ARTIGOS ORIGINAIS

DOI: 10.55825.RECET.SBU.0167

INTRAVESICAL ADJUVANT THERAPY WITH GEMCITABINE FOR PATIENTS WITH HIGH-RISK NON-MUSCLE INVASIVE BLADDER CANCER: EXPERIENCE FROM A PUBLIC HOSPITAL IN BRAZIL

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ABSTRACT

INTRODUCTION: Adjuvant intravesical therapy is the treatment of choice for high-risk non-muscle invasive bladder cancer (NMBC), which reduces recurrence and disease progression. Bacillus Calmette-Guerin (BCG) is the main drug used, but it is scarce worldwide. Here, we report the use of intravesical gemcitabine (GEN-IV) in our hospital.

METHODOLOGY: This study included patients with a histological diagnosis of high-risk urothelial NMIBC. Patients underwent a second transurethral resection of bladder tumor (TURB) within 6 weeks of diagnosis. GEM-IV therapy was indicated if T2 progression was not achieved. Follow-up was recommended with cystoscopy and urinary tract ultrasound 1 month after the last cycle of GEN-IV and then every 6 months or until recurrence and/or progression.

RESULTS: This study included 28 patients from July 2017 to June 2019. Of these, 8 were excluded. The average age was 66.9 years. The mean number of lesions detected at baseline TURB was 3.75 and the estimated mean lesion size was 4 cm. With a follow-up of 4.43 years, 40% had no recurrence. Recurrence occurred in 12 patients and the mean time to this event was 15.58. Among those with recurrence, 33.3% had disease progression.

CONCLUSION: GEM-IV therapy demonstrated low toxicity and acceptable rates of recurrence and progression with a follow-up of >4 years. Alternatives must be developed to supply the lack of BCG.

Keywords: Non-muscle-invasive bladder cancer; Administration, Intravesical; BCG; Gemcitabine.

INTRODUCTION

Bladder cancer is the 10th most commonly diagnosed cancer worldwide, with approximately 573,000 new cases and 213,000 deaths in 2020 (1). Approximately 70% of bladder cancers are classified as NMIBC at diagnosis and T1 represents 20% of all non-muscle-invasive bladder cancer (NMIBC). NMIBC presents 31%–78% of recurrence and 0.8%–45% of progression, with 10%–34% of patients diagnosed with T1 tumors dying within 5 years (2).

A meta-analysis of prognostic factors in high-grade T1 (HGT1) bladder cancer suggests that increased depth of tumor invasion, presence of carcinoma in situ (CIS), lymphovascular invasion, female sex, tumor size greater than 3 cm, nonuse of bacillus Calmette-Guerin (BCG), and multiple tumors negatively affect progression and cancer specific-survival (3). Thus, patients with high risk are often candidates for adjuvant intravesical therapy to decrease the risk of recurrence and progression. The European Organization for Research and Treatment of Cancer classification (T1 and/or high grade and/or more of 3 lesions and/or at least one lesion largen than 3 cm) was used to define patients with high-risk NMIBC (4).

BCG is the main drug used in adjuvant intravesical therapy after transurethral resection of bladder tumor (TURBT). Several studies have demonstrated the potential to decrease recurrence and progression rates, especially in high-risk diseases (5). However, other strategies have been used to replace BCG due to the BCG shortage worldwide and its suspended production by regulatory departments in Brazil (6, 7).

OBJECTIVES

This study aims to evaluate the rate of recurrence and progression of intravesical adjuvant therapy with gemcitabine after TURBT in high-risk urothelial NMIBC.

METHODS

This study included patients of both sexes, aged ≥ 18 years, with a diagnosis of high-risk urothelial NMIBC. Patients with synchronous or previous urothelial carcinoma of the upper urinary tract, those undergoing any treatment for NMIBC other than TURBT, and those who lost follow-up were excluded from the study.

The study was conducted at the Hospital das Clínicas of the Federal University of Pernambuco after approval by the ethics and research committee of the Health Sciences Center. Patients with high-risk urothelial NMIBC who agreed to participate in the study signed an informed consent form. Patients underwent a second TURBT up to 6 weeks after the high-risk urothelial NMIBC diagnosis. Intravesical therapy with gemcitabine was indicated if T2 progression is not achieved.

Intravesical therapy was performed in an outpatient setting and followed by the steps described below: spontaneous bladder emptying; bladder catheterization with 12 Fr catheter; gemcitabine instillation at 2 grams diluted in 50 ml of 0.9% saline solution remaining in the bladder for 1 h; spontaneous bladder emptying. Instillations were performed once a week for 6 weeks. Recurrence was defined as the presence of a bladder lesion in control cystoscopy, proved by pathological study and progression as a recurrence with pathological stage T2. Follow-up was recommended with cystoscopy and urinary tract ultrasound 1 month after the last cycle of intravesical gemcitabine and then every six months or until recurrence and/or progression, in addition to a urine analysis and culture collected 1 month after the last application and in the presence of voiding symptoms. Patients who did not present recurrence by cystoscopy underwent urinary cytology (3 samples) at the end of follow-up. CT scans of the abdomen and chest with contrast were performed in all patients who showed disease progression or recurrence with option for cystectomy.

RESULTS

This study recruited 28 patients from July 2017 to June 2019. Of them, 8 were lost to follow-up and were excluded, leaving 20 patients (14 males and 6 females). The average age was 66.9 + 6.8 years (range: 52–77 years). In the initial TURBT, the average number of lesions detected was 3.75 ± 1.62 (range: 1–8 lesions) and the estimated lesion size was 4 + 1.72 cm (range: 1.5–7.0 cm). Table 1 shows the histopathological findings of the first TURBT. All 20 patients underwent a second TURBT within 6 weeks. Table 2 shows the histopathological findings.

Patients were referred to intravesical therapy with gemcitabine after the second TURBT. The time between the second TURBT and the start of intravesical therapy was 12.65 ± 4.20 weeks (range: 7–20 weeks). All patients completed treatment, with no serious adverse effects. Follow-up was performed with cystoscopy and urinary tract ultrasound, with an average time of 4.43 years, with the last assessment of patients who did not have a recurrence performed from September to December 2022.

Of the 20 patients, eight (40%) had no recurrence and all had three samples of urine cytology negative for high-grade urothelial car-

Table 1 - Pathological findings of the first TURBT.

	n	%
T-stage (TNM)		
pTa	7	35
pT1	13	65
Grade		
Low-grade	5	25
High-grade	15	75
CIS*		
Yes	1	5
No	19	95

*CIS: carcinoma *in situ*

Table 2 - Pathological findings of the second TURBT.

	n	%
Lesions in the 2nd TURBT		
Yes	15	75
No	5	25
Stage T (TNM)*		
pTa	4	26.7
pT1	11	73.3
Grade		
Low-grade	2	13.3
High-grade	13	86.7

* If there was a tumor
TURBT: transurethral resection of bladder tumor

cinoma at the last evaluation. Recurrence was experienced by 12 patients and the time to this event was 15.58 ± 3.09 months (range: 15–40 months). Of the patients who had a recurrence, 4 (33.3%–20% of all patients) experienced disease progression. Two of them underwent palliative treatment due to precarious clinical conditions and later died. The other two patients were lost to follow-up but were classified as progression, but with no information about the death.

Of the eight patients who had recurrence without progression, one died of another cause and three underwent radical cystectomy, with one patient dying from surgical complications. The other four patients were being followed-up. Table 3 and Figure 1 summarize the evolution of the patients.

Lesions were found in the second TURBT in 15 patients. Of these patients, ten (66.6%) had a recurrence, and of the five patients who did not present with lesions in the second TURBT, two (40%) presented recurrence. However, no statistically significant difference was observed related to the presence of lesions in the second TURBT and recurrence after intravesical therapy with gemcitabine ($p = 0.347$ – Fisher's Exact Test).

The median time to start intravesical therapy after the second TURBT was 14 and 10 weeks for patients with and without recurrences, respectively. This analysis revealed no statistically significant difference ($p = 0.069$ – Mann–Whitney Test).

DISCUSSION

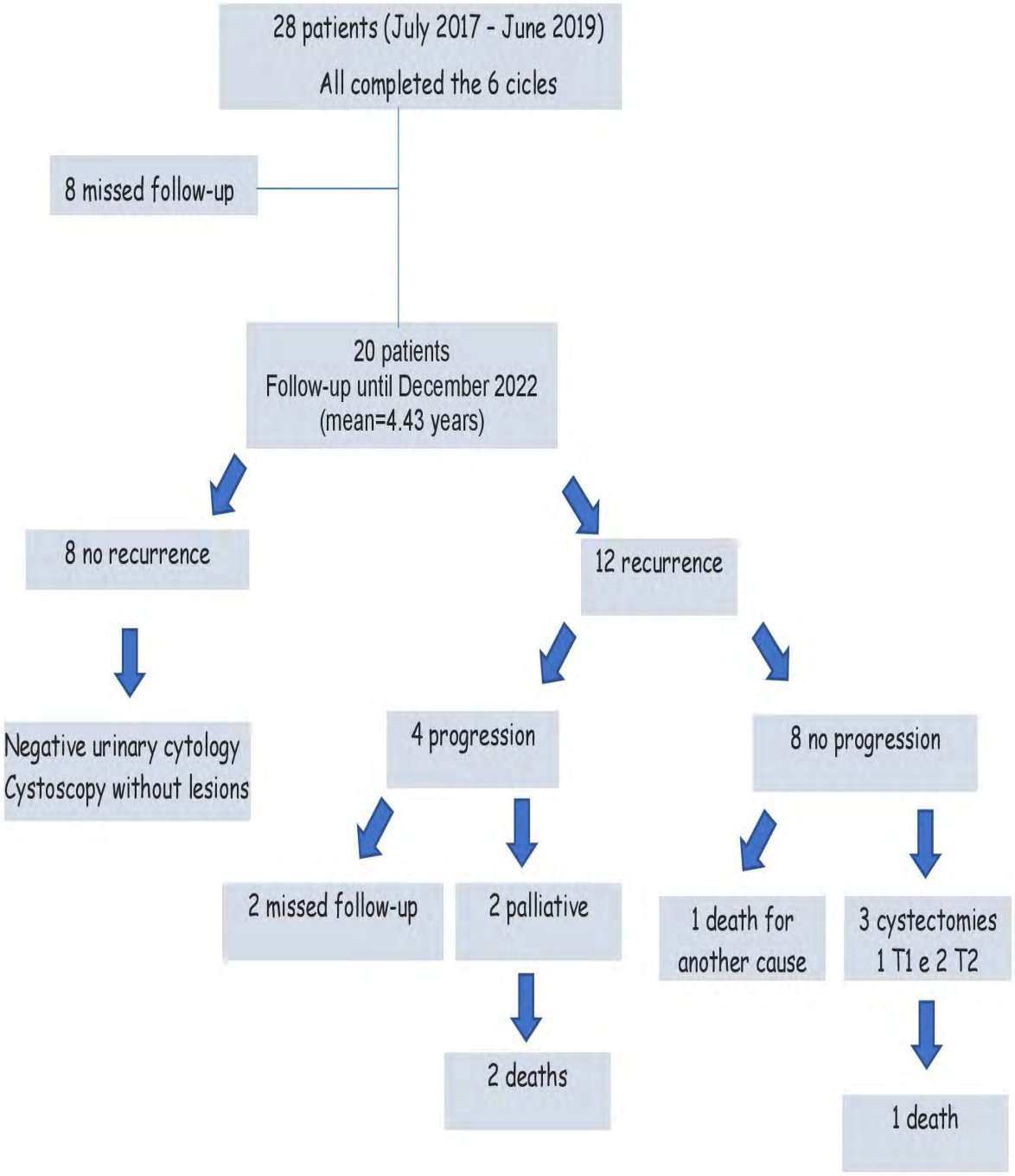
Adjuvant intravesical therapy is an important tool in the treatment of high-risk urothelial NMIBC. BCG is the main drug used in this scenario, having a positive impact on recurrence rates and disease progression (8). However, other strategies should be replaced because of the scarcity of BCG worldwide and

Table 3 - Outcomes of patients who had recurrence.

	n	%
Recurrence		
Yes	12	60
No	8	40
Progression		
Yes	4	33.3
No	8	66.6
Further treatment		
TURBT	5	41.6
Cystectomy	3	25
Palliative	2	16.6
Missed follow-up	2	16.6
Stage T (TNM): if cystectomy		
pT1	1	33.3
pT2	2	66.6
Grade: if Cystectomy		
Low-grade	0	0
High-grade	3	100

TURBT: transurethral resection of bladder tumor

Figure 1 - Summary of the evolution of the patients participating in the study.



the suspension of production in Brazil (6, 7). Gemcitabine is one of the drugs that is used in adjuvant intravesical therapy, whose studies show variable results in the literature (9). Our prospective evaluation of case series included patients with high-risk urothelial NMIBC treated with intravesical gemcitabine. The high-risk criteria used were T1 and/or high-grade and/or more than 3 lesions and/or at least 1 lesion of greater than 3 cm (4, 10).

All patients completed the six cycles of intravesical gemcitabine, demonstrating that the drug causes few significant adverse effects and is well tolerated. The recurrence and progression rates in our evaluation were 60% and 20%, respectively. Porena et al. de-

monstrated that the recurrence rate in patients treated with BCG was 28.1% × 53.1% in patients who received gemcitabine and with no disease progression at a mean follow-up of 44 months. The dose used was 2 g; however, the patient remained with the solution for 2 h in the bladder, unlike our study, and the beginning of intravesical therapy was performed 14 days after the second TURBT, and maintenance was performed with 3, 6, 12, 18, 24, 30, and 36 months after (11). Another study compared gemcitabine with 1/3 dose of BCG. Gemcitabine at 2 g was administered, with a monthly maintenance dose for 1 year. Recurrence and progression were experienced by 23.7% and 5% of patients in the BCG group versus 26.2% and 8.19% in the gemcitabine group, respectively, at 1 year (12).

Two statistical analyses were performed to identify any risk factors for disease recurrence. Of the 15 patients who had a lesion in the second TURBT, 66% had a recurrence, and of 5 who had no lesion, 40% had a recurrence, with no statistically significant difference despite the difference in proportion between the groups (p = 0.347).

The other assessment was concerning the time to start intravesical therapy after the second TURBT. The average time to onset was 14 and 10 weeks for the group with and without recurrence, respectively. This analysis revealed no statistical significance despite the trend toward recurrence with a longer time to start intravesical therapy (p = 0.069). The delay in starting intravesical therapy certainly had an impact on the data in this study. With a larger sample, perhaps we could demonstrate differences between groups. The delay in chemotherapy treatment occurred due to logistical difficulties common to the brazilian health system.

This study has limitations, including the absence of a control group. This is explained by the unavailability of BCG (at the time of the study there was no national production) and by evidence from studies reporting the benefit of intravesical gemcitabine. We also had a high rate of recurrence and progression. No maintenance dose and delay in starting intravesical therapy may be responsible for the high rate. When this study was designed, some data in the literature suggested an oncological benefit even in the absence of maintenance doses (13).

Additionally, we had difficulties in conducting adequate follow-up, especially in 2020 and 2021, due to the coronavirus disease-2019 pandemic. During which, many patients did not undergo cystoscopy and ultrasound regularly, which may have impaired the evolution of the disease, especially concerning progression and mortality (14). Although this study has a small number of patients, it is a reliable portrait of the reality of a SUS tertiary service in the face of a shortage of inputs. Conversely, we had a long follow-up, of almost four and a half months, unlike some studies with lower recurrence and progression rates.

Of the four patients who presented with progression, 2 did not have performance status to undergo cystectomy, underwent palliative treatment, and died. The other two were lost to follow-up, but they were included in the statistics of this group as they had already progressed. Of the patients who had a recurrence and did not progress, four are still being followed with no new recurrence or progression, one died from a cause other than bladder cancer and three underwent radical cystectomy after staging with CT scans of the abdomen and chest with contrast. Of these three, one had stage T1 and two had stage T2 (one died of surgical complications).

Urinary cytology has a high sensitivity for high-grade tumors (84%) and low sensitivity for low-grade tumors (16%). Urinary cytology was performed at the end of the follow-up in patients who did not present with recurrence or progression by imaging tests and/or cystoscopy, providing greater security to determine no recurrence (15).

Finally, the management of patients with high-risk NMIBC is challenging. Treat-

ment with intravesical BCG has its availability compromised by all that has already been mentioned and has a high toxicity profile when available (16). Radical cystectomy is an alternative but with high complication rates. A better selection of patients is essential to define those who could benefit from early surgical treatment. 3) The association of chemotherapy drugs, such as gemcitabine and docetaxel, for intravesical instillation has been highlighted in the absence of BCG, with little toxicity and good survival rates without of recurrence and progression (17).

CONCLUSION

Although this paper presents limitations regarding the number of patients included in the sample, intravesical therapy with gemcitabine has demonstrated low toxicity and acceptable recurrence and progression rates with a follow-up of >4 years. Other alternatives must be developed to supply a shortage of BCG.

CONFLICT OF INTEREST

None declared.

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Submissão em:
10/2023

Aceito para publicação em:
02/2024