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TREATMENT OF PATIENTS WITH SUPERFICIAL BLADDER CANCER STRATIFIED BY RISK GROUPS TREATED WITH LYOPHILIZED MOREAU-RIO DE JANEIRO BCG STRAIN

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ABSTRACT

Introduction: The Moreau-Rio de Janeiro BCG strain is considered the most effective to stimulate immunologic activity in mice. The objective of this prospective study was to evaluate BCG results for patients with superficial bladder cancer stratified by risk groups.

Material and Methods: From April 1988 to May 2000, 100 patients were treated by transurethral resection for bladder tumor, followed by intravesical instillation of 40 mg BCG, with induction and maintenance cycles. Fisher exact test and Chi-square test, with 95% significance, were used to evaluate possible associations among variables. The Kaplan-Meier method was used to evaluate the disease-free interval and patients' survival, while log-rank test was used to compare the curves among the groups.

Results: The median follow-up was 69.3 months and varied from 10 to 153 months. Overall recurrence and progression rates were 55% and 13%, respectively. The medium time to recurrence was 9.4 months and to progression was 24.4 months. The cancer specific survive was 90%.

Univariate analysis revealed that tumor recurrence was significantly associated with weekly BCG failure (p=0.011), multifocality (p=0.001), number of recurrences after primary therapy (p=0.001) and the need to Mitomycin C instillation (p=0.001). However, no variable was significantly associated with recurrence in multivariate analysis. There were significant associations, in univariate analysis, between disease progression and the following variables: tumor grade, weekly and 15-days BCG failure, both as first line and second line therapy, recurrence and need of Mitomycin C therapy. Independent variables to progression were 6.7 relative risk to weekly BCG failure, tumor grade and 15-days BCG (p= 0.08; CI=0.79-56.7), 2.4 (p= 0.11; CI=0.80-7.15) and 1.5 (p=0.23; CI=1.05-2.13), respectively.

Patient stratification by risk groups were able to predict progression (p=0.045), but not recurrence (p=0.311). Disease progression rates were 3.2%, 12.2% e 25%, in low, intermediate and high risk groups, respectively. The BCG administration was well tolerated, and 21 patients (21%) didn't present any side effects.

Conclusions: Intravesical instillation of BCG was overall well tolerated. Adjuvant BCG didn't decrease significantly recurrence rates, and 16% of the patients underwent alternative therapy with intravesical Mitomycin to prevent new recurrences. The risk group classification was able to select patients with high risk to progression. Tumor grade, BCG failure as first and second line therapies, were predictive factors of poor prognosis. BCG of Moreau-Rio de Janeiro strain was well tolerated, similar to other strains used in literature.

Key words: bladder neoplasms; treatment; immunotherapy; BCG vaccine
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INTRODUCTION

Transitional cell carcinoma of the bladder is the 7th most common cancer affecting men, and the 10th among women in Brazil (1). In USA, it is the 4th neoplasm among men, and the 6th among women (2).

Transitional cell carcinoma of the bladder presents initially in superficial stages in 70% of the

cases, of which 30% are multiple tumors (3,4). Fifty to 75% of patients treated by endoscopic resection of the bladder tumor present subsequent recurrences, and 10-20% progress to invasive bladder cancer. Multiplicity is directly associated to the possibility of tumoral recurrence. The risk of recurrence in patients with solitary tumor is 46%, and with multiple tumors is 73%; the latter generally present lower disease-free period (4,5).

Invasive carcinoma of the lamina propria (T_1) represents 30% of superficial bladder cancer cases. Among these, approximately 50% are grade 2, and about 40% grade 3, according to Mostofi classification (6). Patients with T_1G3 have the worst prognosis, for they present high risk of recurrence (50-80%) and disease progression (33% to 48%, in 2-5 years of follow-up (3-5,7).

Several studies report correlation between a high risk of tumoral progression and histopathological factors, including grade 3 carcinomas over 3cm, carcinoma in situ associated with stage T_1 with vascular and lymphatic invasion, multifocality, short time period between recurrences, and those who remain presenting positive urinary cytology after TURBT (4-8). Recently, a new classification of superficial transitional cell carcinoma of the bladder, stratified by risk group of tumoral progression, was proposed, based on prognostic factors (9-12).

In 1976, Morales et al. reported the intravesical use of Calmette-Guérin bacillus for treating superficial carcinoma of the bladder. The strain Moreau-Rio de Janeiro was considered the most virulent among the 9 lyophilized BCG strains used in the world (5,7,8,14,15).

The aim of this prospective study was to evaluate the outcomes of the use of BCG Moreau-Rio de Janeiro inpatients with superficial cell carcinoma of the bladder, stratified by risk group.

MATERIALS AND METHODS

This series is formed by 100 patients treated between April 1988 and May 2000. All patients had superficial cell carcinoma of the bladder, histologically classified as stage pTis, pTa, and pT_1, according to pTNM classification, and to WHO's classification system (6).

The special physical examination was done in men by rectal exam, to evaluate the prostate and presence of vesical or pelvic palpable mass. For women the tumor was evaluated by vaginal exam.

Pre-operative and follow-up endoscopic studies of patients were performed with local anesthesia. Patients were told not to empty the bladder before endoscopy. After urethral passage of the cystoscope, the study was initiated by collecting urine for oncotic cytology. A 20 mL syringe was connected to the endoscope, through which was performed urine barbotage, with successive movements of urine aspiration and injection, 5 times. The urine was collected in 50 mL recipients and immediately fixed in 70% alcohol. Tumor and questionable urothelium regions, as characterized by hyperemia and/or elevated surface, were submitted to cold biopsy. Tumors were then drawn in cystoscopic forms, including localization, size, and number of lesions.

During the pre-operative period, patients were submitted to routine laboratory exams for clinical and anesthetic risk assessment. As for imaging methods, all patients were submitted to chest X-ray and abdominal and pelvic ultrasound; CT scan was indicated only for selected cases, aiming to improve the definition of the clinical stage.

Patients included in this study underwent TURBT, and completed at least the first cycle of BCG. Patients with papillary tumor in prostatic urethra and/or important LUTS were submitted to TUR of prostate and bladder tumor at the same time. Patients maintained Owen catheter with saline irrigation, until haematuria ceased. Most patients were discharged on 2nd post-operative day, after removing the catheter.

At the ambulatory visit, we performed urine analysis type I, with culture and oncotic cytology. Patients were suspected to have CIS when cytological study was class V. In theses situations, we performed a new cystoscopy, with random vesical biopsy to detect in histological study the possible urothelial focus of CIS.

The age of studied patients ranged from 26 to 87 years, median 65 years, and mean 62.9 years.

Regarding race, there were 93 whites and 7 black patients. Eighty-one patients were male. Fifty-five percent were smokers, and 40 (48.1%) have smoked for 10 to 30 years.

Stage pTa and pT_1 were identified in 67% and 33% of patients, respectively. Histopathologic grades G1, G2, and G3, were diagnosed in 31, 50, and 19% of patients, respectively.

Time to disease progression in the post-operative period was calculated from the initial haematuria date to the diagnosis, and among the 66 patients presenting the disease for the first time, ranged from less than 1 month to 60 months, median of 4 months. Among 34 patents admitted to the hospital to treat recurrences, time has ranged from 3 months to 226 months, median of 74 months.

The distribution of patients classified by risk groups, according to criteria established by Millan-Rodrigues et al. (12), may be observed in Table-1.

Adjuvant Therapy

Patients were treated after TURBT with lyophilized BCG of Moreau-Rio de Janeiro strain, with 40mg ($2x10^8$ colonies/units of *Mycobacterium bovis*) in intravesical applications, beginning two weeks after the surgery.

Treatment with BCG was made with induction and maintenance cycle, defined in 1988 standard protocol (Figure-1). Some cases of superficial tumors recurrence more than two times received Mitomycin C, in an attempt to control the disease.

All therapeutic cycles were performed with 6 applications of immune- or chemotherapy. Lyophilized BCG was applied in 20 cL of saline solution, and applied through an urethral catheter. Patients were oriented to retain it in bladder during 2 hours. No intradermal vaccine was administered.

Maintenance cycle was administered in the absence of recurrence or positive cytology after a weekly cycle. Similarly, 6 applications were performed each 15 days. If after the 15-days cycle the patient did not have evidence of tumor, the monthly cycle was initiated. At the end of each cycle the patient was submitted to urinary cystoscopy and cytology. After this period, the patient was followed with urinary cytology and cystoscopy every 6 months.

Patients with recurrence at any time during BCG cycle was once again submitted to endoscopic surgery and a new induction cycle. BCG treatment failure was defined as persistence of superficial tumor recurrence or progression to invasive cancer.

Statistical Method

Fisher exact test and Chi-square test, with significance levels of 95%, were used to evaluate the association among variables. Disease-free interval (in months) was defined as time between surgery date and disease recurrence. The method of Kaplan-Meier

Table 1 *- Risk group classification.*

Risk Groups	Pathology	(%)
Low	Grade 1 stage Ta Grade 1 stage T1, single tumor	31
Intermediate	Grade 1 stage T1, multiple tumors Grade 2 stage Ta Grade 2 stage T1, single tumor	41
High	Grade 2 stage T1, multiple tumors Grade 3 stage Ta Grade 3 stage T1 Ca in situ association	28

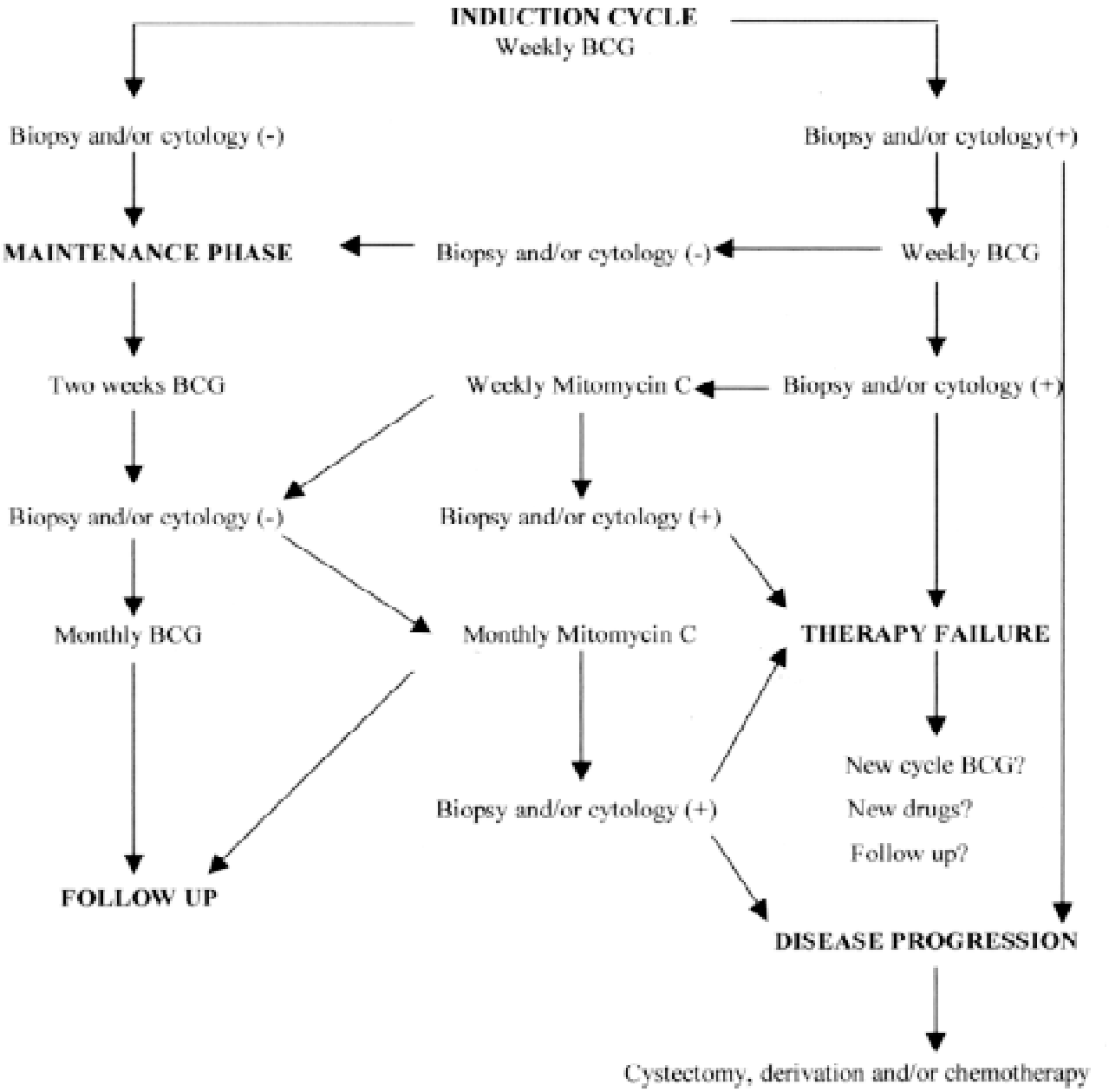

Figure 1 - *BCG and alternative Mitomycin C instilations by cycles.*

Conduct in Recurrence: *Reinduction with BCG or Mitomycin C cycle was analyzed individually, according to patient and urinary tract conditions, and recurrence tumor features: tumoral grade and size, papillary tumor endoscopic aspects (filiform or with large base), multifocality, time to recurrence, previous history to recurrent tumor and association with CIS.*

Table 2- *Results after BCG induction.*

Cystoscopy	Frequency	(%)
Normal	19	20
Inflammation	53	55.79
Tumor recurrence	22	23.16
Disease progression	1	1.05

was used to evaluate patient's disease-free interval and survival, while log-rank test was used to compare curves among the groups (17,19).

RESULTS

Mean follow-up of 100 patients evaluated was of 69.3 months, and ranged from 10 to 153 months. Recurrence and disease progression occurred in 55% and 13% of the patients, respectively. Mean time to recurrence was 9,4 months, and ranged from 2.1 to 59.6 months. Mean time for disease progression was 24.4 months, and ranged from 4.7 to 109.4 months.

After induction cycle, 72 (75.79%) patients did not present recurrence, 23 (23.21%) had superficial tumor recurrence, and 1 case (1.05%) had disease progression. Five patients did not perform weekly BCG for varied reasons, initiating immunotherapy in 15 days BCG cycle. Weekly BCG induced 55.8 of cystitis, defined as focal hyperemia at control cystoscopy. This data is shown at Table-2. Urinary cytology was class 1, 3, and 5, in 74%, 11.58%, and 9.47%, respectively. Cancer-specific survival curve and survival, according to therapeutic results after weekly BCG cycle may be seen in Figures-2 and 3, respectively. Recurrence rate dropped about 5% in 15-days and monthly cycles (Table-3).

Table 3 *- Tumor recurrence after BCG cycles.*

Tumor Recurrence by Cycles	Frequency	(%)
Weekly	22	23.16
Two weekly	4	5.13
Monthly	3	6.12

After weekly cycle, 22 out of 23 patients presenting recurrence underwent TUR and a new induction cycle with BCG, and 1 patient, due to the progression of the disease, was submitted to radical cystectomy. From 78 patients completing 15-days cycle, there were 4 (5.13%) recurrences, and 2 (2.56%) progressions. Fifty three (67.9) patients presented endoscopic signs of cystitis. Urinary cytology was suspected (class 3) in 6 (7.69%), and positive (class 5) in 5 (6.41%) patients.

Forty-nine patients underwent monthly cycles and there were 3 (6.12%) recurrences and no progression, and among these, 29 (59.1%) patients presented endoscopic signs of cystitis. Urinary cytology was suspicious in 1 (2.0%) and positive in 1 (2.0%) patient.

During a mean follow-up of 69.3 months, 45 patients did not present recurrence. Thirty patients presented one recurrence, 10 presented 2 recurrences, 11 presented 3 to 5 recurrences, and 4 patients presented 6 to 14 recurrences. Many of theses recurrences were identified at control cystoscopy, and treated during this procedure by excising the small papillary polyp with a cold biopsy forceps. There were no upper urinary tract lesions.

Sixteen patients received Mitomycin C 20mg, 6 weekly applications, due to recurrence after the second BCG induction cycle. Among these patients, 6 (37.5%) had disease progression ($p<0.001$).

Univariate analysis for recurrence was significant to weekly or induction BCG failure ($p=0.011$), multifocality ($p=0.001$), number of recurrences ($p=0.001$), and Mitomycin C use due to BCG failure ($p=0.001$). However, multivariate analysis for recurrence was inconsistent to the analyzed values.

Univariate analysis for progression was significant for tumor grade, weekly and 15-days BCG failure, presence of recurrence, and Mitomycin C cycle. Prognostic factors significant for disease progression by multivariate analysis were just tumor grade and weekly and 15-days BCG failure, with relative risk of 6.7 ($p=0.08$; CI=0.79-56.7); 2.4 ($p=0.11$; CI=0.80-7.15); and 1.5 ($p=0.23$; CI=1.05-2.13), respectively.

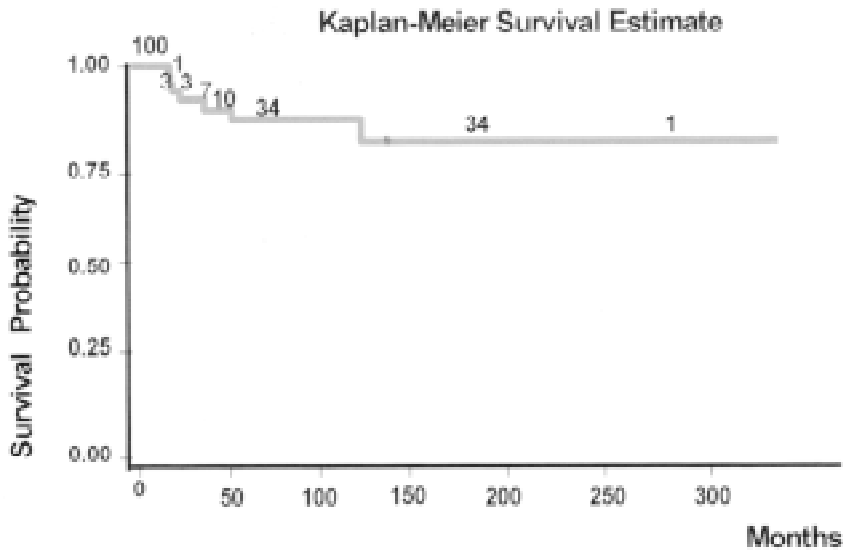

Figure 2 – *Cancer-specific survival curve*

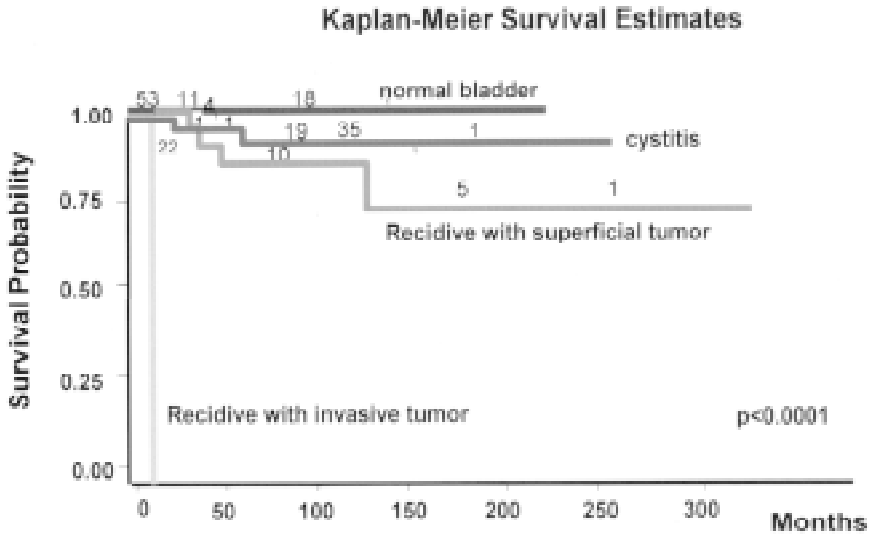

Figure 3 *- Post-weekly BCG suvival curve*

When patients were evaluated according to Millan-Rodrigues et al. group risk, there was no significant difference for recurrence (p=0.311), but actually there was for progression (p=0.045).

Disease progression occurred in 1 of 31 (3.2%), 5 of 41 (12.2%) and 7 of 28 (25%) of patients in low, intermediate, and high risk groups, respectively. Relative risk of progression among groups was 2.58 (p=0.013; CI=1.21-5.50), Table-4.

BCG administration was well tolerated, and 21 (21%) patients did not have any side effects. BCG complication was considered mild (24hrs disuria and/or haematuria) for 53 (53%) patients; moderated (48hrs, fever and/or disuria and haematuria, and worsened LUTS) for 21 (21%) patients; and severe (BCG discontinuation and treatment with isoniazide) for 3 (3%) patients.

Regarding clinical conditions at final follow-up: 60 (60%) patients were alive and free from disease; 2 (2%) were alive with cancer; 10 (10%) were dead from causes not related to cancer; 7 (7%) were dead due to disease progression; and 21 (21%) were lost from follow-up. During mean follow-up time of 70 months, overall cancer-specific survival was 90%.

DISCUSSION

Differences of BCG strains related to bacillus viability, dose, number of colonies, and immunological differences, makes difficult to compare clinically imunotherapic outcomes in patients with superficial carcinoma of the bladder (5,7,8). Sher et al. tested the virulence of six strains of *M. bovis* in mice, and Moreau-Rio de Janeiro strain was considered the most virulent and effective for stimulating the reticule-endothelial system. The less virulent strain was the Japanese, and those of intermediate virulence were the strains Tice and Pasteur. One question suggested in this study was the severity of local cystitis and higher risk of sepsis of the Brazilian strain in its clinical application (14).

An important feature of superficial cell cancer of the bladder is its unpredictable frequency of recurrence after the treatment of the primary tumor. It is usually said that the disease is not limited to papillary lesions, solitary or multifocal in bladder, but affects the whole urothelium, because recurrence is consequence of the transformed urothelium. After initial treatment there are at least 50% less recurrence in the follow-up of patients with stages Ta and T_1. It is estimated that more than 15% of theses patients present progression (7,8).

Recurrence and disease progression reported in patients with superficial cell carcinoma of the bladder in stage pT_1 treated by TURBT, without adjuvant treatment with BCG, range from 59% to 79%, and 12.5% to 48%, respectively, during a follow-up from 33.8 to 81.5 months (4,20-22). Recurrence and disease progression reported in patients with superficial cell carcinoma of the bladder in stage pT_1 treated by TURBT and adjuvant treatment with BCG, ranges from 23.5% to 34%, and from 7% to 17%, respectively, in a follow-up from 30.2 to 59 months (23-26). In the present study, in a mean of 70 months of follow-up, recurrence and progression rates of patients in stage pT_1 was 57.6% and 12,1%, respectively. In our study, recurrence rates for patients in stage pT_1 was higher than in the group reported in literature, perhaps influenced by the number of patients with multifocal lesions (48.5%) of patients with pT_1.

Table 4 *- Relative risk to progression disease by multivariate analysis.*

Variable	RR	p value	CI
Recurrence after weekly cycle	6.7	0.08	0.76 - 56.7
Grade	2.4	0.11	0.80 - 7.15
Recurrence after 2 weeks cycle	1.5	0.23	1.05 - 2.13

CI = confidence interval

Millan-Rodrigues et al. divided patients in 3 risk groups, based on multifocality, grade, and stage of lesions (12). The importance of this classification lies in its clinical functionality. Multifocality was the best factor to predict recurrence, with relative risk of 2, followed by tumoral size over 3cm and presence of CIS, with relative risk of 1.65 each. Grade 3 of disease was the best predictive factor for progression and mortality, with a relative risk of 19.9.

In this paper, univariate analysis of recurrence was significant for weekly BCG failure (p=0.011), multifocality (p=0.001), number of recurrences (p=0.001), and application of Mitomycin C for BCG failure (p=0.001). However, multivariate analysis of recurrence was not consistent for any of the prognostic factors analyzed.

Univariate analysis for progression was significant for tumor grade, weekly and 15-days BCG failure, tumoral recurrence and cycle of Mitomycin C. Multivariate analysis for disease progression was significant and with relative risk of 6.7 (p=0.08; CI=0.79-56.7); 2.4 (p=0.11; CI=0.80-7.15); and 1.5 (p=0.23; CI=1.05-2.13) only for tumoral recurrence after weekly cystoscopy, tumor grade and for tumoral recurrence after 15-days cystoscopy, respectively. Millan-Rodrigues et al. observed 15% of disease progression in the high risk group, and in our study we observed 25% and, thus, these patients need a careful follow-up, including late follow-up, for progression may be detected in up to 20% in 5 years follow-up. The follow-up should preferentially be done by endoscopy in the first 3 years, and interspersed with imaging studies after this period.

Recurrence after induction cycle seems to be a strong indicator to predict which patients present a great potential for disease progression (27-29). In this paper, early recurrence after BCG application was the most important factor to disease progression, with a 6.7 risk. Our results are supported by other reports in the literature (5,8,29,30).

When patients were evaluated according to Millan-Rodrigues et al classification, there was no significant difference for recurrence (p=0.311), but there was actually a significant difference for progression (p=0.045). Thus, to our patients, the proposed classification was significant solely to discriminate patients presenting high risk for progression. Tumor grade and weekly and 15-days BCG failure were predictive factors of bad prognosis in patients with superficial cell cancer of the bladder.

Nowadays, BCG administration in maintenance phase up to 3 years is accepted. BCG maintenance, as defined by Lamm, is applied in series of 3 weekly instillations, applied at 3rd and 6th months and, after that phase, each 6 months during 3 years. Improvement of free-disease survival went from 36% in the group receiving only induction cycle to 77% in maintenance group (p<0.001). This study also demonstrated that BCG maintenance increased time to disease progression or death (p=0.04), and suggested being beneficial for patients survival (p=0.08) (31). At the present study, BCG maintenance may influence the 13% rate of progression in mean 69 months follow-up.

BCG irritative reactions in the bladder occur in 90% of patients. It is observed mainly in the day of the application, but it can persist for days. Low grade fever, haematuria and malaise may occur in 10-25% of patients (32). In this study, theses symptoms occurred in 21 patients (21%). Severe reactions occurred in 3 (3%) patients.

CONCLUSIONS

Moreau-Rio de Janeiro BCG strain may be considered efficient to patients with superficial bladder cancer, as it reduces disease progression compared to the results in the literature for patients without adjuvant treatment. BCG did not reduce significantly recurrence rates, as 16% of patients underwent alternative regimen with Mitomycin C to prevent new recurrences. Classification by risk group was important only to discriminate patients with high risk for progression. BCG failure after weekly cycle, tumor grade and 15-days BCG cycle failure were predictive factors of bad prognosis. Moreau-Rio de Janeiro BCG strain was well tolerated and showed therapeutic results similar to other strains used in the literature.

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EDITORIAL COMMENT

The authors describe a good series with follow-up of 100 patients with superficial urothelial carcinoma of the bladder treated with 40mg intravesical BCG (Moreau-Rio de Janeiro strain).

Tumors presented in initial stage in approximately 70% of cases, of which 30% were multiple and 43% were over 3cm. Recurrence and disease progression occurred in 55% and 13% of the patients, respectively, and time to recurrence varied from 2.1 to 59.6 months. The authors also describe that early recurrence after BCG instillation was the most important factor for disease progression.

In my opinion, this recurrence rate is too high, and could represent residual tumor since, according to the authors, 43% were over 3cm, and over 28% were T_1 or high grade. Herr studied 150 patients submitted to endoscopic resection of bladder tumor (TUR), and all patients were operated by the author. After 2-6 weeks these patients were re-submitted to TUR and, in 114 (76%) patients he found residual tumor, and for 96 patients this was superficial urothelial carcinoma. After re-TUR, it was verified that 29% (28 patients) were understaged and tumor was actually invasive. The results of re-TUR

modified therapeutic management in 33% of the cases.

Thus, as the authors didn't perform at least one early cystoscopy (until 6 weeks after TUR), this high recurrence rate may be due to residual tumor and not recurrence, since in this series 43% were over 3cm, and time to recurrence was short (from 2.1 months). When we started to make routine re-TUR in patients with over 3cm, T_1 or high grade tumors, we have verified a high recurrence rate and a residual tumor rate similar to Herr's study.

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