

Will a new intravesical chemotherapy agent improve the treatment of non-muscle-invasive bladder cancer?

Original article van der Heijden AG *et al.* (2006) Phase II marker lesion study with intravesical instillation of apaziquone for superficial bladder cancer: toxicity and marker response. *J Urol* 176: 1349–1353

SYNOPSIS

KEYWORDS bladder cancer, chemotherapy, intravesical instillation, marker lesion study, superficial apaziquone

BACKGROUND

Frequent adverse events are associated with bacillus Calmette–Guérin (BCG) therapy; there is a need, therefore, for new therapies to treat superficial bladder cancer effectively and safely. Apaziquone is a derivative of mitomycin C that has shown promise as a bladder cancer treatment in preclinical trials.

OBJECTIVE

To evaluate the efficacy and safety of intravesical instillation of apaziquone in patients with intermediate or high-risk superficial bladder cancer.

DESIGN AND INTERVENTION

This multicenter, phase II marker-lesion study enrolled patients with multiple pTa or pT1, G1 or G2 transitional-cell carcinomas of the bladder. Patients underwent transurethral resection of all visible tumors with the exception of one marker-lesion of 0.5–1.0 cm. Random biopsies of normal tissue were also taken. Exclusion criteria were muscle-invasive disease, carcinoma *in situ*, grade 3 tumors, and chemotherapy or immunotherapy within the previous 3 months. Patients received the first of six weekly instillations of 4 mg apaziquone within 15 days of resection. Retention time and evidence of local toxicity were recorded, and urinalysis and urine culture were performed following treatment sessions. Each fortnight patients underwent whole blood count, and kidney and liver function tests. At 2–4 weeks after the final instillation, tumor response was assessed using video-assisted resection. The

marker lesion site was biopsied and any residual tumor was resected. Patients were classified as having had a complete response (negative biopsy and no new tumors), disease progression (tumor >T1), or no response (tumor ≤T1). Partial response was not considered.

OUTCOME MEASURES

The main end point was complete response after six consecutive instillations of apaziquone. Other end points included disease progression and adverse events.

RESULTS

In total, 46 patients were enrolled in the study. Median patient age was 67.5 years (range 37–93 years), and 91% of patients were male. Primary disease was present in 20% of patients, while 80% had recurrent disease. In total, 25 patients had undergone chemotherapy previously, including 10 patients who had also received intravesical BCG. One patient withdrew before the last instillation was administered owing to hematuria and dysuria, but was found to have complete response on follow-up cystoscopy. Of the 45 patients who completed the study, 67% had a complete response to the treatment and 33% had no response (stable marker lesion but no new tumors). No patients experienced disease progression. Serious adverse events were reported in four patients (bladder perforation unrelated to apaziquone, grade 3 chemical cystitis, grade 2 hematuria, and grade 3 urinary frequency). Side effects that led to treatment postponement for 1 week occurred in 15 patients.

CONCLUSION

The authors concluded that the complete response rate after intravesical instillation of apaziquone was promising and warranted further investigation. Side effects were considered comparable to those associated with other chemotherapy drugs, but less severe than those associated with BCG therapy.

COMMENTARY

Eila Skinner

Non-muscle-invasive bladder cancer continues to be a serious clinical problem. There are estimated to be over 150,000 patients in the US with a history of superficial cancer, who are under active surveillance for recurrence. The risk of recurrence and progression to muscle-invasive disease (and ultimately metastasis) can be predicted on the basis of a number of factors, including high tumor grade, multifocality, invasion into the lamina propria, and associated carcinoma *in situ*.

Intravesical therapy has been the standard treatment for patients with non-muscle-invasive disease who are at high risk of recurrence and progression. The history of intravesical therapy began with chemotherapy (thioTEPA and doxorubicin), but was quickly supplanted by BCG immunotherapy. BCG has significantly improved the response rates for carcinoma *in situ* and, with the addition of maintenance therapy, might be able to reduce disease progression for high-risk patients.¹ Some patients, however, experience unacceptable local or systemic side effects after BCG treatment, and patients who fail to respond are at increased risk of subsequent disease progression and metastasis. In addition, over half of high-risk patients who are treated with intravesical BCG ultimately require cystectomy or die of their disease within 15 years.² There is clearly a need for more effective local intravesical therapies for these high-risk patients.

New systemic chemotherapies that are effective in metastatic transitional cell carcinoma, including gemcitabine and docetaxel, were tested as intravesical agents in 2006. Both of these agents have been shown to be effective and well tolerated in early phase I and II studies.^{3,4} This study by van der Heijden *et al.* is unusual in that the authors used apaziquone—an agent related to mitomycin C that is inactive as a systemic agent, perhaps because it is rapidly cleared from the circulation and has poor penetration into avascular tissue. Neither of these limitations apply to intravesical instillation. As expected, apaziquone showed little systemic absorption or toxicity

when used intravesically, and had activity similar to mitomycin C, BCG and epirubicin when tested against low-grade marker lesions.

It is not clear from this study whether the use of apaziquone would really constitute an important advance compared with the other drugs currently available for intravesical administration in patients with bladder cancer. Although apaziquone is active *in vitro* at lower concentrations than mitomycin C, it did not demonstrate significantly better efficacy in this marker-lesion study. Drug concentration and urinary acidity significantly influences the efficacy of mitomycin C in high-risk patients;⁵ Knowledge of whether similar conditions apply for intravesical administration of apaziquone would be helpful. Unfortunately, with the exception of Au *et al.*,⁵ few intravesical studies have examined the selection of dose, frequency, duration of treatment or dwell time. Finally, while marker-lesion studies that investigate antitumor activity in low-grade tumors are helpful, the more clinically important question is what role intravesical agents have in the prevention of disease recurrence and progression in high-risk patients and those who have not responded to previous therapies. We will have to await studies that address this question with apaziquone before we can determine its relative position in our armamentarium of intravesical agents.

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Competing interests

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PRACTICE POINT

With increasing interest in intravesical chemotherapy, apaziquone could prove to be a promising new addition to our armamentarium of intravesical chemotherapies currently being tested, but further research is needed