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Clinical Progress of Hyperthermic Intravesical Chemotherapy after Transurethral Resection of the Bladder Tumour

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Abstract

In recent years, the incidence rate of bladder cancer has been getting higher and younger, and bladder cancer is prone to recurrence. HIVEC after transurethral resection of bladder tumours has been gradually applied in the clinic, and the effect of preventing postoperative recurrence is remarkable. With the gradual improvement of the intravesical hyperthermic perfusion system, hyperthermic perfusion chemotherapy is more and more widely used in bladder cancer and peritoneal metastatic tumours, and it is safe and effective. BR-TRG-I body cavity hyperthermic perfusion therapeutic instrument developed by China is the most ideal perfusion equipment system for HIVEC, which is used for bladder and intraperitoneal hyperthermic perfusion chemotherapy. Because of the easy recurrence of bladder cancer, the treatment of bladder cancer and reducing the recurrence rate are still worldwide problems. Based on the current research situation at home and abroad, this paper briefly summarizes the clinical progress and application of HIVEC after transurethral resection of a bladder tumour.

Keywords

Bladder cancer, Transurethral resection of bladder tumour, Hyperthermic intravesical chemotherapy, Hyperthermia

Background

Globally, bladder cancer is the 10th most common malignancy among all malignancies [1] and is the most common malignancy in the urinary tract. Most bladder cancers are non-muscle invasive bladder cancer (NMIBC), accounting for about 70%-75% of patients. Most patients have a survival rate of more than 80% at 5 years with measures such as transurethral resection of the bladder tumour (TURBT)+ Intravesical chemotherapy to defend the bladder and delay disease progression, but 50%-80% of patients with NMIBC still have recurrence after TURBT [2, 3]. Postoperative intravesical therapy includes intravesical chemotherapy, intravesical immunotherapy, electrochemical intravesical therapy, photodynamic therapy, and HIVEC. Among them, HIVEC as a new therapy in recent years, compared with traditional therapy, can not only improve the local effect of chemotherapy drugs in the treatment of bladder cancer but also reduce the risk of recurrence of bladder cancer. HIVEC is mainly suitable for NMIBC, including low-risk NMIBC, intermediate-risk NMIBC, high-risk NMIBC, and patients with contraindications or treatment failure of BCG. It is mainly used to reduce local recurrence after TURBT. This article reviews the application status of HIVEC in bladder cancer.

1. Definition and theoretical basis of hyperthermic bladder perfusion therapy

Hyperthermic intravesical chemotherapy (HIVEC) is based on intravesical chemotherapy, which can increase the thermodynamic effect of anti-tumour drugs. HIVEC is a comprehensive combination of hyperthermia and chemotherapy to treat bladder cancer and reduce the recurrence rate of bladder cancer after the operation. To improve the clinical efficacy of bladder cancer.

1.1 Hyperthermia has a direct killing effect on cancer cells

Under normal circumstances, healthy tissue cells can tolerate a high temperature of 47℃ for 1h. However, for malignant tumour tissue cells, a prolonged 43℃ high temperature can cause irreversible damage [4]. The temperature of HIVEC was set at 40-44℃ and lasted for about 1h so that the cancer tissues and cancer cells could be killed directly by heat without destroying normal bladder tissues. At present, there are the following explanations for the direct killing effect of hyperthermia on cancer tissues [5]: (1) Under high temperatures, the temperature exceeds the optimal temperature of modifying enzymes in cancer cells, which inactivates them and leads to DNA modification, DNA replication, transcription and translation damage of cancer cells, thereby inducing apoptosis of cancer cells; (2) Under high-temperature conditions, the blood vessels of cancer cells cannot expand, increase blood flow and heat dissipation with the increase of body temperature, which increases the local high temperature in tumour tissue. Moreover, the thermal effect will damage the blood vessels of cancer tissue, which is easy to form thrombosis and/or occlusion, resulting in ischemia, hypoxia and necrosis of cancer tissue. (3) In the high-temperature environment, high temperature increases the production of heat shock proteins in the body, thereby activating the direct killing effect of autoimmune cells on cancer tissues or cells; (4) Hyperthermia can increase the activity of lysosomes in cancer cells, thus dissolving the cells; (5) Hyperthermia can cause the contraction of blood vessels in cancer tissue, make cancer cells in a malnutrition state of hypoxia, low glucose and low pH value, inhibit the generation of tumour vascular endothelial cells, reduce the neovascularization in cancer tissue, and thus inhibit the growth of cancer cells.

1.2 Hyperthermia and chemotherapy have a synergistic anti-tumour effect

High temperature can increase the anti-tumour effect of chemotherapeutic drugs [6-8]: high temperature can increase the molecular movement of chemotherapeutic drugs, thereby increasing the binding rate of chemotherapeutic drugs to tumour cells and improving the anti-tumour effect. Under hyperthermia, the damage to the cell membrane of cancer cells increases their permeability, and chemotherapeutic drugs are more likely to enter the cancer cells to give full play to the anti-tumour effect. Hyperthermia has a strong killing effect on S-phase tumour cells, and chemotherapy has a strong killing effect on non-S-phase tumour cells. The combination of hyperthermia and chemotherapy can improve the anti-tumour efficacy and reduce the risk of recurrence. Hyperthermia can increase the sensitivity of chemotherapy drugs and reduce the probability of chemoresistance.

2. Evolution and progress of intravesical hyperthermic instillation system

Bladder hyperthermia was first reported by Hall in 1974, which used high temperatures to treat bladder cancer and achieved good clinical efficacy. After clinical development and evolution, the following perfusion therapies have been gradually formed: (1) Simple hyperthermic perfusion [9]: After TURBT, the chemotherapy drugs are directly dissolved in the pre-heated perfusion fluid (such as normal saline, distilled water, etc.), and then they are infused into the bladder cavity. Although this therapy is simple, due to the strong body temperature regulation mechanism and the absorption of heat by the bladder wall, the rapid heat loss and short maintenance time of the liquid infused into the bladder cavity can not achieve the purpose of constant temperature. Therefore, this therapy can only be regarded as simple hyperthermic perfusion, rather than HIVEC in the true sense. (2) Microwave heating perfusion [10]: Synergo SB-TS 101 intravesical hyperthermia system is implemented through a special urinary catheter consisting of an intraluminal microwave treatment electrode and five thermocouples. Hyperthermia is delivered to the bladder cavity by direct irradiation. Three thermocouples measure the temperature of the surface layer of the bladder wall, and the other two are used to measure the temperature of the urethral sphincter region or the prostatic urethra. The perfusate is drained from a closed system to avoid thermal injury to the urethra. All physical parameters, including RF power and temperature, were monitored with a computerized setup and dedicated software, with RF power at 915MHz, temperature controlled between 40 and 42^{o}C, and treatment time of at least 40 min. This method can not achieve the purpose of constant temperature completely, and the accuracy of temperature control is not high, which will affect the efficacy of HIVEC. In addition, because of the radiation effect of high-frequency

microwaves, there is a certain safety hazard to the medical staff who operate. (3) High-precision continuous cyclic HIVEC: BR-TRG-I body cavity hyperthermic perfusion therapeutic instrument independently developed by Cui Shuzhong [11] is the most ideal perfusion equipment system for HIVEC implementation at present, which is used for HIVEC in the bladder and abdominal cavity. The equipment adopts two circulation pipelines inside and outside. The inner circulation pipeline is for the perfusion fluid containing chemotherapy drugs to circulate between the bladder cavity and the perfusion bag, and the outer circulation pipeline is a closed circulation system. The heater is used to supplement the heat loss in the inner circulation pipeline. It can ensure that the temperature in the bladder cavity is constant at the set treatment temperature. The specific methods were as follows: after TURBT, the three-lumen catheter was indwelling, the disposable body cavity hyperthermic perfusion therapy pipe was connected to the BR-TRG-I body cavity hyperthermic perfusion therapeutic instrument, the injection water dissolved in perfusion chemotherapy was poured into the liquid reservoir bag, the treatment temperature was set at 43℃, the treatment time was 1h, and the perfusion speed was 200ml/min. The inlet and outlet water pipes were clamped, and the temperature was raised to about 43℃ by preheating. The inlet and outlet water pipes were opened, and the perfusion fluid was heated in the bladder cavity. The device not only can accurately control the temperature but also can continuously recirculate the hyperthermic perfusion fluid into the bladder cavity to remove the free cancer cells and necrotic tissues in the bladder cavity, which improves efficacy.

3. Clinical efficacy of HIVEC

Liu Meide et al. [12] randomly divided 40 patients with non-muscle invasive bladder cancer treated by TURBT into the control group (mitomycin perfusion chemotherapy alone) and the experimental group (mitomycin HIVEC). Compared with the control group, the patients treated by the experimental group had a higher 3-year disease-free survival rate, a lower recurrence rate within 3 years, and a relatively longer median survival time. HIVEC is effective in the treatment of non-muscle invasive bladder cancer, which can effectively prevent tumour recurrence and prolong the disease-free survival rate of patients. Gao Fei et al. [13] also found in patients with superficial bladder cancer who received intravesical chemotherapy one week after TURBT that the postoperative recurrence rate of patients treated with hyperthermic perfusion of mitomycin was lower than that of patients treated with only mitomycin perfusion chemotherapy, and the survival rate was longer than that of patients treated with only mitomycin perfusion chemotherapy. Therefore, HIVEC with mitomycin combined with TURBT can significantly reduce the recurrence rate and improve the survival rate of NMIBC patients, which is worthy of clinical promotion. Wang Shu et al. [14] retrospectively analyzed 74 patients with NMIBC and divided them into the treatment group and control group. All patients were treated with TURBT. The postoperative treatment group was treated with BR-TRG-I intravesical hyperthermic perfusion of pirarubicin, and the control group was treated with intravesical perfusion of pirarubicin alone. The treatment effect, 2-year recurrence rate and incidence of adverse reactions were compared between the two groups. The results showed that the 2-year recurrence rate of the treatment group and the control group was 8.1% and 51.4%, respectively. The incidence of adverse reactions in the treatment group and the control group was 13.5% and 5.4%, respectively. There was no significant difference in the incidence of adverse reactions between the two groups. Conclusions HIVEC can significantly reduce the 2-year recurrence rate of NMIBC patients after TURBT without increasing the related adverse reactions, which is worthy of clinical promotion. However, it still needs to be verified by multi-centre randomized prospective clinical trials. Liu Qingyuan et al. [15] 288 NMIBC patients, after TURBT, the control group was given mitomycin HIVEC alone, and the experimental group was given mitomycin HIVEC with BR-TRG-I body cavity hyperthermic perfusion therapy system 3 days after surgery, and then changed to conventional perfusion chemotherapy after four times. The recurrence status and adverse reactions of the two groups were observed. Results: There was no significant difference in the incidence of adverse reactions between the two groups. The total recurrence rate of the experimental group was lower than that of the control group. In conclusion, using a Chinese self-developed BR-TRG-I intravesical hyperthermic perfusion therapy system to give mitomycin HIVEC after transurethral resection of NMIBC can reduce the postoperative recurrence rate of bladder cancer without increasing adverse reactions.Shuzhong Cui et al. [16] diagnosed 560 patients with primary or recurrent NMIBC in 1 of 6 tertiary centres. This retrospective study demonstrated that HIVEC+ IVEC treatment resulted in a higher 2-year RFS and a lower incidence of RC compared with IVEC treatment in intermediate-risk NMIBC patients. This study also showed that HIVEC can reduce the recurrence rate and the incidence of RC after TURBT, but it still needs to be further verified by large multicenter prospective studies.

Geijsen ED et al. [17] performed low-dose mitomycin C (40mg) and intravesical hyperthermic instillation chemotherapy on 20 patients with NMIBC. The 2-year disease-free survival rate was 78%. This study shows that intravesical chemotherapy combined with hyperthermia is safe and effective, and can improve the disease-free sur-

vival rate, which brings good news to the majority of patients with bladder cancer. Grimberg DC et al. [18] administered a high-dose HIVEC MMC regimen to 14 patients with intermediate and high-risk NMIBC. The authors concluded that high-dose MMC HIVEC is a safe and well-tolerated alternative to BCG in the context of a global shortage. A higher systemic effect rate implies increased drug release, which may improve efficacy. Sousa A et al. [9] treated 40 patients with intermediate and high-risk NMIBC with HIVEC using the Combat BRS system. The 4-year cumulative recurrence rate was 20.8%. The 2-year cumulative recurrence rate in the adjuvant HIVEC group was 12.5%. Thermotherapeutic MMC cycling using Combat's HIVEC therapy is safe and effective, achieving success rates in both neoadjuvant and adjuvant therapy. van Valkenburg FJP [19] et al. demonstrated that MMC for HIVEC treatment of NMIBC had lower concentrations in normal bladder tissue mucosa than in cancerous tissue, demonstrating the safety and reliability of HIVEC. Doisy Let al. [20] also demonstrated that HIVEC is clinically more effective than conventional treatment in high-risk NMIBC and can be tried as neoadjuvant therapy. On the contrary, radical cystectomy should still be the gold standard for patients with intermediate and high-risk non-muscle invasive bladder cancer who have failed BCG therapy, but HIVEC can be cautiously selected for patients who are not eligible for surgery and have a full understanding of the risk of progression to muscle-invasive disease.

4. Summary and Outlook

HIVEC has a great application prospect in the treatment of NMIBC. Compared with conventional intravesical chemotherapy, HIVEC improves RFS, OS and bladder preservation rate, reduces the recurrence rate after TURBT, and has a high safety factor and few systemic side effects. With the continuous improvement of HIVEC systems, such as BR-TRG-I /II body cavity hyperthermic perfusion therapy system independently developed by our country, it can maintain a constant perfusion temperature, which can not only play the role of hyperthermia but also enhance the effect of chemotherapy drugs. HIVEC will be further promoted and promoted in the treatment of bladder cancer, which is a new treatment option for bladder preservation and can even be promoted to local adjuvant therapy for patients with unresectable bladder cancer or neoadjuvant therapy for patients with resectable bladder cancer.

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