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ORIGINAL REPORT

Randomized Phase III Trial on Gemcitabine Versus Mytomicin in Recurrent Superficial Bladder Cancer: Evaluation of Efficacy and Tolerance

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ABSTRACT

Purpose
Approximately 30% to 40% patients with a superficial bladder cancer treated with Bacille Calmette-Guerin (BCG) or epirubicin do not respond; of the initial responders, 35% have a relapse within 5 years. We compare the therapeutic efficacy and toxicity of intravescical infusions of gemcitabine (GEM) with mitomycin (MMC) in patients with a recurrent superficial bladder cancer.

Patients and Methods
Patients with a history of a previously treated, recurrent Ta-T1, G1-G3 bladder transitional cell carcinoma were enrolled in the study. The patients received a 6-week course of GEM infusions or 4-week course of MMC. In both arms, for the initial responders who remained free of recurrences, maintenance therapy consisted of 10 monthly treatments during the first year.

Results
A total of 120 patients were enrolled and randomly assigned to either the MMC or GEM treatment arm. At the end of the study, 109 patients (55 in MMC and 54 in GEM) were assessable. The median duration of follow-up was 36 months for either arm. In the GEM arm, 39 (72%) of 54 patients remained free of recurrence versus 33 (61%) of 55 in MMC arm. Among patients with recurrences, 10 in the MMC arm and six in the GEM arm also had a progressive disease by stage. The incidence of chemical cystitis in the MMC arm was statistically higher than in the GEM arm ($P = .012$).

Conclusion
This study demonstrates that GEM has better efficacy and lower toxicity than MMC; therefore, GEM appears as a logical candidate for intrabladder therapy in patients with refractory transitional cancer.

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INTRODUCTION

Bladder transitional cell carcinoma remains a significant health problem, and bladder cancer is the fifth most common cancer in Western countries.[1] At initial presentation, 70% of bladder cancers are superficial and include carcinoma in situ, Ta, and T1 disease. Transurethral resection (TUR) is the primary mode of clinical management for both diagnosis and treatment of superficial bladder cancer, but 60% to 70% of these cancers recur and 20% progress to higher stage.[2] TUR is commonly followed by intravescical infusion of either chemotherapy or immunemodulating agents in order to reduce the incidence of recurrence and progression.

Bacille Calmette-Guèrin (BCG) is the most effective agent in the prevention of recurrence demonstrating to decrease the rate of progression; however, only one third of patients respond to BCG, and it can induce a range of adverse effects from mild dysuria to systemic tuberculosis.[3]

Several conventional cytotoxic agents have been used for prophylaxis of recurrences after resection.[4] Adjuvant intravescical infusion for recurrent tumors with chemotherapy or immunotherapy is not yet clearly established. Patients for whom BCG fails are a challenge for the urologist and oncologist, with the need for careful individualization of therapy by experienced professionals.

Among the compounds used in intravescical therapy mitomycin (MMC) is one of the most common. In fact, this antitumor antibiotic, accordingly to the manufacturer's labeling, is indicated in intravescical infusion at the dose of 40 mg.[5] The European Urological Association guidelines recommend 20 to 40 mg as the standard dose of MMC.[5]

MMC has been shown to be active in treating superficial bladder cancer, and given in multiple

infusions produces response rates ranging between 40% and 50%.[6] MMC is, at the present, one of the standard chemotherapy agents in the treatment of superficial bladder cancer.[7] In two recent studies, MMC was compared with BCG showing a slightly decreased activity in the treatment of the disease and prevention of recurrence.[8,9]

Multiple infusions of MMC, however, are associated with an increased incidence of adverse effects.[10] In fact, chemical cystitis and allergic reactions are quite common and disappear after cessation of therapy.

The new pyrimidine analog gemcitabine (GEM) exhibits antitumor activity against a variety of solid tumors including advanced bladder cancer.[11] In fact, it is active and well tolerated when used in the treatment of metastatic bladder cancer.[11] The proven efficacy of systemic therapy against advanced bladder cancer led urologists to consider GEM as a potential new agent for the treatment of superficial transitional cell carcinoma by intravescical administration. Its pharmacologic characteristics make it an excellent choice for intravescical use; in fact, it has high mucosal but low plasma absorption.[12]

The safety of GEM intravescical administration up to 2,000 mg in 50 mL saline is well documented.[13,14] A recent multicenter study demonstrated that GEM is a tolerable and feasible therapeutic option[15] even if comparative randomized phase III studies should provide additional information on GEM for patients with superficial bladder cancer.[16]

To ascertain the relative benefit of MMC and GEM in patients with refractory cancer, we performed a randomized comparison of these two agents. Both drugs were given to patients with superficial bladder cancer who had recurrent disease.

PATIENTS AND METHODS

Patients with a history of histologically proven recurrent transitional cell carcinoma of the bladder at stages Ta and T1 of any grade, were enrolled in the study. In details, patients with superficial bladder cancer whose disease has either progressed or relapsed after BCG intravescical infusion or were ineligible for BCG treatment were included. Before random assignment, subjects were stratified on age (represented as different serial decades), stage (Ta or T1), and histologic grade (grade 1 to 2 or 3). Subjects were randomly assigned to treatment in a 1:1 allocation within each stratum to MMC or GEM intravescical infusion. They received 40 mg of MMC or 2,000 mg of GEM diluted in 50 mL of normal saline. The institutional review board approval was obtained and data were collected in a prospective fashion.

Patients were instructed to retain the drug for 1 hour before voiding, but no positional changes were allowed. Exclusion criteria included prior radiation to the pelvis and intractable urinary tract infections. The study included blood chemistry and urine tests before treatment and every 2 weeks during the treatment to evaluate systemic adverse effects. All patients provided written informed consent before entry into the trial.

Patients in the MMC treatment arm received an early infusion of the diluted drug within 2 days after TUR, followed by 4 weekly treatments. Subjects in GEM arm received a 6-week induction course of infusion. In both arms, for the initial responders who remained free of recurrences, maintenance therapy consisted of 10 monthly treatments during the first year. Patients in both groups were monitored for toxicity and received oral antimicrobial agents for 2 days after each infusion. Although failure did not exclude subjects from further therapy, we stopped the study follow-up of the patients with visible tumor recurrences (established by histologic examination) at their demonstration.

Of the initial 120 individuals, 109 were evaluated, the remainder being ineligible due to protocol violation, loss to follow-up, or other reasons.

Objectives and Statistical Methods

The main end points used to assess the efficacy of GEM and MMC treatments were the time of first recurrence (disease-free interval—the total time between the random assignment and the date of the first positive cystoscopy), the relative risk of recurrence estimated by the life-table method, and the recurrence rate per 100 patient-months (defined as the number of positive for tumor cystoscopies divided by the total number of follow-up months for all patients in each group and then multiplied by the factor 100 for simplicity). Cumulative rates of tumor progression by stage and muscle invasion were also estimated and compared. The intention was to enter at least 104 assessable subjects (52 in each treatment arm). Time to tumor recurrence was determined by Kaplan-Meier product-limit method.[17] Proportional hazards regression (considering age, sex, stage, and treatment as covariates) analysis of survival was performed using the Cox proportional hazards model.[18] The two-sided Fisher's exact test was used in order to compare the distribution of toxicities between different groups. The differences in terms of time to tumor recurrence according to different categories of risk were evaluated by the log-rank test. SPSS software (version 14.00; SPSS, Chicago, IL) was used for statistical analysis. A P value of less than .05 was considered to indicate statistical significance in two-sided test.

RESULTS

Patient Characteristics

A total of 120 patients were enrolled and randomly assigned to either the MMC treatment arm or GEM treatment arm from March 2003 to November 2005. Of the enrolled patients, three had a protocol violations, four did not complete the treatments because of adverse reactions or other reasons, and four refused follow-up (Fig 1) The remaining 109 patients (47 males and 8 females in the MMC arm v 46 males and 8 females in the GEM arm) completed the planned treatment and were assessable. The mean age (standard deviation) was

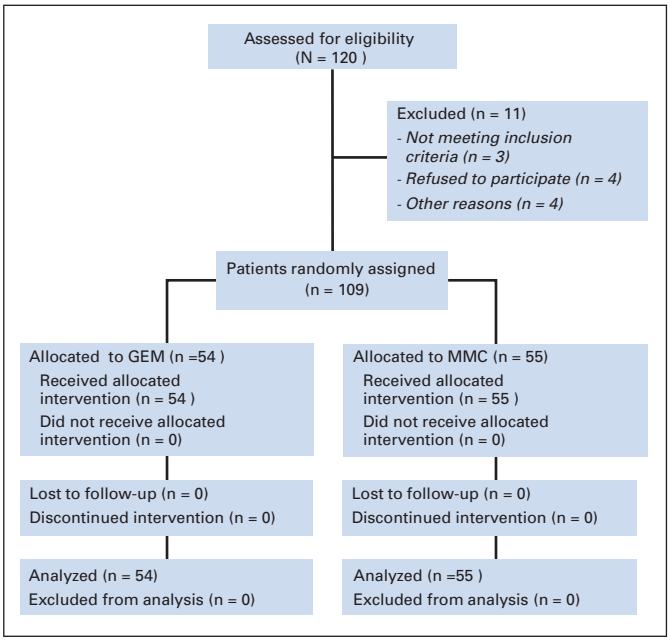

Fig 1. CONSORT diagram. GEM, gemcitabine; MMC, mitomycin.

67.9 ± 10.2 years (median, 70 years) and 64.9 ± 10.55 years (median, 66.5 years) for the patients enrolled in the MMC arm and GEM arm, respectively. The median duration of follow-up (identical for both groups) was 36 months. Previous treatment with BCG was administered in 45 and 46 patients in MMC and GEM groups, respectively. No patient developed signs and/or symptoms of local and systemic tuberculosis that were specifically investigated before and during BCG intravescical infusions. In contrast, epirubicin was previously given to 10 and eight patients in the MMC and GEM groups, respectively. Epirubicin was administered to patients who were intolerant to BCG (dysuria and/or ematuria). Table 1 presents the patients' and tumor characteristics.

Clinical Activity and Prevention of Recurrences

The overall treatment results are summarized in Table 2. The advantage of GEM administration versus that one of MMC is suggested by comparing the differential Kaplan-Meier disease-free survival curves between the two arms of treatment (Fig 2; $P = .0021$); the advantage in disease-free survival for the GEM arm was maintained also in grade 3 neoplasms (Fig 3; $P = .049$). The statistical significance of the differences in the two arms were detected by log-rank test. No differences were discovered in grade 1, grade 2, T1 cancer, or in the number of cancer between two arms of treatment. No interactions between treatment groups and clinical parameters (age, sex, and stage) was identified using multivariate Cox regression model.

Among patients with recurrences, 10 in the MMC arm and six in the GEM group, respectively, had progressive disease by stage and five and three, respectively, had either local urothelial spread or muscle infiltration. These differences were not statistically significant. Two patients, one in each arm, developed metastases.

Table 1. Patient and Tumor Characteristics

Characteristic	No. MMC Group	No. GEM Group
Sex		
Male	47	46
Female	8	8
Mean age, years	67.9	64.9
SD	10.2	10.5
History		
Recurrent single tumor	34	29
Recurrent multiple tumors	21	25
Size of largest tumor, cm		
< 2.0	33	36
> 2.0	22	18
Stage		
Ta	35	37
T1	20	17
Grade		
1	14	11
2	27	28
3	14	15
Previous treatment		
BCG	45	46
Epirubicin	10	8

Abbreviations: MMC, mytomycin; GEM, gemcitabine; SD, standard deviation; BCG, Bacille Calmette-Guerin.

Table 2. Responses to Therapy by Treatment Assignment

Parameter	MMC Group	GEM Group	*P*
Total No. of patients	55	54	—
Median time to tumor recurrence, months	15.0	Not reached	—
Relative risk of recurrences	0.94	0.72	.291
Recurrence rate/100 patient-months	1.72	1.26	.31
Patients with tumor progression by stage	10	6	.140

Abbreviations: MMC, mytomycin; GEM, gemcitabine.

Toxicity Evaluation

Local toxicity in both treatment groups was acceptable (Table 3). In most cases, it was mild and brief, and was limited usually to grade two dysuria in five (9.2%) and suprapubic pain in six patients (11%), in the GEM group, and dysuria in 11 (20%) and suprapubic pain in four patients (7.2%), in the MMC arm of treatment. Other adverse effects were hematuria in two (3.7%) versus four patients (7.2%), local reactions in two (3.7%) versus five patients (9.0%) and skin reactions in three (5.5%) versus six patients (10.9%) in the GEM and MMC arm, respectively. However, these differences did not achieve the statistical significance. The incidence of chemical cystitis (21.1% in MMC and 5.5% in GEM arm) and dysuria frequency (20.0% in MMC and 9.2% in GEM arm) were statistically higher in MMC arm than that in GEM group ($P = .013$ and $P = .023$, respectively). Globally, the incidence of adverse effects was lower in the GEM (38.8%) than in the MMC arm (72.2%; $P = .021$). The incidence of local adverse effects sufficiently severe to delay intravescical treatment was 10% for MMC and 5% for GEM. Systemic toxicity was never life-threatening and no hematologic or biochemical abnormalities were noted in the follow-up blood samples.

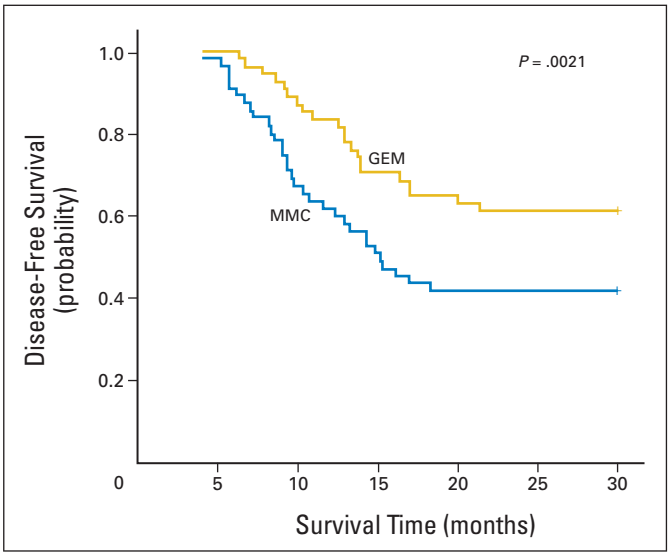

Fig 2. Kaplan-Meier estimate of disease-free survival time from study entry for patients on gemcitabine (GEM) or mitomycin (MMC) arms. *P* values were derived from a log-rank test.

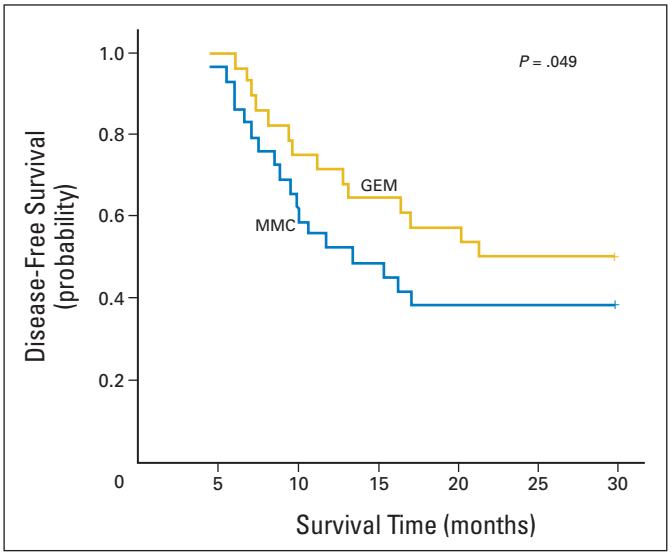

Fig 3. Kaplan-Meier estimate of disease-free survival time from study entry for patients with a grade 3 superficial bladder cancer. *P* values were derived from a log-rank test. MMC, mytomycin; GEM, gemcitabine.

DISCUSSION

To reduce bladder cancer recurrence and progression after TUR, adjuvant BCG therapy is recommended as a first-line of treatment. Nevertheless, 43% of patients have a residual tumor after this treatment, and after a new BCG administration 20% of patients can be defined as truly BCG refractory.[19] Patients with tumor recurrence after BCG and especially those with recurrence before 2 years should be considered for alternative therapies.

Despite years of study, the optimal intravescical regimen for these patients has not yet been established, and cystectomy remains the only proven curative option. However, some patients are not candidate for radical surgery due to comorbidities and other refuses; furthermore, radical cystectomy is associated with 28% morbidity and 2.5% mortality.[20] Many experimental modalities are now available for treating patients with superficial bladder cancer who have failed BCG; optimized chemotherapy with MMC and GEM have shown some encouraging results.[4] The mechanisms of action of the two drugs are quite different even if the two agents are both classical cytotoxic drugs affecting DNA integrity. In fact, MMC acts through the formation of DNA adducts that cause DNA damages thus stopping the replication of cancer cells. MMC is activated in tumor cells through the formation of reducing equivalents.[21] In contrast, GEM is a difluoro-2′,2′-deoxycytidine that requires activation through the synthesis of its phosphorylated metabolites and acts by inducing DNA damage, by blocking the DNA repair system and affecting the deoxy-nucleotide synthesis.[22] Several studies are now available on both agents as second-line therapy of superficial bladder carcinoma. In a recent study by Gardmark et al,[8] the efficacy of 40-mg MMC was compared with BCG in 261 patients, and the results suggested that the two regimens did not differ for their effects on disease progression. Recently, Ojea et al[9] compared a low-dose of 27-mg BCG to 13.5-mg BCG, using 30 mg MMC as the third arm of comparison. A total of 430 patients with intermediate-risk superficial bladder cancer were randomly assigned into three groups. There were no statistically significant differences between 27-mg BCG and 13.5-mg BCG ($P = .165$) or between 13.5-mg BCG and 30-mg MMC ($P = .183$). However, Cox proportional hazards regression showed that disease-free interval in the multivariate analysis was significantly better for primary disease and treatment with 27-mg BCG.[9] Moreover, in a randomized study of 261 patients with superficial bladder carcinoma, the cross-over treatment was successful in 19% with second-line MMC after BCG failure treatment.[23] In contrast, the safety of GEM intravescical administration up to 2,000 mg in 50 mL saline is well documented. In fact, Morabito et al[15] developed a multicenter Italian study for patients with multitreated bladder cancer to evaluate the tolerability of this drug. In this study, 61 of 64 patients completed the cycle demonstrating that GEM is a tolerable and feasible therapeutic option for these patients. Complete response (CRS) obtained with GEM (evaluated on target lesions of the bladder) ranged from 44.0% to 66.6%.[24-28] Recently, in a phase II study, Dalbagni et al[30] confirmed the efficacy of an intensive schedule of intravescical GEM administration in BCG-refractory transitional cell carcinoma of bladder patients; in that study, 50% of patients achieved a CR, and 23% demonstrated a partial response with a very low toxicity.[29,30] In fact, of the 30 patients included in the study, 15 (50%) obtained a CR and the 1-year recurrence-free survival rate for patients with a CR was 21%. Dalbagni et al confirmed that this drug represents a suitable choice for some patients who refuse cystectomy. In a smaller study, Bassi et al[31] treated nine patients refractory to intravescical BCG, followed by 12 monthly infusions in four complete responders who achieved a clinical response with 7 to 33 months disease-free survival. Other recent studies showed that GEM is active in BCG-refractory patients with a favorable safety profile. In this regard, Bartoletti et al[32] found recurrence at 1 year in six of 24 intermediate-risk and seven of 16 high-risk BCG-refractory patients treated with intravescical GEM. In that study,[32] intravescical GEM was administered as a prophylactic treatment in a mixed series of superficial bladder cancer that included also high-risk tumors. Notably, the excellent results in terms of 1-year recurrence-free survival were achieved employing a 3-year maintenance schedule identical to the one currently suggested for BCG.

In this study, the comparison of GEM and MMC shows that GEM has a better chemopreventive activity than MMC. The percentage of patients with recurrence on intravescical chemotherapy for GEM significantly differs from that one observed in MMC-treated patients. In fact, at 36 months of follow-up only 28% patients recurred in the GEM arm versus 39% in the MMC arm. Interestingly, median time to recurrence was 15 months in the MMC arm while it was not

Table 3. Incidence of Adverse Effects by Treatment Groups

	GEM (n = 54)		MMC (n = 55)		
Symptom	No. of Patients	%	No. of Patients	%	*P*
Dysuria	5	9.2	11	20	**.023**
Suprapubic pain	6	11	4	7.2	.949
Hematuria	2	3.7	4	7.2	.601
Chemical cystitis	3	5.5	12	21.1	**.013**
Local reactions	2	3.7	5	9	.465
Skin reaction	3	5.5	6	10.9	.505
Total	21	38.8	40	72.2	**.021**

NOTE. Bold font shows statistically significant differences between GEM and MMC arms. Fisher's exact test (two sided) was used for *P* value calculation.
Abbreviations: MMC, mytomycin; GEM, gemcitabine.

reached in the GEM arm. The analysis of risk of recurrences in the different subsets of patients stratified for grade and T stage demonstrated a higher benefit for patients with grade 3 tumors treated with GEM if compared with the MMC arm as calculated with the log-rank test. In our study, we found a positive trend regarding tumor progression in GEM arm, even if the rates did not significantly differ between the two treatment groups.

Moreover, the incidence of toxic adverse effects was significantly lower with GEM than with MMC. These results, according to previous studies,[33] confirmed that chemical cystitis manifesting as irritative lower urinary tract symptoms represents the most adverse effect of MMC. Local toxicity of GEM was minimal and generally rapidly self-resolving. The results of our study have confirmed the good tolerability of GEM as previously described in another phase II prospective multicenter study: among 166 patients, 81.3% did not report any local adverse effects during the treatment period.[30] Severe local toxicity requiring treatment delay was more prominent in the MMC treatment arm.

Our results provide suggestions relevant to the clinical application of intravescically administered therapy for BCG-refractory patients. This study indicates that our GEM regimen may modify the biologic behavior of recurrent superficial transitional cell carcinoma of the bladder and suggests that patients with tumors at grade 3 are more appropriate for GEM therapy.

To the best of our knowledge, this is the first report specifically dealing with the use of GEM for its better clinical activity and favorable toxicity profile. Therefore, GEM appears a logical candidate for intravescical therapy for patients with refractory transitional cell carcinoma, in whom this cytotoxic drug may represent a valid alternative to cystectomy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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