



Bladder Cancer

A Multicentre, Randomised Prospective Trial Comparing Three Intravesical Adjuvant Therapies for Intermediate-Risk Superficial Bladder Cancer: Low-Dose Bacillus Calmette-Guerin (27 mg) versus Very Low-Dose Bacillus Calmette-Guerin (13.5 mg) versus Mitomycin C

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Abstract

Objective: The primary aim was to search for lower doses of Bacillus Calmette-Guerin (BCG) that are effective and have lower toxicity.

Methods: A low dose of BCG 27 mg was compared with BCG 13.5 mg, using mitomycin C (MMC) 30 mg as the third arm of comparison. A total of 430 patients with intermediate-risk superficial bladder cancer were randomised into three groups. Instillations were repeated once a week for 6 wk followed by another six instillations given once every 2 wk during 12 wk.

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Results: There was a significantly longer disease-free interval for BCG 27 mg versus MMC 30 mg ($p = 0.006$). There were no statistically significant differences between BCG 27 mg and BCG 13.5 mg ($p = 0.165$) or between BCG 13.5 mg and MMC 30 mg ($p = 0.183$). Cox proportional hazards regression showed that disease-free interval in the multivariate analysis was significantly better for primary disease and treatment with BCG 27 mg.

There were no significant differences among the three groups with regards to time to progression and cancer-specific survival time. Local and systemic toxicity were higher in both BCG treatment groups.

Conclusions: One third of the standard dose, BCG 27 mg, seems to be the minimum effective dose as adjuvant treatment for intermediate-risk superficial bladder cancer, being more effective than MMC 30 mg. One sixth of the standard dose, BCG 13.5 mg, has the same efficacy as MMC 30 mg but it is more toxic.

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1. Introduction

Intravesical instillation of Bacillus Calmette-Guerin (BCG) is the most effective adjuvant therapy after transurethral resection of intermediate- or high-risk superficial bladder tumours and is the first-line treatment for patients with carcinoma in situ. The intravesical instillation of BCG reduces the risk of recurrence and delays the time to recurrence compared with transurethral resection alone or other drugs given intravesically. It also significantly reduces the risk of progression after transurethral resection in patients with this kind of tumour who receive maintenance treatment. Nevertheless, treatment with BCG is not free from complications. Irritative local symptomatology can appear in up to 91% of patients as well as other complications at different rates [1–5].

BCG efficacy and toxicity are dose-dependent; the problem lies in finding a very low BCG dose that is effective and has low toxicity. In 1991 the results of a randomised study [6] to evaluate the effectiveness and toxicity of a 75 mg dose of Pasteur strain BCG in the treatment of superficial bladder cancer were reported; the standard dose of Pasteur strain BCG is 150 mg. The conclusions were that half of the standard BCG dose is effective as adjuvant treatment against recurrent superficial papillary tumours and as treatment of carcinoma in situ. Complete response rates were similar to those achieved using standard dose. Furthermore, treatment-related toxicity appeared to be significantly lower than that reported in previous studies with higher doses. In 1992 the results of a randomised study [7] comparing the standard 120 mg dose of Armand Frappier BCG with a 60 mg dose, were reported. This study suggested that high doses of BCG, and therefore high toxicity,

were necessary to eradicate carcinoma in situ; on the other hand lower doses, with less toxicity, might be adequate to prevent tumour recurrences. In 2002 the results of the CUETO (Club Urológico Español de Tratamiento Oncológico) study 90.008 [8] were published. This randomised study compared a standard dose of 81 mg of BCG Connaught strain with a low dose of 27 mg as adjuvant treatment in superficial bladder tumours. The toxicity was lower in the group of patients who had received the 27 mg BCG dose. There were no statistically significant differences related to recurrence and progression between the two groups; nevertheless, the study left some doubts with regards to the low-dose efficacy in high-risk tumours.

To complement the CUETO study 90.008, the same group designed and performed two further studies: CUETO 95.011 and CUETO 95.012.

The randomised study 95.012 [9] compared a standard 81 mg dose of BCG Connaught strain with a low dose of 27 mg in high-risk superficial bladder tumours: carcinoma in situ and T1G3 tumours. The results suggested that a third of the dose of intravesical BCG was as effective as the standard dose against progression in patients with high-risk stages of superficial bladder carcinoma, but with significantly less toxicity.

The primary aim of the present multicentre, randomised CUETO study 95011 is to continue searching for lower doses of BCG that are effective and have low toxicity as adjuvant treatment for superficial bladder cancer. To this end, the outcome of intravesical instillations with 27 mg of BCG Connaught strain was compared with that of instillations with 13.5 mg of BCG Connaught strain, using a group treated with mitomycin C (MMC) 30 mg as a third arm of comparison.

2. Materials and methods

2.1. Study design

Eligible patients were those of intermediate risk, with stages TaG2 and T1G1–2 superficial bladder tumours, but without carcinoma in situ. Exclusion criteria were all TaG1 tumours; high-risk tumours (primary carcinoma in situ, concomitant carcinoma in situ, and T1G3 tumours); concurrent or previous muscle-invasive disease; concurrent or previous tumour in the upper urinary tract or prostatic urethra; intravesical treatment with MMC or BCG during the previous 6 mo; chronic urinary tract infection; cured or active tuberculosis; less than 2 yr of life expectancy; physical or psychic disability; bladder capacity below 200 ml; hypersensitivity to MMC; any other malignancy except basal cell carcinoma of skin; previous pelvic irradiation; creatinine higher than twice the standard (standard serum creatinine: ≤ 1.25 mg/ml); glutamate oxaloacetic transaminase (GOT) and glutamate pyruvic transaminase (GPT) higher than twice the standard (standard serum GOT ≤ 40 IU and serum GPT ≤ 30 IU); pregnancy or lactation; and any other disease with immunodeficiency.

Patients were randomly allocated to three groups to receive intravesically MMC 30 mg, BCG 27 mg, or BCG 13.5 mg. The Connaught strain was used. The instillations started 14–21 days after transurethral resection with histological confirmation of bladder cancer. The instillations were repeated once a week for 6 wk followed by another six instillations given once every 2 wk during 12 wk. If a Ta–1 recurrence was diagnosed during the instillation period, a further transurethral resection was performed, and the patient continued the initially assigned same treatment. The patients were endoscopically assessed every 3 mo during the first year and then every 4 mo for the next 4 yr. If recurrence was detected, the tumour was resected. If recurrence was not detected but urinary cytology was positive, biopsies of bladder and prostatic urethra were taken and the upper urinary tract was examined. Patients were withdrawn from the study if progression of disease, bladder carcinoma in situ, tumour in the upper urinary tract, tumour in prostatic urethra, or grade 3–4 toxicity was observed. Ethics approval was received from the Committee of Clinical Trials at each participating centre.

2.2. End points

The variables analysed were recurrence rate, number of recurrences, recurrence index/100 patients per month, progression rate, cancer-specific death rate, disease-free interval, time to progression, cancer-specific survival time, and adverse effects.

2.3. Statistical analysis

Quantitative data are described by the mean (SD) or median (range) and qualitative data as counts and percentages. Homogeneity between groups for quantitative data was tested with analysis of variance for unrelated samples and the qualitative data by the chi-square test. The disease-free interval (time to first recurrence), time to progression, and

cancer-specific time to survival were estimated by the Kaplan-Meier method. Pair-wise comparisons were performed by the log-rank test with Bonferroni correction (significance level $0.05/3 = 0.0167$). Univariate and stepwise multivariate Cox regression models were used to assess the independent effect of treatment on failure rates, unadjusted and adjusted by several variables. Variables with three levels (number of tumours, TG category, and treatment) were coded in models as two dummy variables with the one having minimum risk used as the reference group (“reference cell coding” method). Two-sided tests were used, and a p value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Patient characteristics

From March 1995 to May 1998, 430 patients from 15 hospitals were randomised. Of these 430 patients, 149 were allocated to the group receiving MMC 30 mg, 142 to the group receiving BCG 27 mg, and 139 to the group receiving BCG 13.5 mg (Table 1). The median follow-up was 52.6 mo (range: 0–111, SD = 29.5) for the MMC 30 mg group; 57.3 mo (range: 0–114, SD = 26.8) for the BCG 27 mg group; 61.2 mo (range: 0–112, SD = 26.1) for the BCG 13.5 mg group. A total of 397 (92.3%) patients completed the treatment: 137 (91.9%) patients in the MMC 30 mg group, 125 (88.0%) in the BCG 27 mg group, and 135 (97.1%) in the BCG 13.5 mg group. Thirty-three (7.7%) patients did not complete treatment and were withdrawn from the study, but they were followed for recurrence and the other end points (Table 2).

3.2. Recurrences

The recurrence rate and the number of recurrences are shown in Table 3. There was a significantly longer disease-free interval for BCG 27 mg versus MMC 30 mg. The Kaplan-Meier curves for the time to first recurrence were given by treatment group in Fig. 1. An overall log-rank test comparing the three groups was done simultaneously ($p = 0.002$). Unadjusted pair-wise comparisons yielded a significant difference between BCG 27 mg versus MMC 30 mg ($p = 0.006$); there were no statistically significant differences between BCG 27 mg and BCG 13.5 mg ($p = 0.165$) or between BCG 13.5 mg and MMC 30 mg ($p = 0.183$). The results of stepwise Cox proportional hazards regression univariate and multivariate analyses to evaluate the relative importance of individual factors for recurrence and progression are shown in Table 4. The disease-free interval in the univariate analysis was significantly longer for primary disease, unifocal tumour, and treatment

Table 1 – Patient characteristics

Characteristic	MMC 30 mg	BCG 27 mg	BCG 13.5 mg	Total
No. of patients	149	142	139	430
Median age (SD)	63.5 (11.9)	65.1 (11.5)	64.9 (10.1)	64.5 (11.2)
Age, no. (%):				
≤65 yr	75 (50.3)	64 (45.1)	64 (46.0)	203 (47.2)
>65 yr	74 (49.7)	78 (54.9)	77 (54.0)	227 (52.8)
Sex				
Male	130 (87.2)	125 (88.0)	119 (85.6)	374 (87.0)
Female	19 (12.8)	17 (12.0)	20 (14.4)	56 (13.0)
Disease status				
Primary	111 (74.5)	98 (69.0)	107 (77.0)	316 (73.5)
Recurrent	38 (25.5)	44 (31.0)	32 (23.0)	114 (26.5)
No. of tumours				
1	79 (53.0)	69 (48.6)	63 (45.3)	211 (49.1)
2	22 (14.8)	20 (14.1)	17 (12.2)	59 (13.7)
3	14 (9.4)	14 (9.9)	18 (12.9)	46 (10.7)
>3	34 (22.8)	39 (27.4)	41 (29.6)	116 (26.5)
Tumour size				
≤1 cm	40 (26.8)	42 (29.6)	33 (23.7)	115 (26.7)
2 cm	42 (28.3)	46 (32.4)	44 (31.7)	132 (30.7)
3 cm	34 (22.8)	29 (20.4)	31 (22.3)	94 (21.9)
>3 cm	33 (22.1)	25 (17.6)	31 (22.3)	89 (20.7)
TG categories				
TaG2	14 (9.4)	23 (16.2)	20 (14.4)	57 (13.3)
T1G1	34 (22.8)	31 (21.8)	32 (23.0)	97 (22.6)
T1G2	101 (67.8)	88 (62.0)	87 (62.6)	276 (64.2)

MMC, mitomycin C; BCG, Bacillus Calmette-Guerin.

with BCG 27 mg. The disease-free interval in the multivariate analysis was significantly better for primary disease and treatment with BCG 27 mg.

3.3. Progression

The progression rate is shown in Table 3. The types of progression are specified in Table 5. Likewise, there was no statistically significant difference in the time to progression among the three groups. The Kaplan-Meier curves and log-rank test of time to progression did not show statistically significant differences among the three groups. In the univariate and multivariate Cox analyses, the intrave-

sical instillation did not influence the time to progression. The variables that influenced the time to progression in the multivariate analysis were recurrent disease status and T1G2 category (Table 4).

3.4. Survival

The cancer-specific death rate is shown in Table 3. The causes of death are specified in Table 5. There was a large difference in the total number of deaths in the three treatment groups: 27 on MMC, 13 on BCG 27 mg, and 17 on BCG 13.5 mg. There were no significant differences in cancer-specific survival time: unstratified hazard ratio (95% confidence

Table 2 – Compliance and reasons for withdrawal

Compliance	MMC 30 mg	BCG 27 mg	BCG 13.5 mg	Total
Completed treatment	137 (91.9%)	125 (88.0%)	135 (97.1%)	397 (92.3%)
Did not complete treatment	12 (8.1%)	17 (12.0%)	4 (2.9%)	33 (7.7%)
Lost to follow-up	1	2	0	3
Refusal	1	0	1	2
Withdrew owing to toxicity	0	6	1	7
Muscular invasion	1	0	0	1
Protocol violation	4	0	0	4
Other reasons	5	9	2	16

MMC, mitomycin C; BCG, Bacillus Calmette-Guerin.

Table 3 – Patients with recurrences, progression, and cancer-specific death

Results	MMC 30 mg	BCG 27 mg	BCG 13.5 mg
No. of patients with recurrences	58 (38.9%)	38 (26.8%)	50 (36.0%)
No. of recurrences	75	47	63
Recurrence index/100 patients per month	0.957	0.575	0.740
Progression	14 (9.4%)	14 (9.9%)	18 (12.9%)
Cancer-specific death	7 (4.7%)	3 (2.1%)	5 (3.6%)

MMC, mitomycin C; BCG, Bacillus Calmette-Guerin.

interval) is 2.45 (0.63–9.46) MMC 30 mg, 1 BCG 27 mg, and 1.60 (0.38–6.72) BCG 13.5 mg (BCG 27 mg vs. MMC 30 mg, $p = 0.195$; BCG 27 mg vs. BCG 13.5 mg, $p = 0.517$). The Kaplan-Meier curves and log-rank test of the cancer-specific survival time did not show statistically significant differences in any comparison.

3.5. Side-effects

Local toxicity was observed in 45 (30.2%) patients in the MMC 30 mg group, 93 (65.4%) in the BCG 27 mg group, and 89 (64.0%) in the BCG 13.5 mg group. Similar results were observed for the systemic toxicity: 7 (4.6%) patients in the MMC 30 mg group, 16 (11.2%) patients in the BCG 27 mg group, and 15 (10.7%) patients in the BCG 13.5 mg group. Local and systemic toxicity were higher with statistically significant difference in both groups treated with BCG compared with the group treated with MMC. There were no significant differences in adverse

effects between the two BCG treatment groups (Table 6).

4. Discussion

High-risk superficial bladder tumour is the major European indication for BCG to avoid the recurrence and/or progression. The most important prognostic factors for recurrence are the number of tumours, their size, and the prior recurrence rate. The most important prognostic factors for progression are the T category, grade, and the presence of carcinoma in situ—factors that represent the biological aggressiveness of the disease. BCG is relatively less effective for low-grade tumours, independently of the age, and for patients older than 80 yr. In case of BCG failure, the outcome is bad. Standard treatment in failing patients remains cystoprostatectomy. Conservative but investigative alternatives are interferon-alpha, intravesical hyperthermia, or photodynamic ther-

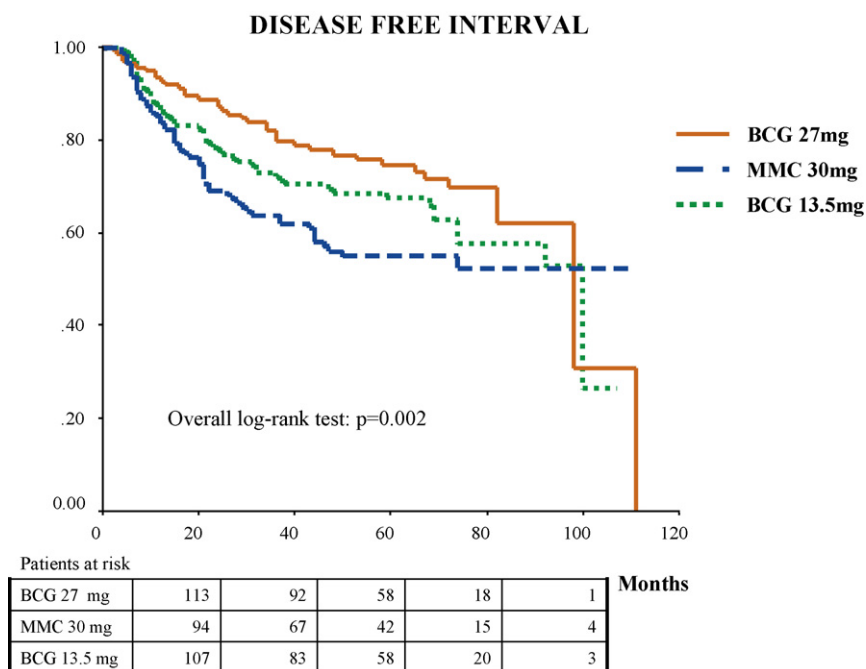


Fig. 1 – Kaplan-Meier curves for the disease-free interval.

Table 4 – Disease-free interval and time to progression (Cox models) by univariate and multivariate analyses

Variable	Disease-free interval		Time to progression	
	Univariate (unadjusted) HR (95%CI) [p]	Multivariate (adjusted) HR (95%CI) [p]	Univariate (unadjusted) HR (95%CI) [p]	Multivariate (adjusted) HR (95%CI) [p]
Age				
≤65 yr	1		1	
>65 yr	1.20 (0.87–1.67) [0.262]		1.34 (0.75–2.42) [0.322]	
Disease status				
Primary	1	1	1	1
Recurrent	2.43 (1.74–3.39) [<0.001]	2.53 (1.81–3.54) [<0.001]	2.33 (1.29–4.21) [0.005]	2.66 (1.47–4.83) [0.001]
No. of tumours				
1	1		1	
2–3	1.88 (1.23–2.87) [0.004]		0.82 (0.32–2.11) [0.677]	
>3	2.91 (1.98–4.17) [<0.001]		3.00 (1.57–5.75) [<0.001]	
Size				
≤2 cm	1		1	
>2 cm	0.97 (0.70–1.36) [0.880]		0.73 (0.40–1.35) [0.320]	
TG Category				
TaG2	1		1	1
T1G1	1.69 (0.92–3.10) [0.091]		3.16 (0.66–15.10) [0.150]	3.15 (0.69–15.06) [0.151]
T1G2	1.50 (0.86–2.59) [0.152]		4.79 (1.14–20.06) [0.032]	5.57 (1.32–23.40) [0.019]
Treatment				
MMC 30 mg	1.74 (1.15–2.62) [0.008]	1.86 (1.23–2.81) [0.003]	0.98 (0.47–2.06) [0.960]	
BCG 27 mg	1	1	1	
BCG 13.5 mg	1.35 (0.89–2.06) [0.163]	1.49 (0.97–2.28) [0.065]	1.16 (0.57–2.34) [0.681]	

HR, hazard ratio; 95%CI, 95% confidence interval; MMC, mitomycin C; BCG, Bacillus Calmette-Guerin.

apy. However, treatment with BCG is not free from complication [10–14].

Previous prospective studies and review articles have suggested that one third of the standard dose of BCG is as effective as the standard dose, whereas the number of local and systemic side-effects is decreased [6–9,15–19]. In 1995 a phase 2 study [16] evaluated the feasibility, response, and toxicity of

27 mg BCG dose (Connaught strain) in patients with high-risk superficial transitional cell carcinoma. The results of the study suggested that one third of the standard BCG dose could be successfully used as adjuvant therapy for high-risk patients. Toxicity included local reactions such as severe dysuria, urinary frequency, and significant haematuria. In 2001 the European Organisation for the Research

Table 5 – Cause of progression and cause of death

	MMC 30 mg	BCG 27 mg	BCG 13.5 mg	Total
Cause of progression				
Muscular invasion	10	9	10	29
Local extension	0	1	1	2
Metastatic dissemination	3	3	4	10
Locoregional extension	1	0	1	2
Other	0	1	2	3
Total	14	14	18	46
Cause of death				
Cancer specific	7	3	5	15
Cardiovascular	10	3	8	21
Comorbidity	2	0	1	3
New tumour	7	2	2	11
Other	1	5	1	7
Total	27	13	17	57

MMC, mitomycin C; BCG, Bacillus Calmette-Guerin.

Table 6 – Side-effects categorized as local or systemic toxicity

Patients, no. (%)	MMC 30 mg		BCG 27 mg		BCG 13.5 mg	
	Local	Systemic	Local	Systemic	Local	Systemic
With no toxicity	104 (69.8)	142 (95.3)	49 (34.5)	126 (88.7)	50 (36.0)	124 (89.2)
With toxicity						
Grades 1–2	40 (26.8)	5 (3.4)	73 (51.4)	11 (7.7)	79 (56.8)	12 (8.6)
Grades 3–4	5 (3.4)	2 (1.3)	20 (14.1)	5 (3.5)	10 (7.3)	3 (2.2)

MMC, mitomycin C; BCG, Bacillus Calmette-Guerin.

The comparisons of no toxicity, grades 1–2, and grades 3–4 are based on a test with degrees of freedom: $(r-1)(c-1)$, where r is the number of rows and c is the number of columns in the table:

p value, Pearson chi-square (no toxicity, toxicity grades 1–2, toxicity grades 3–4), local = 0.000

MMC 30 mg vs. BCG 27 mg: $p = 0.000$

MMC 30 mg vs. BCG 13.5 mg: $p = 0.000$

BCG 27 mg vs. BCG 13.5 mg: $p = 0.17$

p value, Pearson chi-square (no toxicity, toxicity grades 1–2, toxicity grades 3–4), systemic = 0.000

MMC 30 mg vs. BCG 27 mg: $p = 0.000$

MMC 30 mg vs. BCG 13.5 mg: $p = 0.000$

BCG 27 mg vs. BCG 13.5 mg: $p = 0.768$

p value, Pearson chi-square (no toxicity, yes toxicity), local or systemic = 0.000

MMC 30 mg vs. BCG 27 mg: $p = 0.000$

MMC 30 mg vs. BCG 13.5 mg: $p = 0.000$

BCG 27 mg vs. BCG 13.5 mg: $p = 0.896$

and Treatment of Cancer (EORTC) Genitourinary Group [17] examined the ablative activity and incidence of side-effects of intravesical 30 mg Connaught BCG given for a papillary marker lesion of the bladder. They concluded that 30 mg BCG has a clear ablative effect on superficial bladder cancer with a 61% response rate. Local side-effects included dysuria in 54% of the patients and macroscopic haematuria in 39%. In 2002 a study [18] investigated whether a proinflammatory cytokine interleukin-8 (IL-8) could be used as a predictor for response to a standard dose of 120 mg BCG Danish 1331 strain and to one third the standard BCG dose of 40 mg in patients with superficial bladder cancer. There was no difference with respect to recurrence and progression between the two BCG treatment groups. The quantitative IL-8 response to standard dose and to the one-third dose was similar. In 2002 and 2005 the previously mentioned CUETO 90.008 [8] and 95.012 [9] studies also showed that one third of the standard BCG dose was as effective as the standard dose and was less toxic. In 2004 another phase 2 study [19] also evaluated one third of the standard BCG dose. The conclusion was that this low-dose BCG could be an option as adjuvant therapy for superficial bladder cancer, with acceptable toxicity and good compliance.

In the present study, the MMC 30 mg dose and treatment regimen of 18 wk were a usual treatment at the moment of starting the study. For this reason, we chose the same treatment regimen, induction plus maintenance, for BCG. The most

important prognostic factor for recurrence is disease status recurrent, not BCG treatment. The most important prognostic factors for progression are disease status recurrent and T1G2 category. Age is not predictive of response. We want to remark that there are no tumours of high risk and that the comparison is between patients older and younger than 65 yr.

The present study suggests that one third of the standard BCG dose could be recommended as adjuvant treatment for superficial bladder tumours of intermediate risk and is more effective than MMC 30 mg. The disease-free interval in the univariate and multivariate analyses was significantly longer for treatment with BCG 27 mg. The number of recurrences was lower in the BCG 27 mg group than in the MMC 30 mg group: 47 and 75, respectively. A cost assessment revealed that instillations of one third of the standard dose of BCG is less expensive than instillations of MMC 30 mg. The cost of a transurethral resection of a bladder tumour, estimated by the Spanish National Health System for the year 2006, was €2194.73 (DRG-311 [Diagnosis Related Group-311] *transurethral procedure without complications*). The amount spent on each “intravesical instillation procedure” was estimated by the Spanish National Health System at €323.82 for the year 2006. Multiplying the recurrence index/100 patients per month by the cost of each *transurethral procedure without complications*—without considering the effect that transurethral resection has on work, family, and personal aspects—shows that the MMC

30 mg group is more expensive than the BCG group. In the MMC 30 mg group, the cost for 100 patients per month is 0.957×2194.73 (DRG 311) = 2099.65€. In the BCG 27 mg group, the cost for 100 patients per month is 0.575×2194.73 = 1261.96€. MMC is more expensive in the long run because there are more recurrences and hence more additional treatments, including transurethral resections, have to be done in the MMC group. It is true that one third of the standard dose of BCG is more toxic than MMC 30 mg, but it is very difficult to estimate the impact of toxicity on the cost of the procedure because the side-effects during the instillation stage are mostly slight, irritative local symptoms, or general symptoms, which, in most cases, cease spontaneously or with the help of anticholinergic medication or paracetamol.

The present study suggests that the minimum effective dose of BCG is one third of the standard dose. We consider that one sixth of the standard dose of BCG is not indicated as adjuvant treatment for superficial bladder cancer of intermediate risk; it has the same efficacy as MMC 30 mg but is more toxic. In fact, the toxicity level of one sixth of the standard dose is similar to that observed with one third of the standard dose.

5. Conclusions

1. One sixth of the standard dose, BCG 13.5 mg, is suboptimal compared with one third of the standard dose, BCG 27 mg. Although the one-sixth dose has the same efficacy as MMC, it is more toxic and therefore should not be recommended as initial adjuvant treatment for intermediate-risk superficial bladder tumours.
2. One third of the standard dose, BCG 27 mg, seems to be the minimum effective dose as adjuvant treatment for intermediate-risk superficial bladder tumours.

Conflicts of interest

The authors have nothing to disclose.

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