Original Article

Gemcitabine Versus Bacille Calmette-Guérin After Initial Bacille Calmette-Guérin Failure in Non-Muscle-Invasive Bladder Cancer

A Multicenter Prospective Randomized Trial

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BACKGROUND: The efficacy of intravesical gemcitabine was evaluated compared with repeated administration of bacille Calmette-Guérin (BCG) after BCG failure in high-risk, non-muscle-invasive bladder cancer (BC). **METHODS:** In this multicenter, prospective, randomized, phase 2 trial, eligible patients were those with high-risk non-muscle-invasive BC, failing 1 course of BCG therapy. All patients were randomly allocated to Group A, receiving intravesical gemcitabine (at a dose of 2000 mg/50 mL) twice weekly for 6 consecutive weeks and then weekly for 3 consecutive weeks at 3, 6, and 12 months, or Group B, receiving intravesical BCG (Connaught strain, 81 mg/50 mL) over a 6-week induction course and each week for 3 weeks at 3, 6, and 12 months. Outcome measures were recurrence rate, time to first recurrence, and progression rate. Treatment-related complications were also evaluated. **RESULTS:** Eighty participants were enrolled, 40 for each group 52.5% in Group A developed disease recurrence versus 87.5% of those in Group B ($P = .002$). There was no statistically significant difference in mean time to the first recurrence (Group A, 3.9 months; Group B, 3.1 months; $P = .09$). Kaplan-Meier analysis of 2-year recurrence-free survival showed significant differences between Group A and B (19% and 3%, respectively, $P < .008$). Seven of 21 (33%) patients in Group A and 13 of 35 (37.5%) patients in Group B had disease progression and underwent radical cystectomy ($P = .12$). Both intravesical administrations were generally well tolerated. **CONCLUSIONS:** Gemcitabine might represent a second-line treatment option after BCG failure in high-risk non-muscle-invasive BC patients. ***Cancer*** **2010;116:1893–900.** © *2010 American Cancer Society.*

KEYWORDS: bacille Calmette-Guérin, failure, gemcitabine, superficial bladder cancer.

The primary therapeutic goal in patients with high-risk non-muscle-invasive bladder cancer (BC) is the prevention or delay of disease progression. Large meta-analyses have shown that bacille Calmette-Guérin (BCG) therapy is associated with a reduction in the risk of tumor progression compared with chemotherapy.[1,2] BCG was also shown to be superior to chemotherapy in reducing tumor recurrence.[3]

Between 20% and 40% of patients apparently fail after BCG with recurring tumors, depending on the follow-up time and their initial risk profile.[4] When BCG is used as therapy, it induces a 70% initial complete response rate, which remains in 50% of patients after long follow-up.[5]

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The fate of patients failing intravesical therapy and showing progression into muscle-invasive disease is surprisingly bad. Examining patients showing progression after BCG treatment, Sylvester et al[1] reported a bladder cancer-specific death rate of 64% at 2.5 years after progression from a superficial tumor. Similar figures were more recently found by a Spanish group.[6]

Thus, the window of opportunity is these patients remains limited, and the management of BCG treatment failures represents an important issue in non-muscle-invasive BC, particularly in high-risk disease. According to the European Association Of Urology,[7] 3 months of BCG therapy can be administered, as this has been associated with a complete response in >50% of patients.[8] Changing from BCG to chemotherapy can provide further remission in selected patients failing BCG therapy. However, in most cases of high-risk BCG failure, immediate cystectomy is strongly advocated.[7]

As some of these patients cannot be submitted to radical surgery because they are unfit for it and/or refuse it, more conservative approaches with other cytotoxic drugs may be considered in this setting.[9]

Gemcitabine, a novel deoxycytidine analog with a broad spectrum of antitumor activity, is considered standard in systemic therapy for advanced bladder cancer.[10] Given its pharmacokinetic properties, gemcitabine has been suggested as an ideal candidate for regional therapy and has been studied for its potential in intravesical use.[11]

Intravesical gemcitabine was first reported as a new treatment option for BCG-refractory non-muscle-invasive BC patients by Dalbagni et al.[12] More recently, the same group reported a phase 2 study assessing the efficacy of gemcitabine administered as an intravesical agent in BCG-refractory patients refusing cystectomy. Thirty eligible patients were included in the study, and the median follow-up for all was 19 months. Of these patients, 15 (50%) achieved a complete response. However, the 2-year disease-free rate was only about 8% (2 of 30), suggesting that durability remains a problem.[13]

The aim of our study was to evaluate the efficacy of intravesical gemcitabine compared with repeated administration of BCG as second-line therapy in high-risk non-muscle-invasive BC patients refusing or not candidates for radical cystectomy after initial BCG failure.

MATERIALS AND METHODS

This is a multicenter, prospective, randomized, phase 2 trial carried out between June 2006 and May 2008. The study was approved by the local research ethical committee of each participating center. Written informed consent was obtained from all patients.

Inclusion Criteria

Eligible patients were those with high-risk non-muscle-invasive BC, based on the European Organization for Research and Treatment of Cancer scoring system,[14] failing BCG therapy,[7] for whom radical cystectomy was indicated but not conducted because of refusal or ineligibility because of age or comorbidities and high anesthesiological risk. Tumors were pathologically staged according to the 1997 TNM classification and graded following the 1998 World Health Organization/International Society of Urologic Pathology scale. Exclusion criteria were concurrent or previous muscle-invasive disease, concurrent or previous tumor in the upper urinary tract or prostatic urethra, chronic urinary tract infection, cured or active tuberculosis, any other malignancy except basal cell carcinoma of skin, previous pelvic irradiation, creatinine higher than twice the standard, glutamate oxaloacetic transaminase and glutamate pyruvic transaminase higher than twice the standard, pregnancy or lactation, and any other disease with immunodeficiency.

Study Design

All patients started treatment after 4 to 6 weeks from the last transurethral resection (TUR), performed after the failure of the first treatment with BCG, as defined by the European Association Of Urology.[7] Re-TUR had been performed in all T1 high-grade cases. By using a central computer-generated randomization list, patients were randomly allocated to 1 of the 2 groups. An open-label study design was used, that is, patients and investigators were not masked as to the drugs they were assigned.

Group A received intravesical gemcitabine, twice weekly (Days 1 and 4) at a dose of 2000 mg/50 mL for 6 consecutive weeks (induction course), and then weekly for 3 consecutive weeks at 3, 6, and 12 months. Group B was given intravesical BCG (Connaught strain, 81 mg/50 mL) over a 6-week induction course and then each week for 3 weeks, at 3, 6, and 12 months.

The prestudy clinical evaluation comprised medical history, general physical examination, electrocardiogram, computed tomography (CT)-urography, chest x-ray, and hematological evaluation (including white blood cell-platelet count, electrolytes, and liver and kidney function). Urine analyses with urine culture were also done weekly during the treatment. Clinical, hematological, and

biochemical assessments were performed every third week and were repeated at the end of treatment.

Cytological analysis of voided urine and cystoscopy were performed at 3-month intervals. Intravenous urography or CT-urography was performed annually.

Recurrence was determined by lesions that were detected at cystoscopy and pathologically confirmed after TUR. A positive cytology alone was not considered as a recurrence. In case of positive cytology, a bladder mapping was performed, and only if there was pathological confirmation of a tumor was a case counted as a recurrence. Time to first recurrence was defined as the time from TUR to the date of the first recurrence.

Progression was defined as an increase in tumor stage and grade. Time to progression was defined as the time between TUR and first progression.

Toxicity was assessed on the first day of each cycle with the use of the Common Toxicity Criteria version 3.0.[15] Grade 3 side effects resulted in patients' exclusion from the study. In the case of grade 2 toxicity, the treatment was delayed for 1 week and repeated. If toxicity relapsed at grade 2, the treatment was stopped. Side effects were checked after each instillation and were recorded in the database. No dose reduction was allowed.

Statistics

The study was designed to compare the effect of gemcitabine with a second cycle of BCG with respect to efficacy and safety. The primary endpoint was the recurrence rate (percentage of recurring patients) at 1-year follow-up. Secondary endpoints were time to recurrence, progression rate, time to progression, and toxicity. Considering that a second course of BCG in this subset of patients might show a recurrence rate of almost 80%,[16] to obtain a significant improvement of a second-line intravesical treatment efficacy, we assumed a recurrence rate of 50% in gemcitabine-treated patients, with an absolute difference of 30% at 1 year. To obtain this result, a final target of 40 patients per group of treatment would allow the study to obtain 80% potency with 5% significance. Considering ineligible cases, we set the number of patients to be recruited as 46 in each group (n = 92 total).

Quantitative data are described by the median (range), and qualitative data are described as counts and percentages. Duration of the disease-free interval was estimated according to the Kaplan-Meier method, and comparison between treatment groups was estimated by means of the log-rank test. Chi-square and Fisher exact test were used to assess the significance of all correlations.

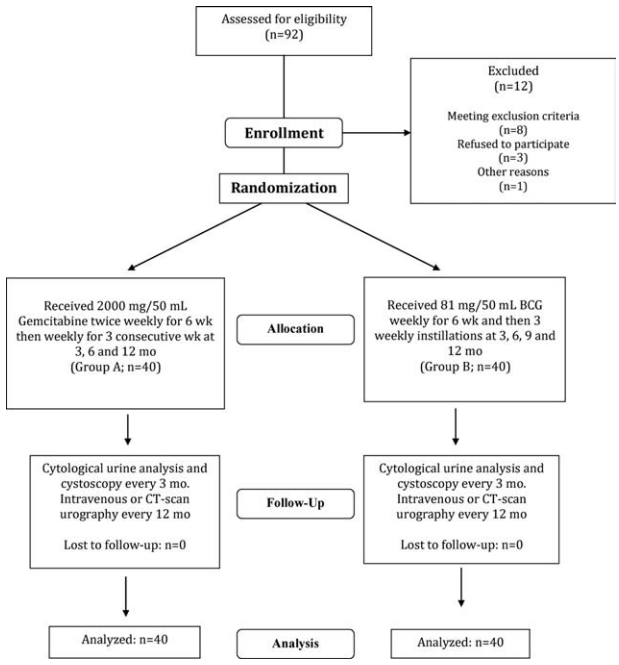

Figure 1. A diagram of the study is shown. BCG indicates bacille Calmette-Guérin; CT, computed tomography.

Statistical significance was achieved if $P < .05$. All reported P values are 2-sided. All data were recorded, collected, and analyzed using standard statistical software.

RESULTS

Of 92 initially screened patients with high-risk non-muscle-invasive BC failing BCG therapy, 80 were eligible and enrolled in this trial (Fig. 1). All patients were randomly assigned to 2 groups of 40 (Groups A and B). The clinical and pathological characteristics of the 2 groups are shown in Table 1. Median follow-up was 15.2 months (range, 6-22) in Group A and 15.8 months (range, 7-21) in Group B.

Disease Recurrence

In Group A, 52.5% (21 of 40) of patients developed disease recurrence versus 87.5% (35 of 40) in Group B ($P = .002$). The difference between the 2 groups in terms of time to first recurrence (Group A: 3.9 months; 95% confidence interval [CI], 3-7; Group B: 3.1 months; 95% CI, 2.2-6) was not statistically significant (hazard ratio [HR], 1.1; CI 95%, 0.8-1.2; $P = .09$). Kaplan-Meier analysis of 2-year recurrence-free survival showed significant differences between Group A (19%; 95% CI, 5-39) and Group B (3%; 95% CI, 0-21; HR, 0.15; 95% CI, 0.1-0.3; $P < .008$; Fig. 2).

Table 1. Baseline Patient Characteristics

Characteristic	Group A (Total=40)	Group B (Total=40)	*P*
Men/Women	27/13	22/18	NS
Mean age, y±SD	69.3±8.4	71.4±7.9	NS
ASA score			**NS**
II	6	8	
III-IV	34	32	
Classification			**NS**
Ta	10	8	
T1	30	32	
Grade (1998 WHO)			**NS**
Low	11	13	
High	29	27	
Number of tumors			**NS**
Single	10	8	
2-7	25	26	
≥8	5	6	
Tumor diameter			**NS**
<3 cm	15	17	
>3 cm	25	23	
Concomitant CIS	12	13	NS
Recurrence rate			**NS**
Primary	3	5	
≤1 per year	10	9	
>1 per year	27	26	
EORTC progression score			**NS**
7-13	5	7	
14-23	35	33	

NS indicates not significant (Fisher exact test); ASA, American Society of Anesthesiologists; WHO, World Health Organization; CIS, carcinoma in situ; EORTC, European Organization for Research and Treatment of Cancer.

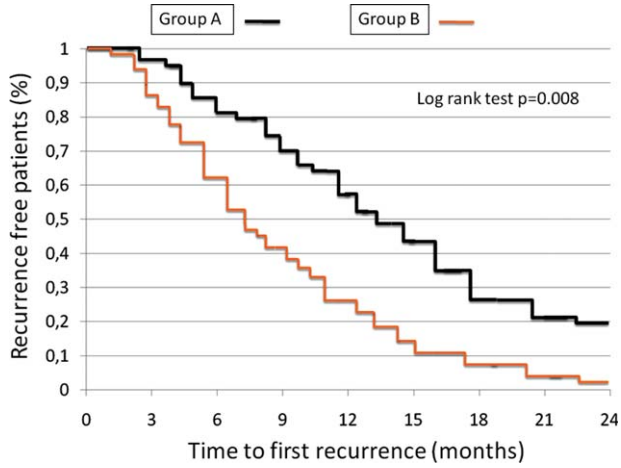

Figure 2. Kaplan-Meier estimation of 2-year recurrence-free survival is shown (Group A, gemcitabine; Group B, bacille Calmette-Guérin).

Table 2. Toxicity in the Treatment Groups

Toxicity	Group A (n=40)	Group B (n=40)	*P*
Dysuria			
Grade 2	4	7	
Grade 3	2	1	
Hematuria			
Grade 2	2	4	
Grade 3	0	1	
Fever			
Grade 2	1	2	
Grade 3	0	1	
Neutropenia-thrombocytopenia			
Grade 2	1	0	
Grade 3	1	0	
Dermatitis			
Grade 2	2	0	
Grade 3	0	0	
Nausea-vomiting			
Grade 2	2	0	
Grade 3	0	0	
Total events			
Grade 2	12	13	.12
Grade 3	3	3	.25

Disease Progression

Seven of 21 (33%) patients in Group A and 13 of 35 (37.5%) patients in Group B had disease progression and underwent radical cystectomy with ileostomy or ureterocutaneostomy. Moreover, 9 of 21 (43%) patients in Group A and 14 of 35 (40%) patients in Group B were submitted to radiation therapy plus systemic chemotherapy. At the time of the last follow-up visit, all patients were alive in Group A, and 1 had died because of metastatic disease in Group B. No statistically significant difference was reported ($P = .12$).

Toxicity

Both intravesical administrations of gemcitabine and BCG were generally well tolerated (Table 2). Overall, few severe (grade 3) adverse events occurred, with no statistically significant difference between the 2 groups. In 2 cases, we observed grade 3 dysuria, and in 1 case, grade 3 thrombocytopenia in Group A. One case of dysuria, 1 of hematuria, and 1 of fever (>38°C) represented the grade 3 events in Group B. In all these 6 cases, treatment was delayed, accounting for a 7.5% delay rate in both groups.

DISCUSSION

Intravesical BCG represents the standard adjuvant treatment in patients with high-risk non-muscle-invasive BC, according to the European Association Of Urology guidelines.[7] However, not all patients benefit from intravesical BCG.[4] The fate of patients failing intravesical therapy and showing progression into muscle-invasive disease is surprisingly bad. Sylvester et al, looking at patients showing progression after BCG treatment, reported that the bladder cancer-specific death rate was 64% at 2.5 years after progression from a superficial tumor.[5] More recently, Huguet et al[6] found that of 62 failures treated with cystectomy, 17 patients appeared to have stage pT2 or higher. The 5-year disease-specific survival of these progressive patients was 38%, significantly lower than nonprogressive patients (90%).

Current options for high-risk BCG failure are radical cystectomy or alternative intravesical therapy. Various immunological and chemotherapeutic regimens have been evaluated for this purpose, but their efficacy is still a matter of debate. To date, radical cystectomy remains the recommended treatment option in these patients.[9] The advantage of cystectomy in non-muscle-invasive BC patients failing BCG is obvious, with a tumor-specific survival between 80% and 90% at 5 years.[17]

Conversely, the price for this potential survival advantage is also obvious. Cystectomy is major surgery, and not everyone is fit or willing to try it. Even in the best hands, the mortality rate is 2% to 3%, and short-term or long-term morbidity occurs in approximately $1/3$ of patients.[17] Thus, many patients are willing to explore alternatives.

One phase 2 trial specifically addressed the efficacy of bropirimine, an oral immunomodulator, in BCG-resistant carcinoma in situ (CIS) of the bladder. Of 65 evaluable patients, 21 had a complete response, including 14 of 47 BCG-resistant patients. Median response duration was >12 months, and only 4 patients progressed to invasive disease or metastasis. Although bropirimine was considered an alternative to cystectomy for some CIS patients after BCG, no further evaluation of the drug has been reported so far.[18]

The combination of interferon alpha (IFN-α) and BCG for BCG failure has been the subject of a large, multicenter, phase 2 trial.[19] Patients previously having BCG failure received IFN-α (50,000,000 U) plus reduced-dose BCG, whereas patients naive to BCG received the same IFN-α dose with standard-dose BCG. All patients who were relapse-free received an additional 3 series of 3-week reduced-dose BCG plus IFN-α treatments at 3, 9, and 15 months after completing induction. Of 1007 valuable patients, 59% and 45% of patients naive to BCG and those having BCG failure, respectively, remained disease-free at a 24-month median follow-up. Stage T1, tumor size >5 cm, prior BCG failure more than once, and multifocality were all statistically significant risk factors for recurrence. The authors concluded that although BCG plus IFN-α can be effectively applied both to patients naive to BCG and to those having BCG failure, certain patient and tumor characteristics influence durable response. Thus the combination of BCG and IFN-α represents a promising second-line regimen after BCG failure, but results should be confirmed.

Thermochemotherapy is also reported to be successful in BCG failure.[20] In 41 patients failing BCG treatment, the 1- and 2-year recurrence rates were 23% and 41%, which are at least as good as the results achieved with BCG and IFN-α. Still, longer follow-up and more results will have to indicate the value of thermochemotherapy in patients in whom BCG fails.

Waidelich et al[21] used photodynamic therapy (PDT) in 24 high-risk BCG-failing patients, including those with CIS. They found that 3 of 5 CIS patients and 4 of 19 patients with papillary tumors were recurrence-free after a median of 36 months. Thus, PDT might be a second-line treatment for patients with tumor recurrence after BCG failure.

Only a few attempts were made to treat BCG failure with conventional intravesical chemotherapy, and some interesting new drugs have been recently studied. Valrubicin, a semisynthetic analog of doxorubicin, is the only drug approved by the US Food and Drug Administration for patients with CIS failing intravesical BCG therapy. This was based on a relatively small, multicenter, phase 2 trial with 90 patients, with only a 21% response rate and 8% disease-free 2-year survival.[22] However, valrubicin currently remains underused.

Attempts have already been made to test the activity of intravesical gemcitabine in high-risk non-muscle-invasive BC patients (Table 3). In their first phase 1 study, Dalbagni et al[12] treated patients refractory to BCG and refusing cystectomy. Four dose levels of gemcitabine were given intravesically for 1 hour twice a week. Patients received 2 courses of 6 instillations. Only 1 patient (highest dose level of 2000 mg in 100 mL) experienced grade 3 toxicity. Eleven patients had negative biopsies after treatment, of whom 7 also had negative cytology. In their more recently reported phase 2 study, the same group

Table 3. Gemcitabine in High-Risk Non–Muscle-Invasive Bladder Cancer: Current Evidence

Author	No. of Patients	Study Type	Schedule	Activity	Toxicity
Bassi 2005[28]	9	Bicenter phase 1	3 dose levels weekly for 6 weeks	4 CR	No systemic absorption with only slightly bladder irritative symptoms
Gacci 2006[24]	9	Multicenter comparative nonrandomized	2000 mg/50 mL weekly for 6 weeks, then weekly for 3 weeks at 3, 6, 12, 18, and 24 months	3 recurrence free, 7 with intact bladder, overall survival 100%	No severe and only 2 minor adverse events
Morabito 2006[16]	64	Multicenter phase 1-2	2000 mg/50 mL weekly for 8 weeks	Not reported	Side effects in 14 patients, 8 of them suspended the treatment
Gunelli 2007[25]	40	Multicenter phase 2	2000 mg/50 mL twice weekly for 6 weeks	38 CR, 14 recurrences	Low urinary and systemic toxicity; no alteration in biochemical profile
Dalbagni 2006[13]	30	Single center phase 2	2000 mg/100 mL twice weekly for 3 weeks and 1 week rest	15 CR, 27/30 patients recurring in the 1st year	Generally well tolerated; 6 patients experienced grade 3 dysuria
Bartoletti 2005[23]	16	Multicenter phase 2	2000 mg/50 mL weekly for 6 weeks	No recurrence in 7 patients	Good tolerability and good patient compliance

BCG indicates bacille Calmette-Guérin; CR, complete response.

treated 30 BCG-refractory patients with biweekly 2000 mg gemcitabine diluted in 100 mL saline solution for 3 weeks, with each course separated by 1 week of rest.[13] Complete disappearance of all evidence of disease was achieved in 50% of patients. However, almost 8% of patients remained disease free at 1 year. This points out that gemcitabine in our study was being used to treat a higher-risk group of patients than in the Dalbagni study.

Bartoletti et al[23] administered intravesical gemcitabine as a prophylactic treatment in BCG-refractory patients. Eighteen of 24 intermediate-risk and 7 of 16 high-risk patients remained recurrence-free. Notably, these excellent results in terms of 1-year recurrence-free survival were achieved using a 3-year maintenance schedule identical to the 1 currently suggested for BCG. The same group of investigators reported a small series of selected BCG-resistant T1G3 patients, unsuitable for radical treatment, who were treated with gemcitabine and compared with 10 pT1G3 patients previously treated with further conservative endovesical BCG administration.[24] Of the 9 patients treated with gemcitabine, 3 were recurrence free after 13, 17, and 21 months, and 7 kept an intact bladder, with an overall survival rate of 100%. Among 10 patients treated with BCG instillation, 1 was recurrence free after 27 months, and 6 kept their bladders, with a survival rate of 80%.

Finally, Gunelli et al[25] presented a phase 2 study evaluating the activity of biweekly intravesical treatment with gemcitabine. Patients with BCG-refractory Ta-1G3 non-muscle-invasive BC underwent TUR of the bladder and then intravesical instillation with 2000 mg diluted in 50 mL saline solution on Days 1 and 3 for 6 consecutive weeks. Thirty-eight (95%) of the 40 patients showed persistent negative post-treatment cystoscopy and cytology 6 months after treatment. At a median follow-up of 28 months, recurrence was noted in 14 patients.

Pharmacokinetic data from several phase 1 studies show clearly that systemic absorption of intravesical gemcitabine at up to 40 mg/mL (2000 mg in 50 mL), when kept in the bladder for up to 2 hours, is minimal and transient, and thus unlikely to produce clinically significant adverse events.[26] Overall, no systemic toxicity exceeding grade II was recorded in any of the phase 1 studies, except for 1 case of grade 3 myelosuppression and thrombocytopenia, reported at 20 mg/mL by Dalbagni et al.[12] In that study, 2 factors in the design may have promoted an increased systemic absorption, resulting in significant hematological toxicity: first, the drug was administered twice a week; second, the low pH of the gemcitabine solution, which was adjusted to prevent bladder irritation, resulted in an increased nonionic form of the drug more likely to diffuse through the bladder mucosa.[27]

Another Italian group reported the preliminary data of a multicenter study on the use of gemcitabine to prevent recurrence of multiply recurring non-muscle-invasive BC after intravesical antiblastic agents and/or BCG.[16] Fifty-three of 61 (86.9%) patients completed the cycle. Side effects appeared in 14 patients; 8 of these had to

suspend treatment. Severe side effects were systemic in 4 patients and local in 4 patients. In 6 patients, pelvic pain, hematuria, strangury, and urinary tract infection were observed, none requiring treatment interruption.

Nine patients with CIS refractory to intravesical BCG were enrolled in a phase 1 study by Bassi et al.[28] Gemcitabine was given once weekly for 6 consecutive weeks at different dose levels. Grade 1 neutropenia was observed in only 1 patient. Grade 1 urinary frequency and hematuria were observed in 1 and 3 patients, respectively. No grades 2 to 4 toxicity or clinically relevant myelosuppression was observed. With regard to activity, 4 complete responses were observed. Thus, gemcitabine was well tolerated, and no systemic absorption with a clinical or pharmacological effect was detected. Only slightly irritative bladder symptoms were observed.

To our knowledge, our study is the first prospective randomized study to compare intravesical gemcitabine to BCG in this selected subset of patients with very high-risk non-muscle-invasive BC, failing first-line adjuvant intravesical BCG, for whom radical cystectomy is indicated. We found gemcitabine to be more effective than BCG in reducing recurrence rates (52.5% vs 87.5%, $P = .002$), whereas no significant difference was found in terms of time to first recurrence (3.9 months vs 3.1 months in Group B, $P = .03$). Note that we had a relatively low disease-free rate in the BCG group. This, together with the high progression rate for the entire group (33% in Group A, 37.5% in Group B, $P = .12$), accounts for the very high-risk profile of our study population.

Disease progression was no different between the groups and was exceedingly high at ~35%. Moreover, 43% of patients needed systemic chemotherapy and/or radiation. The clinical significance of this dismal result deserves comment about the very high-risk nature of such conservative therapy. Indeed, in many ways, this study might be relatively immature, because deaths from bladder cancer would appear to be imminent within the next 1 to 2 years.

Gemcitabine was administered with an extensive schedule (twice weekly for 6 weeks). This compared favorably with the 3-week schedule proposed by Dalbagni et al[13] in their phase 2 study. Gontero and Frea[26] have already questioned whether a more intensive scheme might be appropriate in selected high-risk cases. The major concern was obviously related to the potential toxicity. Urinary symptoms represented the main adverse events in both study groups. They were mostly managed successfully with anticholinergic, antibiotic, and/or anti-inflammatory drugs. Treatment-specific side effects, such as nausea, dermatitis, and thrombocytopenia, were unique to the gemcitabine-treated group, whereas hematuria and cystitis appeared more frequently in the BCG group.

Overall, similarly to the data of Dalbagni et al,[12,13] our data support the use of such an intensive schedule in terms of toxicity profile, because intravesical administration of gemcitabine was generally well tolerated.

Moreover, we followed the maintenance schedule suggested by Gacci et al.[24] Of course, it is clear that no standard regimen exists in this setting, and the optimal frequency and duration of maintenance instillations remain unknown. Thus, further investigation addressing this issue is needed.

It would have been interesting, also, to compare gemcitabine versus 1 of the other treatment options currently available in this setting, namely, thermochemotherapy, PDT, or the combination of IFN-α and BCG. Unfortunately, none of these options was available at our respective centers.

Moreover, albeit prospective and randomized, our trial suffers from some limitations related to the study design. Among them, the relatively small sample size, not guaranteeing against possible clinical imbalance, the limited follow-up period, not allowing definitive oncological conclusions, and the open-label design might account for some initial bias.

Clinical trials of novel intravesical agents in the BCG-failure setting should be supported to improve the standard of care, because treatment options for these patients are severely limited. To date, gemcitabine seems to have fulfilled the requirements to be a promising new candidate for standard intravesical therapy in high-risk non-muscle-invasive BC patients. The Southwest Oncology Group (http://www.clinicaltrials.gov) is recruiting participants in a phase 2 study to assess the efficacy of intravesical gemcitabine in patients with high-risk non-muscle-invasive BC who have failed BCG therapy.

Conclusions

High-risk non-muscle-invasive BC patients in whom BCG fails remain a challenge to the urologist. Even if radical cystectomy still remains the best treatment, some patients refuse it or are unsuitable for it. Gemcitabine used as second-line treatment after BCG failure in high-risk non-muscle-invasive BC patients might represent a safe and effective option. Further clinical research is warranted, as larger phase 3 trials are necessary to corroborate

these findings and to define the best treatment protocol in this setting.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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