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BACILLUS CALMETTE-GUERIN VERSUS CHEMOTHERAPY FOR THE INTRAVESICAL TREATMENT OF PATIENTS WITH CARCINOMA IN SITU OF THE BLADDER: A META-ANALYSIS OF THE PUBLISHED RESULTS OF RANDOMIZED CLINICAL TRIALS

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ABSTRACT

Purpose: We determined the short-term and long-term efficacy of bacillus Calmette-Guerin (BCG) and chemotherapy in the treatment of patients with carcinoma in situ (CIS).

Materials and Methods: A meta-analysis was performed on published results of randomized clinical trials comparing intravesical BCG to intravesical chemotherapy.

Results: Nine randomized trials including 700 patients with CIS compared BCG to either mitomycin C (MMC), epirubicin, adriamycin, or sequential MMC/adriamycin. Of 298 patients on BCG 203 (68.1%) had a complete response compared with 158 of 307 patients on chemotherapy (51.5%), a reduction of 47% in the odds of nonresponse on BCG (OR 0.53, $p = 0.0002$). Based on a median followup of 3.6 years, 161 of 345 patients on BCG (46.7%) had no evidence of disease compared with 93 of 355 patients on chemotherapy (26.2%), a reduction of 59% in the odds of treatment failure on BCG (OR 0.41, $p < 0.0001$). Although the long-term benefit of BCG was smaller in trials with MMC, BCG was superior to MMC in trials with maintenance BCG (OR 0.57, $p = 0.04$). The reduction of 26% in the risk of progression on BCG ($p = 0.20$) is consistent with the reduction of 27% ($p = 0.001$) previously reported in a larger superficial bladder cancer meta-analysis.

Conclusions: Intravesical BCG significantly reduces the risk of short and long-term treatment failure compared with intravesical chemotherapy. Therefore, it is considered to be the intravesical agent of choice in the treatment of CIS.

KEY WORDS: carcinoma in situ, mycobacterium bovis, drug therapy, meta-analysis

Approximately 70% to 80% of all patients with bladder cancer initially present with superficial disease and among these 5% to 10% have carcinoma in situ (CIS).[1] CIS is a flat, high grade lesion of the urothelium which is diagnosed by a combination of cystoscopy, urinary cytology and multiple bladder biopsies. However, it is often underdiagnosed and sometimes misclassified as moderate dysplasia. The 1998 WHO/International Society of Urological Pathology consensus classification expanded the definition of CIS to include lesions previously designated as severe dysplasia or marked atypia.[2]

CIS is a highly malignant carcinoma which, unlike low grade Ta and T1 tumors, is at high risk for progression and death due to bladder cancer. Based on the untreated natural history of CIS, 54% of patients have progression to muscle invasive disease.[1] CIS is often multifocal and unlike papillary tumors cannot be treated by transurethral resection. Intravesical chemotherapy and immunotherapy are the most widely used initial conservative treatments. Cystectomy is generally reserved for patients in whom conservative treatment fails, but may sometimes be used as initial treatment. In a review of 497 patients treated with intravesical chemotherapy, an overall complete response rate of 48% was observed, including 38% with thiotepa, 48% with doxorubicin and 53% with mitomycin C. In 1,496 patients treated with bacillus Calmette-Guerin (BCG) the complete response rate was 72%.[1]

However, there are important limitations to drawing conclusions based on just an overview of complete response rates from a number of different studies, most of which were nonrandomized. There may be important differences between studies with respect to the definition of CIS, patient characteristics, and assessment of response. An initial complete response is not always durable. As 50% or more of complete responders may eventually recur with a high risk of invasion and/or extravesical disease, one must also take into account the long-term disease-free and progression-free rates.

Treatment recommendations should be based on the results of randomized clinical trials with long-term followup. Unfortunately there are relatively few randomized trials in just patients with CIS. Most trials also include patients with papillary tumors and separate results are not always provided for the smaller subgroup of patients with CIS. Thus, the power to detect treatment differences in patients with CIS is low and the reliability of the conclusions is limited.

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For another article on a related topic see page 332.

To compare the effect of intravesical BCG to that of intravesical chemotherapy in patients with carcinoma in situ of the bladder, a meta-analysis of the published results of randomized clinical trials has been performed to have a greater power to detect potential treatment differences and to provide a more precise estimate of the size of any treatment effect.

MATERIALS AND METHODS

Selection criteria. All randomized trials including patients with primary, secondary or concurrent CIS and that compared intravesical BCG to intravesical chemotherapy were considered. Trials which also included some patients classified as having dysplasia were not excluded.

Trials published or accepted for publication before August 2004 were identified by searching MEDLINE, the United States Physicians' Data Query, the Cochrane Central Register of Controlled Trials, and reference lists in trial publications and review articles. Abstracts published in the Journal of Urology and European Urology were also reviewed.

End points. Short-term end points such as the complete response rate (based on negative cystoscopy, cytology and biopsies), and long-term end points such as recurrence (appearance of papillary tumors or CIS) in complete responders, the overall disease-free (no evidence of disease) rate, the rate of progression to muscle invasive disease, stage T2 or higher, and survival were considered.

Statistical considerations. Since individual patient data were not available and the majority of the publications provided only the number of patients who had recurrence, progression and/or died, these end points were analyzed without taking into account the time to the event or censoring.

Odds ratios (OR) for each trial and each end point were calculated based on the number of patients with CIS and the number with treatment failure in each treatment group. Using the observed number of events (O), the expected number of events (E), and the variance of the difference (O − E) from each trial, odds ratios from the individual trials were combined across all trials based on a Peto fixed effects model to get an overall estimate of the OR. Forest plots provide the OR for each individual trial and overall, along with 2-sided 95% confidence intervals (CI).[3] Tests for heterogeneity and interaction assessed whether there was a difference in the size of the treatment effect between trials or groups of studies. All analyses and forest plots were done using SAS version 8®.

RESULTS

Fourteen trials potentially met the selection criteria. Five trials were excluded either because no outcome data for patients with CIS were available,[4,5] patients receiving BCG also received alternating or sequential mitomycin C,[6,7] or the trial was not properly randomized.[8] Nine trials were thus retained.[9–17] For 3 studies additional end point efficacy data not included in the original publication were supplied by the trial organizers.[9–11]

Trial characteristics. Characteristics of the 9 trials are given in table 1. They began patient accrual in the period from 1980 to 1994 and were published between 1990 and 2003. Median followup was 3.6 years with a maximum of 11.9 years. Patients with dysplasia were eligible in 3 trials while in 6 trials patients with just papillary tumors could also be entered. Previous intravesical chemotherapy was not allowed in 5 studies.

Four different chemotherapy regimens were used in the control groups, with mitomycin C (MMC) being the most frequent. One trial included a third arm with thiotepa which has not been taken into account since only 5 patients receiving thiotepa had CIS.[15] Maintenance chemotherapy ranging from 6 months to 3 years was given in 8 studies while 1 to 3 years of maintenance BCG was given in 6 trials. There were 5 different strains of BCG used, namely Pasteur, Connaught, Tice, RIVM and Tokyo.

TABLE 1. *Trial characteristics*

Trials	9
Median pts included (range)	66 (12–168)
Start of pt entry:	
Oldest study	1980
Most recent study	1994
Publication date:	
Oldest	1990
Most recent	2005
Yrs followup:	
Median (range)	3.6 (2.5–5.6)
Max (median + range)	7.7 (4.6–11.9)
Disease type:	
CIS[9–11, 14–16]	6
CIS +/or dysplasia[12, 13, 17]	3
CIS or dysplasia required:	
No[9–12, 14, 15]	6
Yes[13, 16, 17]	3
Prior chemotherapy allowed:	
No[10, 11, 13, 15, 17]	5
Yes[9, 12, 14, 16]	4
Treatment comparisons:	
BCG vs MMC[9–13]	5
BCG vs adriamycin[14, 15]	2
BCG vs epirubicin[16]	1
BCG vs MMC/adriamycin[17]	1
Maintenance chemotherapy:	
No[17]	1
Yes[9–16]	8
Maintenance BCG:	
No[10, 11, 17]	3
Yes[9, 12–16]	6
BCG strain:	
Pasteur[12, 13, 15]	3
Connaught[14, 16]	2
Tice[9]	1
Tice or RIVM[10]	1
RIVM[11]	1
Tokyo[17]	1

Patient characteristics. As provided in table 2, 700 patients with CIS were randomized in these 9 trials, 345 (49.3%) to BCG and 355 (50.7%) to chemotherapy. 594 (84.9%) had CIS and 106 (15.1%) dysplasia. Concomitant papillary tumors were present in 444 patients (63.4%).

Nearly half of the patients, 347 (49.6%), were randomized

TABLE 2. *Patient characteristics*

	No. (%)
Patients receiving:	700
BCG	345 (49.3)
Chemotherapy	355 (50.7)
Disease type:	700
CIS	594 (84.9)
Dysplasia	106 (15.1)
Concomitant papillary tumors:	700
No	256 (36.6)
Yes	444 (63.4)
Treatment comparison:	700
BCG vs MMC[9–13]	347 (49.6)
BCG vs adriamycin[14, 15]	143 (20.4)
BCG vs epirubicin[16]	168 (24.0)
BCG vs MMC/adriamycin[17]	42 (6.0)
Maintenance chemotherapy:	355
No[17]	21 (5.9)
Yes[9–16]	334 (94.1)
Maintenance BCG:	345
No[10, 11, 17]	83 (24.1)
Yes[9, 12–16]	262 (75.9)
BCG strain:	345
Connaught[14, 16]	148 (42.9)
Pasteur[12, 13, 15]	83 (24.1)
Tice[9, 10]	54 (15.7)
RIVM[10, 11]	39 (11.3)
Tokyo[17]	21 (6.1)

in trials comparing BCG to either passive or electromotive MMC. A total of 334 patients (94.1%) randomized to chemotherapy and 262 patients (75.9%) randomized to BCG received some form of maintenance treatment. Connaught was the most frequently used strain, being given to 148 (42.9%) of the patients randomized to BCG.

Complete response. Complete response (CR) was assessed at 3 months and/or 6 months in all but 1 study where the assessment was done at 2 months.[17] Patients who did not respond at 3 months were generally given another course of intravesical treatment.

As shown in the Forest plot in figure 1, 203 patients (68.1%) on BCG had a CR compared with 158 patients (51.5%) on chemotherapy, an absolute difference of 16.6%. This corresponds to a reduction of 47% in the odds of treatment failure with BCG, (OR 0.53, 95% CI from 0.38 to 0.74, p =0.0002). The size of the treatment effect varied somewhat between the different studies (p =0.09), especially in the trials with MMC where the MMC CR rate varied between 44.4% and 93.8%.

Recurrence in complete responders. Among the 203 complete responders on BCG and the 158 complete responders on chemotherapy, 34.0% and 50.0% respectively recurred during followup, a reduction of 53% in the odds of recurrence on BCG, (OR 0.47, 95% CI from 0.31 to 0.73, p =0.0008, fig. 2). The size of the treatment effect differed significantly between the different studies (p =0.006), especially in the trials with MMC.

No evidence of disease (disease-free rate). A total of 161 patients (46.7%) on BCG and 93 patients (26.2%) on chemotherapy had no evidence of disease during followup, an absolute difference of 20.5% and a relative reduction of 59% in the odds of treatment failure on BCG, (OR 0.41, 95% CI from 0.30 to 0.56, p <0.0001, fig. 3). There was a trend or a significant difference in favor of BCG in all studies except for 1 trial with MMC.[10]

Figure 4 shows that the difference in favor of BCG was smaller in trials where MMC was given (p =0.007). In patients treated with MMC, 35.6% had no evidence of disease compared with only 16.9% of patients treated with other chemotherapy regimens.

BCG appeared to be superior to MMC only in the trials where maintenance BCG was given (fig. 5). In 2 small trials comparing MMC to BCG with no maintenance in a total of 90 patients, there was no suggestion of a benefit with BCG. Conversely, in the 3 trials comparing MMC to BCG with maintenance, 49 of 149 patients (32.9%) on MMC and 49 of 108 patients (45.4%) on BCG had no evidence of disease. This represents a reduction of 43% in the odds of treatment failure on BCG (OR 0.57, 95% CI from 0.34 to 0.97, p =0.04, fig. 5).

Progression. As shown in the forest plot in figure 6, progression was reported in 83 (17.5%) of 474 patients, 36 (15.4%) on BCG and 47 (19.6%) on chemotherapy, with a reduction of 26% in the odds of progression for patients receiving BCG (OR 0.74, 95% CI from 0.45 to 1.22, p =0.20). The data are insufficient to assess the role of BCG maintenance on progression or to make a separate analysis in the trials with MMC.

Survival. Death due to bladder cancer was reported in 2 studies:[16,17] 14 (13.3%) of 105 on chemotherapy and 11 (10.5%) of 105 on BCG died due to their disease. Overall 143 of 407 patients died,[13,14,16] 80 (35.9%) of 223 on chemotherapy and 63 (34.2%) of 184 on BCG.

DISCUSSION

Whether the optimal initial therapy for CIS is radical cystectomy or conservative intravesical instillations remains unclear. The decision may well be influenced by whether or not concurrent high grade papillary Ta T1 tumors are present. This important question cannot be answered by this meta-analysis as there are no randomized trials comparing these 2 treatment options. Thus, this meta-analysis only deals with the conservative intravesical treatment of CIS with BCG or chemotherapy.

Complete response rates of 68.1% with BCG and 51.5% with chemotherapy were observed, very similar to the complete response rates of 72% and 48% previously reported in a literature review of approximately 2,000 patients.[1] Although the complete response rates on BCG and chemotherapy are high, the recurrence rate in complete responders is also high, 50% on chemotherapy and 34% on BCG. In the largest study, the median duration of complete response with maintenance BCG was approximately 5 years.[16] This is consistent with the 39% recurrence rate in complete responders based on median followup of 3.6 years in the 3 remaining studies with maintenance BCG.[9,13,14]

Due to the high recurrence rate, the most appropriate end points to assess treatment efficacy in patients with CIS are long-term ones. The recurrence rate in complete responders is a subgroup analysis which can be analyzed only in a subset of trials. Data on progression and survival are incomplete. The long-term disease-free rate is the only end point available for all randomized patients in all trials and is thus the most reliable end point for drawing conclusions on treatment efficacy.

Based on a median followup of 3.6 years, 46.7% of patients on BCG and 26.2% on chemotherapy remained disease-free. Figure 4 shows that MMC is more effective than other chemotherapy regimens in the treatment of CIS, results which are contrary to those for stage Ta T1 tumors where it has not been possible to show a difference in the efficacy of different intravesical chemotherapies.[18]

Subgroup analyses have been kept to a minimum to limit

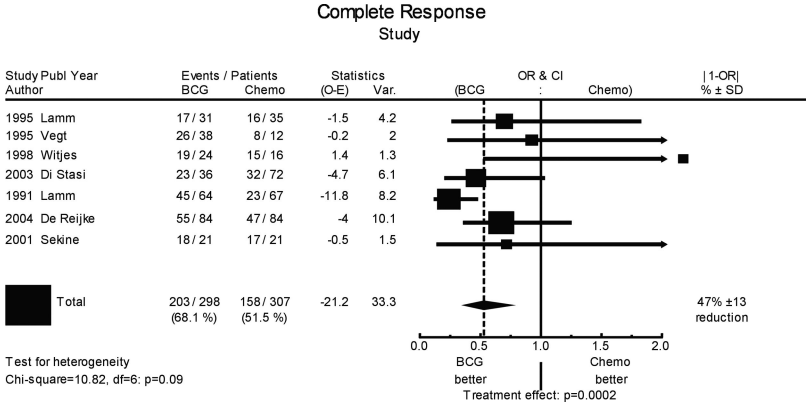

FIG. 1. Forest plot of complete response by study

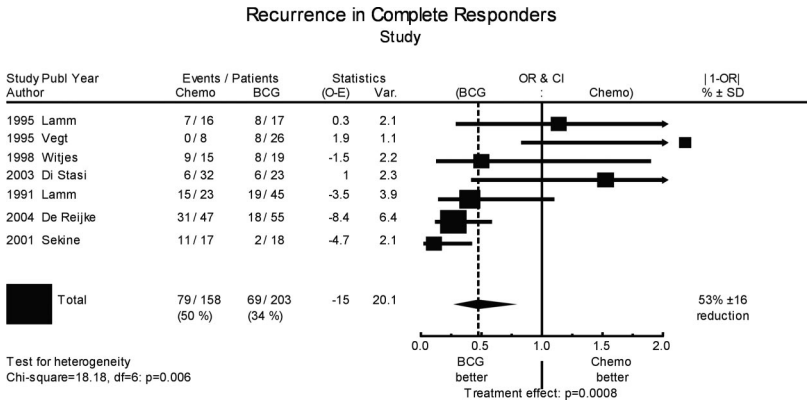

FIG. 2. Forest plot of recurrence in complete responders by study

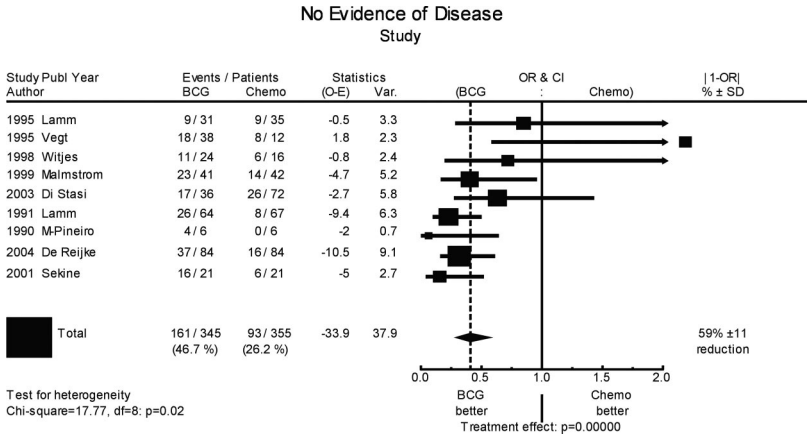

FIG. 3. Forest plot of no evidence of disease by study

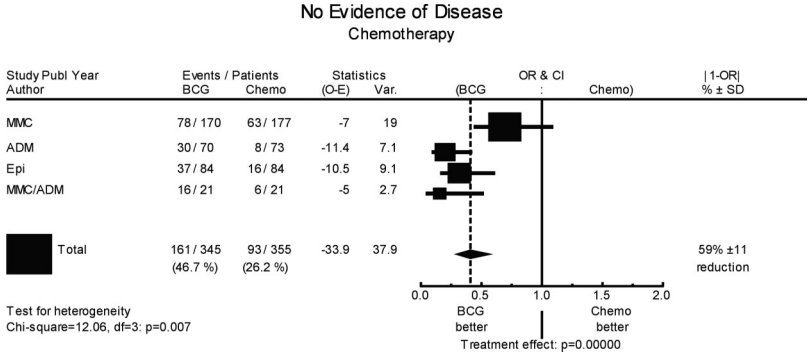

FIG. 4. Forest plot of no evidence of disease according to chemotherapy regimen

the risk of drawing erroneous conclusions based on small patient numbers. They have been performed only for the largest treatment subgroup, the comparison of BCG to MMC since this has been the subject of other recent meta-analyses,[19–21] using the most reliable end point, the disease-free rate. However, even for this end point the power of the comparison of BCG to MMC is limited since it is based on only 5 trials and 347 patients. The long-term disease-free rate on MMC was 35.6% compared with 45.9% on BCG, a reduction of 31% in the odds of treatment failure on BCG ($p = 0.10$). However, in the 3 MMC trials where maintenance BCG was given, there was a reduction of 43% ($p = 0.04$). This is in agreement with 3 previous superficial bladder cancer meta-analyses that all came to the conclusion that maintenance is required for BCG to be effective.[19,20,22] While it is clear that an induction course of 6 weeks only is suboptimal in many patients, the optimal maintenance dose and schedule still remains to be identified. The conclusions of this meta-analysis are also similar to those of 3 others that concluded that BCG is superior to MMC in the treatment of superficial bladder cancer.[19–21]

The power to detect differences in progression and survival is very limited. Progression data were available for 6 trials and 474 patients (68%) while only 2 trials provided disease specific survival data for 210 patients (30%). In addition, the median followup was only 3.6 years. Thus, there is insufficient power to detect as significant the reduction of 26% in the risk of progression on BCG ($p = 0.20$). Nevertheless, this reduction is consistent with the reduction of 27% ($p = 0.001$) observed in a much larger and more powerful meta-analysis of 4,800 patients where the benefit of BCG was similar in patients with Ta T1 lesions and in those with carcinoma in situ.[22] As was the case here, none of the previous meta-analyses had sufficient power to compare maintenance BCG

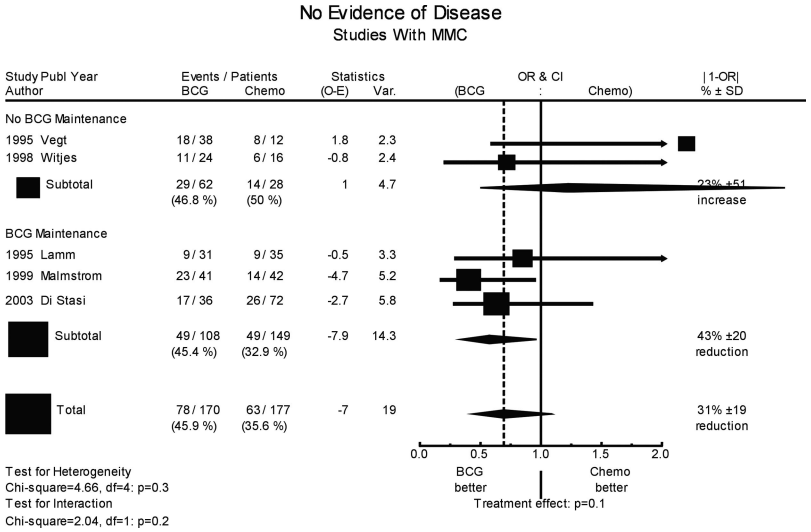

FIG. 5. Forest plot of no evidence of disease in studies with MMC according to BCG maintenance

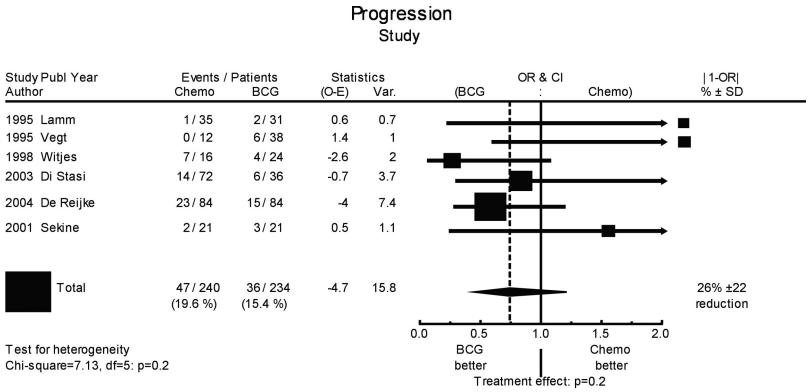

FIG. 6. Forest plot of progression by study

to MMC with respect to progression in patients with CIS.[20–22]

The adverse effects of intravesical BCG, local and systemic, which are more pronounced than with intravesical chemotherapy, are well documented in the individual studies included in the meta-analysis and are not repeated here. The assumption that BCG induced side effects increase with time during maintenance does not appear to be correct.[23]

The quality of the trials and data reported in the publications upon which this meta-analysis is based are not optimal. Data were available for only 700 patients included in 9 randomized trials, with 6 trials also including patients with just papillary tumors. Information on complete response was available for only 7 trials and 605 patients (86%) and progression data were available for only 6 trials and 474 patients (68%). The duration of followup was variable but generally short (median 3.6 years), further limiting the quality of the progression and survival data. In addition, the results of the studies comparing BCG to MMC were quite heterogeneous, due not only to different policies for BCG maintenance treatment, but also to large differences in the complete response rate on MMC. Without individual patient data, the effect on the outcome of potential prognostic factors such as the type of CIS (primary, secondary, concurrent) cannot be taken into account.

Although the strength and quality of the data for this meta-analysis may be less than that of previous ones[19–22] it has nevertheless shown that intravesical BCG is more effective than intravesical chemotherapy for the complete response rate and the long-term disease-free rate. It is also consistent with the results of previous meta-analyses that have shown that BCG is more effective than MMC when maintenance BCG is given[19–20] and that BCG reduces the risk of progression to muscle invasive disease.[20,22]

CONCLUSIONS

Intravesical BCG significantly reduces the risk of short-term and long-term treatment failure compared with intravesical chemotherapy in the treatment of carcinoma in situ. Therefore, it is considered to be the initial intravesical agent of choice in the treatment of this disease.

C. Tangen and J. Vriesema provided additional summary data for 2 trials.

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EDITORIAL COMMENT

In patients with biopsy proven CIS of the bladder, BCG undoubtedly can have a key therapeutic role. By combining a number of randomized clinical trials, this meta-analysis confirms its benefits in disease-free rate and progression rate compared to other intravesical chemotherapy agents considered as a group. However, the BCG advantage in patients with CIS compared specifically to mitomycin C was smaller. To examine this comparison further, a subset analysis was performed based on 3 studies that used maintenance BCG versus mitomycin C. This analysis did confirm BCG's superiority in disease-free status but no findings were reported in disease progression and survival rates. Although subset analysis provides useful information, once performed it can often beg for the completion of other comparisons and their results, such as an evaluation of other specific agents and outcomes such as progression. Moreover, the 3 studies with maintenance BCG used different treatments schedules and doses. Malmstrom et al used 120 mg weekly for 6 weeks, then monthly for 12 months, then every 3 months for another year (reference 12 in article). Di Stasi et al used an 81 mg dose weekly for 6 weeks, and then almost half the patients (44%) received another 6 treatments weekly for initial nonresponse, followed by monthly treatments for 10 more months (reference 13 in article). Finally Lamm et al's BCG dosing was 50 mg weekly for 6 weeks, then a dose at weeks 8 and 12, then monthly up to 1 year (reference 9 in article). Importantly, none of these maintenance schedules used the more recently prospectively evaluated Southwest Oncology Group-8507 protocol.[1]

Where does this leave us? With more questions to try to answer. Maintenance BCG does seem to provide better treatment efficacy but the best dosing and/or schedule regimen still are unverified. In addition, what is the real impact of BCG on progression and survival rates? The authors analyze the current studies involving intravesical therapy, and provide an important service and information by focusing on CIS, a disease much different from other superficial disease types. Although the recurrence rate may decrease with intravesical therapy, careful monitoring and vigilance are required. This meta-analysis establishes an important framework that raises more questions that will need to be answered as studies mature and future studies are completed.

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1. Lamm, D. L., Blumenstein, B. A., Crissman, J. D., Montie, J. E., Gottesman, J. E., Lowe, B. A. et al: Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol, **163:** 1124, 2000

REPLY BY AUTHORS

Due to the limited number of patients with CIS and the relatively short duration of followup in most phase 3 trials comparing intravesical chemotherapy and immunotherapy, individual studies do not provide sufficient data for making treatment decisions based on

long-term end points—hence the reason for this meta-analysis. However, this meta-analysis does not provide an answer to all questions of interest. We cannot from these data alone conclude that BCG is superior to chemotherapy for progression of or survival with CIS. The results are consistent with other larger superficial bladder cancer meta-analyses in which maintenance BCG has been shown to be superior to chemotherapy, mitomycin C in particular, for progression. Due to its nature, this meta-analysis includes studies with different doses and treatment schedules. As for superficial bladder cancer in general, we still do not know the optimal dose and induction/maintenance schedule. Thus while this meta-analysis does supply important information, we agree that for the treatment of CIS, many more questions remain to be answered via properly designed and adequately powered, randomized phase 3 clinical trials.