor recurrence compared to those treated with the initial induction program only.[9]

In 1990, BCG was approved by the Food and Drug Administration (FDA) as a primary treatment for the bladder carcinoma in situ (CIS) and as a preventive treatment for papillary tumors, thus BCG became essential in complementary treatment for NMIBC.[10]

METHODS AND MATERIALS

This prospective study has been conducted in urology department at Tishreen University Hospital from 2023 to 2024.

Patients diagnosed with bladder transitional cell carcinoma by transurethral resection with no muscular invasion in pathology and who had a high or intermediate risk for tumor recurrence were included.

Exclusion criteria were: non transitional cell bladder tumor, low risk for tumor recurrence according to EAU Guidelines 2018, incomplete transurethral resection, previous intravesical chemotherapy, BCG contraindications, sever complication of the treatment and patients with incomplete follow-up period.

Patients data collected: date of diagnosis, sex, age, stage, grade, tumour size, multifocality, presence of concomitant CIS, and presence of detrusor muscle in the resected material.

BCG immunotherapy Onco TICE (CFU=2-8×108) was given according to the manufacturer's recommendations as an induction course of 6 weekly instillations.

Maintenance treatment 3 weekly instillations every 3 months for 1 year, was given as a single standard.

The follow-up program included a cystoscopy every 3 months with biopsies from the site of the previous curettage or new recurrence.

RESULTS

75 patients were conducted in our study. The median age of patients was (63.92±5.3) years, 74.7% of them aged between (55-69) years and 25.3% aged between (70-75) years.51(68%) of patients were males and 24(32%) were females. Tumor stage was Ta, T1 and TIS in (16%), (74.7%) and (9.3%) respectively. High grade(HG) patients were more common than low grade(LG) (77.3) vs (22.7%) respectively. In most cases there was no concomitant CIS (92%), however in (8%) there was a concomitant CIS. Tumor sized 3 cm or more in (65.3%) and (34.7%) sized less than 3cm. About (60%) of cases have multifocal tumors, while (40%) 0f cases have single focal tumors. History of recurrence was found in (57.3%) of cases.

Table 1: Baseline characteristics of 75 patients.

Variable		Number	%
Age group	(55-69)y	56	74.7%
	(70-75)y	19	25.3%
gender	Male	51	68%
	Female	24	32%
Stage	Ta	12	16%
	T1	56	74.7%
	TIS	7	9.3%
Grade	HG	58	77.3%
	LG	17	22.7%
concomitant CIS	Yes	6	8%
	No	69	92%
Size	<3	26	34.7%
	≥3	49	65.3%
Number of tumors	Single	30	40%
	Multiple	45	60%
Previous Recurrence	No	32	42.7%
	Yes	43	57.3%

After the BCG induction therapy and maintenance programs recurrence occurs in 26 (43.7%) cases only. Of these recurrent cases tumors <3 cm counted 7(26.9%) while tumors ≥3 cm counted about 19(73.1%). T1 tumors were more common than Ta and TIS in the recurrent cases (21(80.8%), 3(11.5%) and 2(7.7%)) respectively. However, in comparison with non-recurrent cases of each we didn't found an important significance in these groups ($p > 0.05$).

High grade tumors recorded 23 recurrence cases (88.5%), while only 3 recurrent tumors were low grade (11.5%) with an important significance when compared with non-recurrent cases of the same groups ($p < 0.05$). As well as multifocal tumors were more common than single tumors in the recurrent cases (20(76.9%) vs 6(23.1%)) with an important significance ($p < 0.05$).

Primary tumors were less common than cases with previous recurrence history in the recorded recurrent cases (7.7%) and (92.3%) respectively with an important

significance (p<0.05). In contrast the tumors without concomitant CIS were more common than tumors with concomitant CIS (19.2%) and (80.8%) with an important significance (p <0.05).

The main side effects caused by therapy were frequency (86.7%), BCG-induced cystitis (65.3%) and hematuria (36%). On the other hand most of the systemic side effects were either mild or intermediate. It included fever(33.3%), fatigue (30.7%) and flu-like symptoms (29.3%). However, high fever and chills occurred in one case (1.3%), it was severing enough to stop the therapy.

Table 2: Recurrence Rate According to Different Variables.

Variable		Recurrence N(%)	Non-recurrence N(%)	p-vlue
Size	**<3**	**7(26.9%)**	**19(38.8%)**	**0.07**
	≤3	**19(73.1%)**	**30(61.2%)**	
Stage	**Ta**	**3(11.5%)**	**9(18.4%)**	**0.6**
	T1	**21(80.8%)**	**35(71.4%)**	
	TIS	**2(7.7%)**	**5(10.2%)**	
Grade	**HG**	**23(88.5%)**	**35(71.4%)**	**0.04**
	LG	**3(11.5%)**	**14(28.6%)**	
Number of tumors	**Single**	**6(23.1%)**	**24(49%)**	**0.02**
	Multiple	**20(76.9%)**	**25(51%)**	
Previous Recurrence	**No**	**2(7.7%)**	**30(61.2%)**	**0.0001**
	Yes	**24(92.3%)**	**19(38.8%)**	
concomitant CIS	**Yes**	**5(19.2%)**	**1(2%)**	**0.009**
	No	**21(80.8%)**	**48(98%)**	

DISCUSSION

Intravesical BCG therapy is being used for last 30 years to treat NMIBC after transurethral resection. Its role in reducing the recurrence rate to half and effect on progression is well established. In this study we investigated BCG-intravesical treatment outcomes in patient with high or intermediated risk NMIBC. The recurrence rate after treatment was only about (43.7%) and it is significantly lower than the recurrence rate without BCG-treatment (60-70%).[2] In a study by Patard et al.[11], the recurrence rate was 50% for TUR-B+BCG vs 90% for TUR-B only. In order to assess disease recurrence, it is appropriate that patients included in our study should be at high risk of recurrence. The inclusion criterion for this study based on medium/high risk for tumour recurrence, which does not necessarily indicate these patients were at high risk of progression.

T1 tumours is most likely to be more aggressive than high-grade Ta tumours.[12] Thus, several studies have shown that BCG reduces recurrence in highrisk NMIBC, and the results in the present study confrm this notion. The role of tumor size has been a matter of controversy in the recent literature. Some reports have recognized a tumor size >3 cm to be predictive of both recurrence and progression or of recurrence only, while other reports have failed to show any clinical value.[13],[14] Jancke G et al concluded in their study that tumors larger than 3 cm were associated with increased risk of recurrence but there was no impact of tumor size on progression.[14] In our study we found that tumor size had an effect on recurrence but this result has no significance.

By evaluation of prognostic factors affecting recurrence in 75 patients with superficial bladder cancer in this study, we found that high tumor grade, multifocal tumors and previous recurrence were powerful predictors. Concomitant CIS has been considered another important prognostic factor in several studies; however, its prevalence has been shown to vary considerably, from 10% in early series[15] up to 50% in more recent reports in which multiple biopsies[13] or restaging TUR[16] were routinely adopted. However, we couldn't improve that presence of concomitant CIS is a powerful predictor for recurrence, due to the rarity of the patient with concomitant CIS in our study. That's why most of the recurrent cases didn't have a concomitant CIS. Unfortunately, the short follow-up period of our study was the main limitation progression to measure the efficacy of BCG on tumor progression.

CONCLUSION

We support the previous studys that intravesical BCG vaccine instillation reduces the recurrence rates in non-muscle-invasive urothelial bladder cancer ptients(NMIBC), especially when a maintenance treatment program is used. This study also supports the recommendation of using BCG as the frst-line supportive treatment in patients with high-risk NMIBC.

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