To the Editors:

Clinical outcomes in a cohort of patients with T1 high grade urothelial bladder cancer not receiving intravesical bacillus Calmette-Guerin: a 15 year experience

S A S Goonewardena[1], U Jayarajah[1], S N Kuruppu[1], H M K B Herath[1], D M H Fernando[1], K Vickneswaran[1]

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Introduction

High grade/ grade-3 tumours (T1-HG/G3) with lamina propria invasion form the highest risk category of non-muscle invasive bladder cancer (NMIBC) for progression to muscle invasive disease and cancer specific mortality[1]. The only treatment modality which can reduce the risk of progression is intravesical Bacillus Calmette Guerin (BCG) immunotherapy and the patient should indeed receive optimal BCG therapy-i.e.BCG induction with a six-week induction course followed by maintenance [2]. In Sri Lanka, T1-HG/G3 patients did not receive intravesical BCG due to non-availability during the study period (2000-2014).

The objective of this study was to evaluate the clinical outcomes of recurrence, progression, recurrence free survival, progression free survival and overall survival in a cohort of patients with T1-HG/G3 detected after transurethral resection of bladder tumour (TURBT) that did not receive intravesical BCG therapy.

Methodology

Patients with primary T1G3 (WHO-1973) T1-HG (ISUP/WHO-2004) NMIBC tumour, formed the retrospective study cohort (prospectively collected data) studied at one of two urology units at the National Hospital of Sri Lanka, Colombo between January-2000 and December-2014. All patients underwent a TURBT and subsequent periodic surveillance with check cystoscopy. Patient and tumour characteristics were documented. Time to first recurrence, progression to muscle invasive disease, and the overall survival were endpoints. Institutional ethical clearance was obtained.

Results

A total of 83 patients had pT1-HG tumours during the 15-year study period. The majority were males (n=76; 91.6%). Median age was 67 years (IQR:59-73). Visible (macroscopic) haematuria was the commonest clinical presentation (n=76; 91.6%). Median duration of symptoms was 1 month (range:0.25-24.0).

The majority were papillary tumours (*n*=58,69.9%), solid tumours were seen in 11 (13.2%) and mixed tumours (presence of papillary and solid components) were seen in 14 (16.9%) patients. Majority were solitary tumours (*n*=58;69.9%) but 15 (18%) had three or more tumours. None of the patients had concomitant Tis (carcinoma in-situ). Muscle in the tissue specimen was seen in 48 (57.8%) patients. Eighteen (21.7%) were lost to follow up after the first surgery. The median duration of the first recurrence was 4.7 months (IQR:2.9-17.1) and progression was 18 months (IQR:5.6-42.2). Sixteen patients progressed to pT2 while two patients to pT3 and one patient to pT4. The summary of follow up and survival characteristics is given in Table 1.

[1]*Department of Urology, National Hospital of Sri Lanka, Colombo, Sri Lanka.*

Correspondence: SASG, e-mail: <*drsasgurol@yahoo.com*>. Received 14 November 2017 and revised version accepted 05 January 2018.

Table 1. Summary of follow up of pT1-HG bladder tumours

	N	*%*	*Median follow up (months)*
Total number followed up	65/83	78.3%	18.3 (1-189)
Recurrence	48/65	73.8%	22.5 (3-189)
Progression	19/65	29.2%	20.3 (1-126)
Recurrence with no progression	29/65	44.6%	27 (3-189)
No recurrence	17/65	26.2%	15.3 (3-148)

Table 2. Survival characteristics of pT1-HG bladder tumours

	1 year survival N (%)	*5 year survival N (%)*	*10 year survival N (%)*
Overall survival	39 (60%)	12 (18.5%)	6 (9.2%)
Recurrence-free survival	18 (27%)	8 (12.3%)	3 (4.6%)
Progression-free survival	36 (55.4%)	12 (18.5%)	6 (9.2%)

Discussion

This study included 83 consecutive patients not receiving intravesical BCG after the initial TURBT. The sample had a male preponderance (91.6%) with a median age of 67 years. The median duration of first recurrence was 4.7 months (IQR:2.9-17.1) and progression was 18 months (IQR:5.6-42.2).

Intravesical BCG immunotherapy after the initial TURBT was the standard of care in the West for pT1-HG/G3 disease even at the commencement of this study. However due to the non-availability of intravesical BCG in Sri Lanka consequent to the limited health budget during the study period, all patients underwent TURBT followed by cystoscopic bladder surveillance only. A significant number (21.7%) was lost to follow up after the initial TURBT. Even in the recurrence-free patients (26.1% of those followed up) the median follow-up was 15.3 months. This is a reflection of the large catchment population of the institution (over 8 million) and the long distances (over 100-200 km) travelled by patients from home to the hospital. We can assume that most of these patients had not developed recurrent episodes of visible haematuria, a symptom of neglected bladder tumour recurrence, that would compel them to report back to the same urology unit. The median duration of follow-up of the 65 patients (78.3%) eventually studied was 18.3 months.

In the present study, 73.8% developed recurrences and 29.2% progressed to muscle invasive disease. The median follow-up of those who developed recurrences and progression were 22.5 and 20.3 months respectively. The 1, 5 and 10-year recurrence-free survival was 27%, 12.3% and 4.6% respectively and progression-free survival was 60%, 18.5% and 9.2% respectively.

In a study by Peyromaure *et al*. of 57 T1-G3 urothelial bladder cancer (UBC) patients who received intravesical BCG therapy, the median follow up was 53 months (range: 9-110 months). The recurrence rate and the progression rate were 42.1% and 22.8% respectively [3]. Fifty patients (87.7%) had no residual disease after the first BCG course. Margel *et al*. documented a series of 78 patients with T1-HG UBC treated by intravesical BCG with a median follow up of 107 months (range:16-238). The recurrence rate was 35% at a median follow-up of 18.5 months and progression was 18% at a median of 31.4 months following treatment [4]. The 2, 5 and 10 year recurrence-free survival rates were 76%, 72% and 62% respectively and progression-free survival rates were 92%, 82% and 80% respectively [4]. A major limitation of the present study, therefore, is the short median follow-up of 18.3 months.

These studies demonstrate a significant reduction in the recurrence rates and lesser progression rates with longer median follow-up. However, the striking comparison between those who receive intravesical BCG and those who do not in regard to their recurrence-free survival and progression-free survival makes intravesical BCG immunotherapy a mandatory component in the treatment of T1-HG UBC.

In a prospective randomised trial, 86 high grade patients with NMIBC were randomly assigned to receive either TURBT (*n*=43) or TURBT plus intravesical BCG (*n*=43). BCG was administered weekly for 6 weeks only. The 10-year progression free rate was 61.9% for patients treated with BCG and 37% for TURBT alone group [5].

Conclusion

High grade pT1 UBC not treated by intravesical BCG after the initial TURBT demonstrate a high rate of recurrence and greater propensity to progression into muscle invasive bladder cancer. At least a six-week BCG induction course alone (without maintenance) is worthy of consideration in the management of patients with pT1-HG UBC in Sri Lanka where the resources are limited.

Conflicts of interest

There are no conflicts of interest.

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