Intravesical Gemcitabine for High Risk, Nonmuscle Invasive Bladder Cancer after Bacillus Calmette-Guérin Treatment Failure

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Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
CR = complete response
CSS = cancer specific survival
MIBC = muscle invasive bladder cancer
NMIBC = nonMIBC
NR = no response
OS = overall survival
PFS = progression-free survival
PR = partial response
RFS = recurrence-free survival

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Purpose: We report our experience with intravesical gemcitabine for bladder cancer after failed bacillus Calmette-Guérin treatment.

Materials and Methods: We retrospectively reviewed the records of patients at our cancer center treated with intravesical gemcitabine after bacillus Calmette-Guérin failure. We estimated progression-free, recurrence-free and cancer specific survival using the cumulative incidence function, considering death from another cause as a competing risk. Comparisons were made using the Gray test. Overall survival was estimated using the Kaplan-Meier method and differences were compared with the log rank test.

Results: Of 69 patients treated with intravesical gemcitabine 37 had bacillus Calmette-Guérin refractory disease. Median followup in progression-free patients was 3.3 years. Progression-free and cancer specific survival were similar in patients with refractory disease and those with other types of bacillus Calmette-Guérin failure. Overall survival was lower in patients with refractory disease (58% vs 71%) but this was not statistically significant ($p = 0.096$). Of the patients 27 patients experienced a complete response. Progression-free, cancer specific and overall survival did not differ significantly between patients with and without a complete response. Cystectomy was subsequently performed in 20 patients. Those with a complete response had a delayed time to cystectomy and no muscle invasive bladder cancer at cystectomy. There were no serious adverse events and only a minority of patients discontinued treatment due to adverse events.

Conclusions: In our experience intravesical gemcitabine should be considered after bacillus Calmette-Guérin failure in patients with bladder cancer who refuse radical cystectomy or who are not candidates for major surgery.

Key Words: urinary bladder, urinary bladder neoplasms, BCG vaccine, treatment failure, gemcitabine

BCG is considered the most effective intravesical agent for NMIBC and it is recommended for patients at high risk for progression.[1] BCG decreases the risk of recurrence, the development of distant metastasis, and the risk of death and bladder cancer related death compared to intravesical chemotherapy.[2] Failure to achieve a CR after an induction course of BCG or recurrence after BCG treatment is associated with an increased risk of disease progression and poor prognosis.[3,4]

Standard treatment after BCG failure is radical cystectomy. Patients

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who are not candidates for or who are unwilling to undergo cystectomy have limited options.[1] Intravesical valrubicin was approved by the United States Food and Drug Administration for BCG refractory bladder CIS. Several other intravesical therapies were also studied in patients with NMIBC who experience BCG failure, including immunotherapy, chemotherapy and thermochemotherapy.[5,6]

Gemcitabine is a deoxycytidine with a broad-spectrum antitumor effect. It is used in neoadjuvant and adjuvant settings in combination with other chemotherapeutic drugs for MIBC, and for advanced and metastatic tumors.[7–12] We previously reported the results of phase I and II studies of intravesical gemcitabine in patients after BCG failure.[13,14] In the current study we report our experience with intravesical gemcitabine after BCG failure. We explored the effect of the type of BCG failure on the patient response to gemcitabine and compared patient outcomes by the response to gemcitabine treatment.

PATIENTS AND METHODS

After obtaining institutional review board approval, we retrospectively reviewed the charts of patients treated with intravesical gemcitabine for NMIBC at our institution between January 1999 and October 2011. We identified 69 patients with NMIBC who were treated with intravesical gemcitabine after BCG treatment failed.

BCG Failure

A patient was considered to have BCG refractory disease when there was failure to achieve a disease-free state 6 months after initial BCG therapy with maintenance or retreatment at 3 months due to a persistent or rapidly growing recurrent tumor. BCG resistant disease was defined as recurrence 3 months after an induction cycle. BCG relapsing disease was defined as disease recurrence after the patient was disease-free for 6 months. BCG intolerant disease was defined as recurrence after administering a less than adequate course of therapy due to a serious adverse event or symptomatic intolerance requiring the discontinuation of BCG therapy.[15]

Intravesical Gemcitabine Treatment

Patients received 2 courses of intravesical gemcitabine twice weekly for 3 weeks with courses separated by a week of rest for a total of 12 instillations. Intravesical gemcitabine was given at a dose of 2,000 mg instilled in 100 ml saline. Patients were instructed to hold the instillation for 60 minutes.

Responses to intravesical gemcitabine treatment were divided into 3 categories, including 1) CR when no tumor was seen 3 months after treatment and the patient had negative cytology results, 2) PR when no tumor was seen at 3 months but the patient had positive cytology results, and 3) NR when there was a viable tumor 3 months after treatment. Toxicity was assessed after each treatment and reported using National Cancer Institute (NCI) Common Toxicity Criteria (CTC), version 2.0.

Statistical Analysis

Separate analyses were done for OS, PFS, RFS and CSS. Progression was defined as progression to MIBC or the appearance of metastasis. Recurrence was defined as any recurrent bladder cancer.

Kaplan-Meier curves were calculated to determine the difference in OS between patients with BCG refractory disease vs other types of BCG failure and compared with the log rank test. PFS, RFS and CSS were estimated using the cumulative incidence function, considering death from another cause as a competing risk, with comparisons made using the Gray test. The HR and 95% CI were estimated using a Cox proportional hazard model for OS and competing risk analysis for PFS, RFS and CSS. Survival was calculated from the date of BCG failure.

We also analyzed PFS, CSS and OS by the response to gemcitabine therapy (CR vs PR and NR). Separate analyses were done for PFS, CSS and OS using the Kaplan-Meier method and the cumulative incidence function, as described. Landmark analysis was performed using a landmark time of 5 months after the date of gemcitabine initiation to ascertain the response to gemcitabine. Patients were evaluated 1 to 3 weeks after completing treatment. Given the absence of a clinically significant landmark, we chose 5 months as the landmark since this was the time point that excluded the fewest patients.

Two patients who responded after the landmark as well as 3 lost to followup, 1 with progression and 1 who died before the landmark were excluded from PFS analysis. For CSS and OS analysis 2 patients who responded after the landmark and 3 lost to followup before the landmark were excluded. Statistical analysis was done using Stata® 12 and R (R Foundation for Statistical Computing, Vienna, Austria) with the cmprsk package.

RESULTS

Between 1999 and 2011 at our institution 69 patients were treated with intravesical gemcitabine for NMIBC after BCG treatment failed. All patients were offered cystectomy, of whom 5 were not candidates for major surgery, 63 were interested in bladder sparing alternatives and 1 was treated after cystectomy was abandoned due to concern over injuring a single pelvic kidney. Table 1 lists study cohort descriptive characteristics. Therapy was done in 37 (54%) of the 69 patients for BCG refractory disease, in 5 (7%) for BCG resistant disease, in 20 (29%) for BCG recurrent disease and in 5 (7%) for BCG intolerant disease. The reason for BCG failure could not be determined in 2 patients due to insufficient data. There was no great difference between patients with BCG refractory disease and those with another type of BCG failure. However, patients with refractory disease were more likely to have had CIS before BCG (41% vs 29%).

At last followup 11 patients had progressed, 10 had died of bladder cancer and 13 had died of another cause. Median followup was 3.3 years in