Clinical Research Paper

Prophylactic effect of inductive intravesical instillation of Bacillus Calmette-Guerin on postoperative recurrence of bladder cancer

Shan-Hong Yi, Gang Ye,* Xiang-Wei Wang, Huan-Sheng Jin, Yuan-Ning Zhang and Zhi-Lin Yan

Department of Urology; Xinqiao Hospital; Third Military Medical University; Chongqing, P.R. China

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Background and Objective: Intravesical instillation is an important adjuvant therapy that can help prevent postoperative recurrence of superficial bladder transitional cell carcinoma—but the recurrence rate is still high. This study evaluated the prophylactic effect of intravesical instillation of hydroxycamptothecin (HYD) plus Bacillus Calmette-Guerin (BCG) on the postoperative recurrence of bladder transitional cell cancer. Methods: A total of 45 bladder cancer patients who underwent TURBT or partial cystectomy were divided into two groups: 24 patients in the combination group received a single intravesical instillation of HYD in week one after operation and regular intravesical instillation of BCG after week 2; 21 patients in the BCG group received regular intravesical instillation of BCG one week after operation. All the patients were followed up for 24 months. Results: Three patients had recurrence at two, ten and twelve months after the operation in the BCG group; no recurrence developed in the combination group. The recurrence rate was significantly higher in BCG group than in combination group (14.28% vs. 0, p < 0.05). No serious adverse events or complications developed in either groups. Conclusion: Early use of single intravesical instillation of HYD plus subsequent regular intravesical instillation of BCG is markedly effective for preventing postoperative recurrence of bladder transitional cell cancer, with few adverse events.

Superficial bladder cancer will recur in about 50–70% of cases even after surgery, 10–20% with increased malignancy (pathological grade and stage) after tumor recurrence. Therefore, patients are generally given postoperative intravesical instillation chemotherapy (mitomycin, thiopeta, doxorubicin or hydroxycamptothecin, etc.), or immune therapy (Bacillus Calmette-Guerin/BCG) to prevent tumor recurrence and to inhibit the recurred tumor from malignant progress. We treated 24 cases of bladder cancer with single Hydroxycamptothecin (HYD) intravesical instillation, combined with small doses of regular BCG intravesical instillation as immunochemical therapy to prevent the postoperative recurrence of bladder cancer.

Patients and Methods

Patients. A group of 45 bladder cancer patients received surgery in our hospital from July 2004 to July 2007, 32 men and 13 women, aged 34- to 80-years-old, with a median age of 58. All patients had primary tumors. Preoperative cystoscopy and bladder CT scan were used to diagnose bladder papillary tumor, among which 30 cases received a transurethral resection of bladder tumor (TURBT) and 15 cases received bladder partial cystectomy. All larger tumors or tumors suspected to be T2 were given bladder partial cystectomy, i.e., full-thickness of tumor and 2 cm of normal surrounding bladder wall were removed. All visible tumor tissues were removed and electrical incision reached deep muscular layer. Postoperative pathological diagnosis confirmed all cases were bladder papillary transitional cell carcinoma. Basic patient information is summarized in Table 1. Forty-five patients were randomly assigned to two groups; 24 cases in the combination group and 21 cases in the BCG group. There was no statistical difference between the two groups (p > 0.05).

Treatment. All patients received the drug within one week after the operation on the third day after their urine became clear. In the combination group, 15 mg HYD (Harbin Sanlian Pharmaceutical Co.,) was diluted in 50 ml normal saline and injected into the bladder cavity through an indwelling catheter. The patient’s position was converted every 15 min (left lateral, right lateral or supine position) and the catheter was clamped for two h then released to discharge the drug. Bacillus Calmette-Guerin (BCG) instillation was done after one week of HYD instillation once a week for a total of four times, then once every other week four times, and
finally once per month, for a total of two years. The BCG group was instilled for the first time within one week after the operation on the third day after their urine became clear, with treatment length and usage as above. The BCG vaccine was from Lanzhou BioProduct Institute; 60 mg at a time was diluted in 50 ml normal saline and injected into the bladder through a catheter. Posture and retention time were the same as above. Cystoscopy and urine exfoliative cytology were done every three months after discharge, and once every six months after one year for a total of two years.

**Follow-up procedure.** Urine and blood analysis were done before each instillation. Liver and kidney function, biochemistry and cystoscopy were done every three months for one year after the operation, and every six months for two years after the operation. At the time of cystoscopy, pathological examination or random mucosa biopsy were performed on suspected tissues. In recurrent cases, if examination still suggested transitional cell carcinoma and the tumor stage and grade did not increase, we would resect the tumor and repeat intravesical instillation following the original procedure. If the tumor stage and grade increased or repetitively relapsed within one year, radical cystectomy plus urinary diversion operation would be performed.

**Statistical methods.** Analysis among groups used $\chi^2$ (chi-square) test. We adopted SPSS 13.0 software to do the statistical analysis and $p < 0.05$ standard was used for statistical significance.

**Results**

**Adverse effects.** One patient in each group discharged drug fluid at 65 min after initial instillation because of intolerance due to the small bladder capacity after partial cystectomy, while the remaining 43 cases all reserved drug fluid for over two hours. In the BCG group, two patients had a high fever after the initial instillation, and a body temperature reaching 38.7°C. These symptoms were relieved three days after taking anti-TB drugs and conservative therapy. Different degrees of urinary frequency, urgency, urethral burning sensation and mild hematuria appeared in 15 cases successively. Symptom severity and frequency increased following the increased number of BCG instillations, and lasted for 1-3 d, but most symptoms disappeared within one d. After HYD instillation, there was one case of cystitis, one case of urinary tract infection and three cases of bladder irritation. No other serious complications were observed and no abnormality was found in patients’ white blood cells and biochemistry pre- or post-discharge.

**Recurrence rate.** 45 cases were followed up for 24 months. No recurrence was identified in the combination group, while three cases in the BCG group relapsed after two, ten and 12 months, rendering the recurrence rate at 14.28% (3/21). 18 cases did not relapse. $\chi^2$ test demonstrated statistical difference, $p < 0.05$. The primary tumors in relapsed cases were multiple and their pathological grades were T1G2, T1G2 or T2G3; while the recurrent tumors did not occur at the original site, were single and there was no increase in tumor grade. Among the relapsed cases, two patients underwent cystectomy, one patient underwent TURBT, and was then treated by conventional chemotherapy using mitomycin and cisplatin, etc., chemotherapeutic drugs plus BCG. No relapse was found after two years follow-up. One T2G3 grade patient relapsed again five months after operation and was treated by radical cystectomy and urinary diversion, and died after 14 months from distant metastases. None of the remaining patients died from relevant diseases during the follow-up period.

**Discussion**

Bladder cancer is the most common and highly-recurrent malignant tumor in the urinary system. Although the majority of bladder cancer can be cured by surgery or transurethral electrical resection, 50-70% of superficial bladder tumors relapse easily after surgery, and 30-40% of recurrent cases are accompanied by an increase in malignancy and invasive ability. After the operation, intravesical instillation chemotherapy is an effective way to prevent tumor recurrence, and therefore choosing a safe and effective drug for instillation is highly significant.

Bladder cancer recurrence correlates with tumor cell plantation and the tumors multi-origin growth nature—especially during TURBT—many shedding tumor cells plant locally into the bladder mucosa and lead to relapse. Intravesical BCG instillation has good effect in preventing the recurrence of bladder cancer. According to literature reports, its efficacy surpasses thiopeta and doxorubicin. Its working mechanism may be through the activation of humoral...
immune response, which produces a large quantity of antibodies that directly induce tumor cells apoptosis, and through activation of cellular immune response produce lymphatic factors such as IL-2 and INF, etc. Those lymphokines further activate immune effective cells in body, which act on tumor cells and induce tumor cells necrosis or apoptosis. Regular BCG instillation in bladder cavity can enhance immune response, and further increase the anti-tumor effects.

HYD is a trace alkaloid extracted and processed from the Nyssaceae plant Campotheca acuminate, a plant unique to China. Its anti-tumor activity is higher than similar products and has been widely used in a variety of cancer treatment as HYD can quickly enter cells and inhibit DNA synthesis and mitosis. The effect on tumors can be long-lasting after every contact. The mechanism of early postoperative intravesical HYD instillation for preventing or delaying bladder cancer recurrence may be that this drug can effectively kill tumor cells and destroy the remnants of local tumor. However, it has multiple side effects, which mainly manifest in the digestive system and blood system and include nausea, vomiting, diarrhea, melena and a decrease in WBC and platelet count, etc. Bladder cancer chemotherapy usually requires long courses and multiple instillations. The chemotherapy cost increases and serious side effects are hard for patients to tolerate.

Intravesical BCG instillation to prevent bladder cancer has a confirmed effect, but there are also certain toxicities. Strictly professional operation and understanding the disease stage can reduce or avoid complications. Clinically, increasing BCG dose and application frequency in order to enhance the efficacy of BCG can lead to greater side effects. At present, the conventional dose for clinical intravesical BCG instillation is 120 mg, which causes many side effects. Our study found that a single application of HYD intravesical instillation, followed by a small dose of BCG (60 mg), can achieve the desired effect for preventing tumor recurrence, while reducing the side-effects of BCG instillation.

Chemotherapy drugs intravesical instillation combined with immunoreagents to prevent postoperative recurrence of bladder cancer is a new immunoochemistry therapy that overcomes the poor efficacy of immune drugs or chemotherapy drugs alone, and further reduces the postoperative recurrence rate of bladder cancer. Huncharek, et al. proved that chemotherapy drugs regulating the proliferation and anti-tumor activities of lymphokine-activated killer cells are among the mechanisms of their anti-tumor activities. Chemotherapy drug-triggered chemical cystitis leads to increased fibronectin protein activity in bladder mucosa and thus promotes the conjugation of BCG particles with the bladder wall and further increases their immune effects. Engelmann et al. use interferon, mitomycin C or interferon plus mitomycin C for intravesical instillation to prevent bladder cancer recurrence after surgery. Through 6.2 months follow-up on average, the recurrence rate in interferon plus mitomycin C group is zero, which is significantly lower than that in interferon alone and mitomycin C alone. The application of interferon plus THP in intravesical instillation to prevent bladder cancer recurrence has achieved similar results. Qi-Feng Dou, et al. apply BCG and HYD alternatively to instill the bladder cavity. Compared with BCG alone, it has better results. Similarly, we observed the synergistic or additive effect when HYD and BCG are applied together. The prophylactic effect for recurrence is significant; the operation is relatively simple and cost-efficient. Therefore, immunoochemical therapy is superior to single immune drug or chemotherapy alone in reducing tumor recurrence rate and prolonging tumor-free survival.

Our results demonstrated that to treat bladder papillary transitional cell carcinoma, immunoochemical therapy using single-dose HYD early application plus regular small dose BCG in postoperative intravesical instillation is superior to BCG alone in treating and reducing tumor recurrence. This therapy is safe, simple and cost-effective; in addition, it can significantly reduce the side-effects and toxicity of chemotherapy drugs locally and systemically. Furthermore, the combination of those two drugs has a synergistic effect. However, since this study only observed limited cases and followed-up for a limited time, long-term effects still need further investigation.

References