Original Article

Intravesical chemotherapy for intermediate risk non-muscle invasive bladder cancer recurring after a first cycle of intravesical adjuvant therapy

Vincenzo Serretta, Francesco Sommatino, Cristina Scalici Gesolfo, Vito Franco[1], Giuseppe Cicero[2], Rosalinda Allegro[3]

Departments of Surgical and Oncological Sciences, Section of Urology, [1]Sciences for Health Promotion, Section of Anatomic Pathology, [2]Surgical and Oncological Sciences, Section of Medical Oncology, University of Palermo, [3]Department of Statistics, Gruppo Studi Tumori Urologici (GSTU) Foundation, Palermo, Italy

Abstract

Context: The therapeutic strategy in intermediate risk (IR) non-muscle invasive bladder cancer (NMIBC) recurring after intravesical therapy (IT) is not well defined. Most patients are usually retreated by Bacillus Calmette-Guerin (BCG).

Aims: To evaluate the efficacy of intravesical chemotherapy (ICH) given at recurrence after the first cycle of ICH in IR-NMIBC recurring 6 months or later.

Settings and Design: Retrospective analysis of the efficacy of ICH given after previous IT.

Materials and Methods: The clinical files of IR-NMIBC patients recurring later than 6 months after transurethral resection (TUR) and IT and retreated by IT were reviewed. The patients should be at intermediate risk both initially and at the first recurrence. BCG should have been given at full dose. Cytology and cystoscopy were performed 3 monthly for 2 years and then 6 monthly.

Statistical Analysis: The RFS was estimated by the Kaplan-Meier method and the differences between treatment groups were compared by log-rank test. Mann Whitney U-test was used to compare the parameters' distribution for median time to recurrence. Multivariate Cox proportional hazards models were used. **Results:** The study included 179 patients. The first IT was ICH in 146 (81.6%) and BCG in 33 (18.4%), re-IT was ICH in 112 (62.6%) and BCG in 67 (37.4%) patients. Median time to recurrence was 18 and 16 months after first and second IT ($P = 0.32$). At 3 years, 24 (35.8%) and 49 (43.8%) patients recurred after BCG and ICH, respectively ($P = 0.90$). No difference in RFS was found between BCG and ICH given after a first cycle of ICH ($P = 0.23$).

Conclusions: Re-treatment with ICH could represent a legitimate option to BCG in patients harboring IR-NMIBC recurring after TUR and previous ICH. Prospective trials are needed.

Key Words: Bacillus Calmette-Guerin, intermediate risk, intravesical chemotherapy, non muscle invasive bladder cancer, recurrence

Address for correspondence: Prof. Vincenzo Serretta, Via Piero della Francesca 68, Palermo - 90147, Italy. E-mail: vserretta@libero.it
Received: 10.12.2013, **Accepted:** 01.04.2014

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/0974-7796.148582

INTRODUCTION

The EAU guidelines[1] state that an immediate single instillation of chemotherapy following the transurethral resection of bladder tumor (TURBT) should be administered to all patients affected by non-muscle invasive bladder cancer (NMIBC). The need for further adjuvant intravesical therapy (IT) is advocated according to the risk classification

since a single immediate instillation might be an incomplete treatment for intermediate-high risk patients.[2] Currently, there is a wide variation in the management of intermediate risk (IR) NMIBC.[3] Usually a 6-week cycle of instillations of chemotherapy (ICH) or Bacillus Calmette-Guerin (BCG) is given, preferably followed by maintenance for at least 1 year although debate still exists on its usefulness.[4-7]

Up to 50-70% of the patients harboring an IR-NMIBC will show a recurrence after IT. A few of them will be submitted to cystectomy due to a higher risk of progression while the majority will be retreated by IT. It is a common, but empirical, practice to change the agent in IR patients recurring after the first cycle of adjuvant IT. BCG is advocated at recurrence after ICH since considered more effective in reducing recurrence rate, delaying progression and improving survival.[8-10] Nevertheless, some patients are retreated by ICH due to BCG intolerance, shortage or other reasons. Undeniably, the different prognosis between the patients showing an early recurrence and those remaining disease-free for a longer period should be taken into account. No much data are nowadays available on the efficacy of ICH given at recurrence after the first cycle of ICH in IR patients recurring 6 months or later. It could be of particular interest in case of BCG shortage or intolerance. In the present study, we retrospectively analyze the outcome of IR patients retreated by ICH looking, as a comparison, at contemporary IR patients receiving BCG.

MATERIALS AND METHODS

The files of patients harboring IR-NMIBC and treated between 1998 and 2009 were selected according with the precise aim of our study. The study was approved by the Institutional review board. The following selection criteria were adopted:

- IR tumors with a recurrence-risk score between 5 and 9 according to the EORTC Risk Tables. The patients had to be IR both initially and also at the first recurrence
- First recurrence after TURBT plus IT and retreated by IT. A second recurrence was included only if no adjuvant IT was given after TUR. The patients recurring more than twice were excluded
- Intravesical therapy should be started within 21 days after TUR
- BCG should be given at full dose
- The recurrence after the first cycle should not occur earlier than 6 months after TUR
- The patients should receive at least a full cycle of 6 weekly instillations of IT after TURBT and again after the first recurrence
- Only mitomycin c, epirubicin and BCG Connaught strain were adopted as IT.

Mitomycin C was given at the dose of 40 mg diluted in 40 ml and epirubicin at the dose of 80 mg diluted in 50 ml of saline solution. No buffered solution was adopted. BCG Connaught was given at the dose of 81 mg diluted in 50 ml of saline solution. The chemotherapeutic drugs and BCG were maintained into the bladder 1 and 2 hours, respectively. The postponement of the scheduled instillation up to 2 weeks was accepted. The patients not receiving at least 6 instillations were excluded from the study. Both patients receiving maintenance or not were considered. The selection of the drug and of the maintenance regimen was due to both patients' and doctors' decision after counseling.

All patients were submitted to cytology and cystoscopy 3-monthly for the first 2 years and then 6-monthly. The main endpoint was the Recurrence-Free Survival (RFS) after the second IT, defined as the interval of time between the date of the second TURBT and the date of the pathologically confirmed recurrence. The RFS was estimated using the Kaplan-Meier method and the differences between treatment groups were compared using the log-rank test. Mann Whitney U-test was used to compare the parameters' distribution for median time to recurrence. Multivariate Cox proportional hazards models were used to evaluate the recurrence event considering previous recurrence-free interval, T-category, G-grade, multiplicity, first and second IT (comparing BCG versus ICH) and maintenance regimen.

The aim of our study was to evaluate retrospectively the potential efficacy of ICH when optimally given in patients affected by IR-NMIBC recurring after a first full cycle of ICH. Thus, an intention-to-treat analysis was not performed and all the patients not receiving the planned treatment were excluded.

RESULTS

Out of 224 patients, 45 (20.1%) patients, 19 (8.5%) and 26 (12.7%) at first and second cycle of IT respectively, were excluded from the analysis due to treatment interruption during induction. The 6-week cycles was not completed for severe chemical cystitis in 6 patients (13.3%), bacterial cystitis in 2 (4,4%), hematuria in 3 (6,6%) and for other, mainly personal, reasons in 16 (35,5%). In 18 out of 45 patients (40%) the instillation was postponed for longer than 2 weeks, due to moderate local toxicity.

One hundred and seventy-nine patients affected by IR-NMIBC were included according to the selection criteria. The clinical and pathological characteristics of the patients are shown in Table 1. Seventy-four (46.5%) patients had multiple and 72 (40.2%) recurrent lesions.

The first IT and the re-IT are shown in Figure 1. ICH was initially administered in 146 (81.6%) and BCG in 33 (18.4%) patients. The median time to recurrence after the first IT was 18 months. At the second IT, ICH and BCG were administered in 112 (62.2%) and 67 (37.4%) patients, respectively. ICH was repeated in 101 (69.2%) patients while 11 (33.3%) patients only received ICH after BCG. Maintenance of at least 12 months at first and second IT was given in 54 (30.2%) and 63 (35.2%) patients, respectively.

At a median follow-up of 37 months (range 3-156 months) after the second TURBT, 73 (40.1%) patients recurred with a median time to recurrence of 16 months, 24 (35.8%) and 49 (43.8%) after BCG and ICH, respectively. No clinically significant difference emerged in median time to recurrence between first and second IT (18 versus 16 months, $P = 0.32$).

The results of multivariate statistical analysis are given in Table 2. The T-category and the adoption of maintenance at re-treatment resulted significant prognostic parameters for RFS. No difference in RFS was demonstrable between BCG and ICH given as second IT ($P = 0.9$) [Figure 2], even considering patients with a recurrence-free interval shorter ($P = 0.9$) or longer ($P = 0.5$) than 12 months after the first IT. Similarly, no difference in terms of RFS was found between ICH and BCG administered after previous ICH ($P = 0.23$) [Figure 3]. Our study, however, did not reach a statistical power able to demonstrate a significant difference smaller than 20%. Twelve patients (6.7%) had local progression (≥T1) at a median interval of 20 months. The multivariate model should have taken also into account interactions between the first and second treatment with respect to maintenance; however, the number of the events in each subgroup is too small to reach any statistical power.

DISCUSSION

Our study investigates the re-administration of intravesical chemotherapy at recurrence in previously treated patients affected by IR NMIBC. Patients treated in the same period with BCG are included in the study to obtain a synchronous and partially comparable control group. Currently, the therapeutic strategy for IR-NMIBC is not well defined and the concept of ICH or BCG failure is vague.[3,11] It is a general statement

Table 1: Patients' characteristics

No patients	179	
Sex (%)		
Male	153 (85.5)	
Female	26 (14.5)	
Median age (range)	69 years (43-87 years)	
Tumor characteristics	**First-IT**	**Second-IT**
History (%)		
Primary	107 (59.8)	-
Recurrent	72 (40.2)	179 (100)
Multiplicity (%)		
Single	85 (53.5)	74 (41.3)
Multiple	74 (46.5)	105 (58.7)
T- category and G-grade (%)		
Ta G1-2	150 (83.8)	162 (90.5)
T1G1	9 (5.0)	6 (3.4)
T1G2	20 (11.2)	11 (6.1)

IT: Intravesical therapy

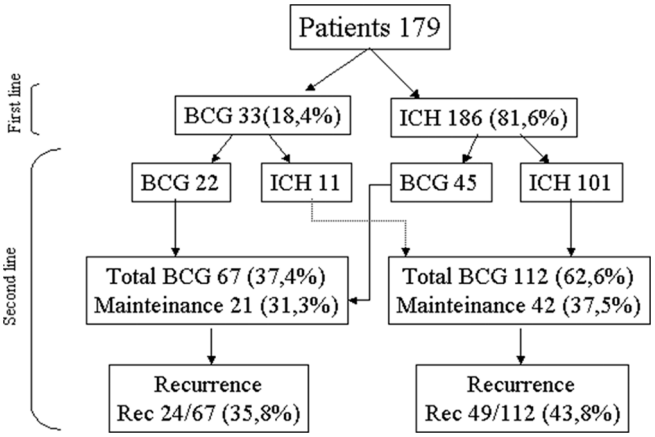

Figure 1: Intravesical therapy administered at first and second recurrence

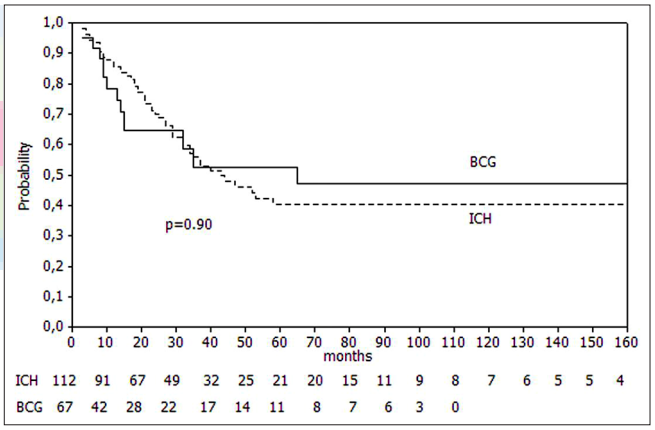

Figure 2: RFS in patients receiving BCG or ICH as re-treatment. ICH: Intravesical chemotherapy, BCG: Bacillus Calmette-Guerin

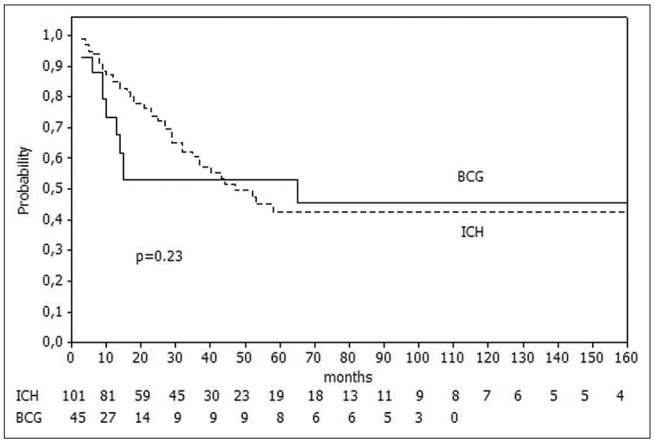

Figure 3: RFS in 146 patients recurring after intravesical chemotherapy ICH: Intravesical chemotherapy, BCG: Bacillus Calmette-Guerin

Table 2: Multivariate cox regression analysis for RFS

Parameter	Object of analysis	Pr>ChiSq	Hazard Ratio	95% hazard ratio confidence limits	
T (at first IT)	T1 *vs* Ta	0.6231	1.293	0.464	3.604
G (at first IT)	G2 *vs* G1	0.6874	0.867	0.432	1.740
T (at second IT)	T1 *vs* Ta	0.0491	0.275	0.076	0.995
G (at second IT)	G2 *vs* G1	0.7265	0.891	0.467	1.699
Maintenance (at first or second IT)		0.0392	1.971	1.034	3.755
Multiplicity (at first IT)		0.7923	1.091	0.571	2.085
Multiplicity (at second IT)		0.6773	0.875	0.467	1.641
Drug at first IT	ICH *vs* BCG	0.7443	1.142	0.515	2.529
Drug at second IT	ICH *vs* BCG	0.3947	0.725	0.345	1.521

IT: Intravesical therapy, BCG: Bacillus calmette-guerin, ICH: Intravesical chemotherapy, RFS: Recurrence-free survival

that recurrence occurring later than 6 months should be not considered the firm sign of failure or resistance. Moreover, most of the papers debate on the management of primary tumors. Only few and small reports can be found in the current literature on the efficacy of intravesical chemotherapy administered for recurrences maintaining the same risk pattern and occurring later than 6 months after the first adjuvant treatment. In patients harboring IR-NMIBC it is not rare that IT is converted from ICH to BCG, although the recurrence, of the same risk category, occurs later than 6 months. Arguably, in the next future BCG will be given more frequently considering the results of the European Organization for Research and Treatment of Cancer (EORTC) trial 30911 showing a benefit from BCG compared with epirubicin in IR patients.[9] In case of BCG intolerance or shortage, it is of main relevance to delineate the different clinical scenarios that can be found in patients with IR-NMIBC.[12] In our study, differently from the EORTC trial 30911, only IR tumors occurring later than 6 months, mean free interval of 18 months, and after an adjuvant IT given for a previous IR tumor, were considered. The aim of our study was to evaluate the potential efficacy of ICH given at recurrence after a first full cycle of ICH. In EORTC trial 30911, although 497 IR-NMIBC patients were included in the final analysis, it was unspecified how many of them were previously treated by mitomycin C or other drugs (only previous BCG and epirubicin were criteria of exclusion). Moreover, the median EORTC recurrence score was 5 (range 3-8) while in our study it was 7, ranging between 5 and 9, denoting the complexity in defining IR among different studies and institutions.

In our institute, the choice of ICH prevailed as first IT in IR tumors, probably due to the fact that when the patients were treated, the results of EORTC trial 30911 were not available and the systemic toxicity of BCG was much more feared than today. At recurrence, the adjuvant IT was changed in 56 (31.3%) patients in spite of a median free interval of 18 months and in the absence of risk-category progression. Particularly, 45 (30.8%) patients received BCG after the first cycle of ICH. Of relevance is the observation that ICH and BCG show similar efficacy in this setting even after a previous full cycle of ICH. Our study is obviously under powered to conclude equivalence between chemotherapy and BCG simply because the difference is not statistically significant and it suffers from all the limitations of retrospective studies brought out in a single institution. We were unable to demonstrate a statistically significant difference smaller than 20% in term of recurrence rate and RFS between the first and second IT and between ICH and BCG due to the small numbers.

However, the main aim of our study was not to compare ICH and BCG but only to show that retreatment by ICH is possible and safe. Many selection bias can influence the results of the study. It is obviously difficult to establish retrospectively the main factors that influenced the choice of the treatment. Some patients received maintenance and others didn't. In our Institute, in the past, chemotherapy was preferred in IR tumors causing an imbalance in the number of patients initially treated with BCG and chemotherapy. However, it can be an advantage for the purposes of our study to consider that nowadays chemotherapy is less frequently administered in IR-NMIBC and will be difficult in the future to investigate intravesical chemotherapy given both at first and second recurrence. The group of patients selected in our study was homogenous in relation to the tumor characteristics and the recurrence risk. This is particularly true if we consider that patients were at IR both initially and also at the first recurrence and that patients recurring earlier than 6 months were excluded.

Since only selected intermediate-risk tumors are considered, our results cannot be extended to other risk categories. Our analysis, according to the aim of the study, was performed in patients completing a full 6-week cycle of intravesical chemotherapy. However, we know that up to 15% of patients do not complete the treatment. Only one third of our patients received maintenance that is considered essential to obtain an efficacy of BCG higher than ICH. The absence of maintenance in almost two thirds of our patients could explain our results since, according to Friedrich and coll.[13] Patients receiving BCG without maintenance have lower recurrence free survival compared to those receiving chemotherapy plus maintenance but, again, this was not the end point of our analysis. As stated above, the major limit of the study is represented by its retrospective design. Our preliminary results should be confirmed by randomized multi-institutional trials entering a larger number of patients. In consideration of the results of recent trials[14] both chemotherapy and BCG should be given for 1 year.

Even if no ultimate conclusion can be drawn, we believe that the results of our study are of interest when BCG cannot be

given, if we consider IR patients recurring later than 6 months after TURBT. In our experience, in such cases, intravesical chemotherapy seems to be a legitimate option.

CONCLUSIONS

Intravesical chemotherapy can be re-administered in selected patients harboring intermediate risk NMI-BC and recurring later than 6 months after a full induction course, without a reduction in RFS greater than 20%. Although a lower difference in RFS between BCG and chemotherapy could be not detected by our study due to the small numbers, our results can be of support for the adoption of intravesical adjuvant chemotherapy in intermediate risk NMIBC in case of BCG shortage or intolerance. Randomized multi-institutional trials should be considered.

ACKNOWLEDGMENTS

We wish to thank the GSTU Foundation for the administrative and statistical support.

REFERENCES

1. Babjuk M, Burger M, Zigeuner R, Shariat SF, van Rhijn BW, Compérat E, *et al*. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2013. Eur Urol 2013;64:639-53.
2. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, *et al*. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466-77.
3. Brausi M, Witjes JA, Lamm D, Persad R, Palou J, Colombel M, *et al*. A review of current guidelines and best practice recommendations for the management of nonmuscle invasive bladder cancer by the International Bladder Cancer Group. J Urol 2011;18:2158-67.
4. Sylvester RJ, Oosterlinck W, Witjes JA. The schedule and duration of intravesical chemotherapy in patients with non–muscle-invasive bladder cancer: A systematic review of the published results of randomized clinical trials. Eur Urol 2008;53:709-19.
5. Herr HW, Dalbagni G, Donat SM. Bacillus Calmette-Guérin without maintenance therapy for high-risk non-muscle-invasive bladder cancer. Eur Urol 2011;60:32-6.
6. Serretta V, Morgia G, Altieri V, Di Lallo A, Ruggiero G, Salzano L, *et al*. Members of Gruppo Studi Tumori Urologici (GSTU) Foundation. A 1-year maintenance after early adjuvant intravesical chemotherapy has a limited efficacy in preventing recurrence of intermediate risk non-muscle-invasive bladder cancer. BJU Int 2010;106:212-7.
7. Sylvester RJ. Intravesical chemotherapy in non–muscle-invasive bladder cancer: What schedule and duration of treatment? Eur Urol 2007;52:951-4.
8. Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: A meta-analysis of the published results of randomized clinical trials. J Urol 2002;168:1964-70.
9. Sylvester RJ, Brausi MA, Kirkels WJ, Hoeltl W, Calais Da Silva F, Powell PH, *et al*. EORTC Genito-Urinary Tract Cancer Group. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol 2010;57:766-73.
10. Dalbagni G. Is intravesical bacillus Calmette- Guérin better than mitomycin for intermediate-risk bladder cancer? Eur Urol 2009;56:257-9.
11. Yates DR, Brausi MA, Catto JW, Dalbagni G, Rouprêt M, Shariat SF, *et al*. Treatment options available for bacillus Calmette-Guerin failure in non-muscle-invasive bladder cancer. Eur Urol 2012;62:1088-96.
12. Witjes JA, Palou J, Soloway M, Lamm D, Kamat AM, Brausi M, *et al*. Current clinical practice gaps in the treatment of intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC) with emphasis on the use of bacillus Calmette-Guérin (BCG): Results of an international individual patient data survey (IPDS). BJU Int 2013;112:742-50.
13. Friedrich MG, Pichlmeier U, Schwaibold H, Conrad S, Huland H. Long-term intravesical adjuvant chemotherapy further reduces recurrence rate compared with short-term intravesical chemotherapy and short-term therapy with Bacillus Calmette-Guérin (BCG) in patients with non-muscle-invasive bladder carcinoma. Eur Urol 2007;52:1123-9.
14. Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, *et al*. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: One-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013;63:462-72.

How to cite this article: Serretta V, Sommatino F, Gesolfo CS, Franco V, Cicero G, Allegro R. Intravesical chemotherapy for intermediate risk non-muscle invasive bladder cancer recurring after a first cycle of intravesical adjuvant therapy. Urol Ann 2015;7:21-5.

Source of Support: Nil, **Conflict of Interest:** None.