SWOG S0353: Phase II Trial of Intravesical Gemcitabine in Patients with Nonmuscle Invasive Bladder Cancer and Recurrence after 2 Prior Courses of Intravesical Bacillus Calmette-Guérin

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Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
CR = complete response
MMC = mitomycin C
RFS = recurrence-free survival
TUR = transurethral resection

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For other articles on related topics see pages 1398 and 1404.

Purpose: Prior phase II studies of intravesical gemcitabine have shown it to be active and well tolerated, but durable responses in patients with nonmuscle invasive bladder cancer who have experienced recurrence after bacillus Calmette-Guérin treatment are uncommon. We performed a multi-institutional phase II study within the SWOG (Southwest Oncology Group) cooperative group to evaluate the potential role of gemcitabine induction plus maintenance therapy in this setting.

Materials and Methods: Eligible patients had recurrent nonmuscle invasive bladder cancer, stage Tis (carcinoma in situ), T1, Ta high grade or multifocal Ta low grade after at least 2 prior courses of bacillus Calmette-Guérin. Patients were treated with 2 gm gemcitabine in 100 cc normal saline intravesically weekly $\times$ 6 and then monthly to 12 months. Cystoscopy and cytology were performed every 3 months, with biopsy at 3 months and then as clinically indicated. Initial complete response was defined as negative cystoscopy, cytology and biopsy at 3 months.

Results: A total of 58 patients were enrolled in the study and 47 were evaluable for response. Median patient age was 70 years (range 50 to 88). Of the evaluable patients 42 (89%) had high risk disease, including high grade Ta in 12 (26%), high grade T1 in 2 (4%) and carcinoma in situ in 28 (60%) with or without papillary lesions. At the initial 3-month evaluation 47% of patients were free of disease. At 1 year disease had not recurred in 28% of the 47 patients, all except 2 from the high risk group, and at 2 years disease had not recurred in 21%.

Conclusions: Intravesical gemcitabine has activity in high risk nonmuscle invasive bladder cancer and offers an option for patients with recurrence after bacillus Calmette-Guérin who are not suitable for cystectomy. However, less than 30% of patients had a durable response at 12 months even with maintenance therapy.

Key Words: urinary bladder neoplasms; administration, intravesical; gemcitabine; neoplasm invasiveness

THE treatment of nonmuscle invasive urothelial carcinoma continues to be a challenge for the practicing urologist. Patients with intermediate and high risk cancers are usually treated with TUR followed by intravesical

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BCG instillations with or without maintenance therapy.[1–3] However, up to 20% of patients are not able to tolerate the treatment and another 20% to 40% will fail to respond or will experience recurrence after the initial response.[4] Intravesical treatments available to these patients include BCG plus interferon-α, MMC, valrubicin, combination chemotherapy, and MMC with electromotive or hyperthermia techniques. Responses to these secondary treatments vary but generally range between 15% and 40% depending on the treatment group. For patients with the highest risk disease, cystectomy may ultimately be the most effective treatment. However, most patients would prefer to avoid cystectomy and many are too frail to be considered for this surgery. Urologists have long recognized the need for new alternative forms of therapy.

Gemcitabine was proposed as a reasonable choice for intravesical therapy based on its known activity against urothelial carcinoma when used systemically. Phase I trials of intravesical therapy have demonstrated a low incidence of local and systemic side effects with treatment, and have identified maximum tolerated doses generally based on volume and solubility rather than toxicity.[5–7] Several phase II studies using a 6-week induction course with weekly or twice weekly dosing have been reported to date. These tend to show a good initial response to treatment but a high failure rate by 1 to 2 years.[8] Monthly maintenance has been shown to significantly improve durable responses with MMC.[9] We hypothesized that intravesical gemcitabine would be effective for intermediate and high risk patients with recurrence after BCG therapy, and that the addition of monthly maintenance would improve the durability of the response.

MATERIALS AND METHODS

Patients were informed of the investigational nature of the study and signed written informed consent in accordance with institutional, federal and Declaration of Helsinki guidelines. The trial is registered with ClinicalTrials.gov Identifier NCT00234039. Patients were enrolled at 16 sites from May 2007 through October 2009.

Patient Eligibility

Eligible patients had recurrent nonmuscle invasive urothelial carcinoma after at least 2 prior courses of intravesical BCG (6 + 6 weeks or 6 + 3 weeks) received up to 3 years before registration. The most recent biopsy, within 60 days of registration and at least 6 weeks after completion of BCG, must have shown high grade stage Ta or T1, multifocal Ta any grade or CIS with or without associated papillary lesions. Eligibility was confirmed by central pathology review. All patients underwent studies showing normal upper tracts within 2 years before registration. Patients were allowed to have received prior post-TUR chemotherapy instillations and no more than 1 induction course of other intravesical chemotherapy during the year before registration. Patients had a Zubrod performance status of 0 to 2, no prior malignancies except for nonmelanoma skin cancer, in situ cervical cancer, adequately treated stage I or II cancer in complete remission, or other treated cancer with remission for more than 5 years, no prior pelvic radiation, and adequate renal and hematologic function at baseline.

Treatment Plan and Patient Evaluation

Patients were treated with 2 gm intravesical gemcitabine in 100 cc saline for 1 hour once weekly for 6 weeks (induction). Patients who had no tumor after induction received maintenance treatments every 4 weeks for a total of 40 weeks (10 treatments). Urinalysis was performed before each treatment to rule out infection, and complete blood count was performed at baseline, weeks 3 and 6, and then monthly. Cystoscopy, cytology and biopsy were performed at 3 months, and then cystoscopy and cytology were performed every 3 months up to month 12, with biopsy performed as clinically indicated. Patients with disease recurrence (defined as the appearance of new lesions of any stage or grade) were removed from protocol treatment. Progression was defined as recurrence with biopsy proven stage T2 disease or greater, cystectomy, or death from any cause.

Study Design

The primary outcome was the absence of tumor at the 3-month evaluation (complete response was defined as negative cystoscopy, urinary cytology and bladder biopsy). It was determined that this regimen would be of further interest if the CR rate was 40% or greater, whereas further testing would not be pursued if the CR rate was 20% or less. The 2-stage study design of Green and Dahlberg was used.[10] Planned accrual in the first stage was 25 eligible patients. If 5 or more CRs were observed, then accrual would continue to a total of 45 eligible patients, with 14 or more CRs considered sufficient activity to warrant further investigation of this regimen. This design had a significance level of 5.2% and a power of 91%.

Secondary end points included recurrence-free survival, progression-free survival and overall survival. Survival curves were plotted using the Kaplan-Meier product limit method. Overall survival was measured from the day of registration to death from any cause. RFS was defined as time from registration to first instance of disease recurrence or death from any cause and progression-free survival was defined similarly.

RESULTS

A total of 58 patients were accrued. Two eligible patients did not receive any protocol treatment, and 9 were ineligible, including 5 due to issues with biopsy timing or pathology specimen submission, 2 with no cancer on pathology review and 2 who had not received the minimum prior BCG treatments. The distribution of all enrolled patients is shown in figure 1.

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