Thermo-chemotherapy for intermediate or high-risk recurrent superficial bladder cancer patients


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Background: The purpose of this study was to evaluate the efficacy of combined local hyperthermia and intravesical mitomycin-C (MMC) in a selected group of patients with intermediate or high-risk recurrent transitional cell carcinoma (TCC) of bladder.

Patients and methods: Forty-seven patients with multiple or recurrent Ta or T1 TCC of the bladder were treated with intravesical MMC and local hyperthermia of the bladder wall. Patients were treated with either a prophylactic protocol (40 mg MMC) after complete transurethral resection of all tumours or with an ablative protocol (80 mg MMC) in patients with viable tumours.

Results: Thirty-two patients were eligible for analysis. The prophylactic protocol was administered to 22 patients. After a mean follow-up of 289 days, 20 patients (91%) were recurrence free. Two patients (9%) had tumour recurrence after a mean period of 431 days. The ablative protocol was administered to 10 patients. Complete tumour ablation was achieved in eight patients (80%) after a mean follow up of 104.5 days.

Conclusions: Our efficacy and safety results confirm those reported in previously published studies, suggesting the promising value of this combined treatment modality for both prophylactic and ablative patients. The ablative protocol offers an alternative therapy for a selected patient population for whom no other treatment option exists.

Key words: bladder cancer, chemo-thermotherapy, mitomycin-C

Introduction

Superficial transitional cell carcinoma of the bladder (STCCB) is characterised by a high recurrence rate (30–85%) after primary transurethral resection of tumour (TUR-T) [1, 2]. Combining thermal energy and chemotherapy instillation offers anticancer advantages over chemotherapy instillation alone to prevent or delay tumour recurrence or progression [3, 4]. Clear synergistic effect of mitomycin-C (MMC) and hyperthermia was demonstrated in four human bladder cancer cell lines [5]. The cytostatic agent uptake by the malignant cells and intracellular distribution are improved by increased cellular permeability. Furthermore drug metabolism and reaction with DNA is increased and DNA repair is inhibited [6].

The Synergo unit SB-TS101 has been devised to deliver local bladder hyperthermia with concomitant intravesical chemotherapy as a prophylactic or ablative therapy for STCCB [4, 7, 8].

In this study we present the effects of combined local hyperthermia and intravesical MMC in a selected group of patients with intermediate or high-risk recurrent TCC of bladder treated in our centre.

Patients and methods

Patients

Between December 2000 and March 2004, 47 patients with recurrent stage Ta and T1, grade G1 to G3 TCC of the bladder were enrolled to this study. All patients were required to have intermediate or high-risk STCCB according to the European Association of Urology (EAU) criteria.

Based on the goal of treatment, patients were divided into two therapeutic groups: prophylactic and ablative. Exclusion criteria were low risk bladder cancer, stage higher than T1, bladder tumour other than TCC, TCC involving the urethra or upper urinary tract, urinary bladder diverticulum larger than 1 cm in diameter, patients after partial cystectomy and any situation impeding a 20F catheterisation.

Clinical and histopathologic characteristics of the studied patients are shown in Table 1. Eight patients were not eligible for analysis (six prophylactic and two ablative). Six of these patients did not meet the inclusion and exclusion criteria [large diverticulum (>1 cm), squamous cell involvement and invasive disease were witnessed in one patient each, tumour outside the urinary bladder was witnessed in three patients]. The remaining two patients did not meet the treatment protocol requirements.

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Chemo-thermotherapy system

The Synergo device (SB-TS101) for chemo-thermotherapy consists of a 915 MHz radiofrequency applicator that delivers heat energy to the bladder wall. The applicator is inserted into the bladder through a 19.5 F catheter. The bladder wall temperature is continuously monitored by three thermocouples located inside the catheter. These thermocouples are spread out of the catheter and pushed tangentially against the bladder wall during treatment by the catheter balloon. The goal temperature is 42 ± 2°C.

The drug solution is constantly pumped out of the bladder and re-instilled after being cooled by the device to avoid overheating the bladder and degradation of the chemotherapeutic drug. A treatment session consists of MMC (Kyowa Hakko Kogyo, Tokyo, Japan) instillation into the bladder (20 mg in the prophylactic protocol and 40 mg in the ablative protocol) dissolved in 50 ml of sterile distilled water.

To better stabilise the dose concentration of the solution throughout the entire session the bladder is emptied after 30 min of heating, and fresh solution of a similar composition is instilled. The treatment is completed after a total period of 60 min and the bladder is evacuated of all its contents. Treatments are performed under local anaesthesia on an ambulatory basis. Patients can resume normal daily activities following the session.

Patient selection

On entry into the study, all patients signed an informed consent form and a cystoscopy was performed. The prophylactic treatment was recommended for patients who underwent complete transurethral resection of all tumours, confirmed by cystoscopy, biopsies and negative urine cytology. The ablative treatment was indicated for patients in whom complete tumour eradication could not be achieved by a single transurethral resection of bladder tumour (TURBT) (multiple sites, high tumour burden and/or difficult anatomic location of tumour), as well as patients who are unable to undergo anaesthesia for medical reasons.

The prophylactic protocol included six to eight weekly sessions followed by four to six monthly sessions to complete a total of 12 sessions. The ablative protocol consisted of eight weekly sessions followed by four monthly sessions. A cystoscopy was recommended to be performed after the fourth weekly session to assess tumour response. If partial response was observed (at least 50% reduction of initial tumour size), the patient continued with either four additional weekly sessions or TUR-T (e.g. when the residual tumour was single and very small). If an inadequate response was observed (<50% reduction of initial tumour size), the patient was classified as a non-responder and was referred to other forms of therapy. Patients that completed treatment and became tumour free underwent four additional monthly sessions.

Patient evaluation

The follow-up regimen included cystoscopy and urine cytology every 3 months for 2 years and every 6 months thereafter. Bladder biopsies from every suspicious lesion were obtained.

For the prophylactic group the endpoint was tumour recurrence by biopsy, while for the ablative group the endpoint was complete ablation of the tumour as proven by multiple random biopsies or mapping TUR-T and urine cytology.

All patients underwent intravenous pyelography prior to treatment and yearly thereafter for evaluation of the upper tract.

All data including adverse events were recorded regarding the treatments and follow-up examinations. A Kaplan–Meier plot was drawn to assess the risk of recurrence. For statistical analysis the Statistical Package for Social Sciences (SPSS) for Windows was used.

Results

Thirty-two patients completed the study according to the planned protocols and had valid cystoscopy results.
Prophylactic protocol

The average number of treatments per patient was 10 sessions. The recurrence-free interval analysis for the 22 patients receiving the prophylactic protocol is shown in Figure 1. Twenty patients (91%) were recurrence free after a mean follow up of 289 days from the first treatment session. Two patients (9%) had tumour recurrence after a mean period of 431 days (417 and 445 days). No progression was witnessed (TaG1, TaG3 prior to treatment and TaG1 in both patients at recurrence).

Ablative protocol

The ablative protocol was administered to 10 patients. Eight patients (80%) achieved a complete response (CR) to the therapy. Time to CR was 104.5 days while follow-up time was 200 days. Two patients (20%) were considered as displaying a partial response (PR) after four sessions. One patient paused treatment due to co-morbidity after six sessions and another patient is waiting the results of cystoscopy and biopsy.

Of the eight CR patients, two patients reached CR after four and six weekly sessions, respectively. An additional three patients were reported as CR after eight sessions but no data is available regarding their status after the first four sessions.

Mean follow-up time for all ablative patients was 169.4 days and the average number of treatments per patient was 8.9.

Safety analysis

The safety analysis for all treatments is presented in Table 2 for all 47 intent-to-treat patients. Some of the adverse events are presented per treatment so a patient may have the same event more than once.

Posterior wall thermal reaction was the most prominent phenomenon (19.5%) found only by cystoscopy. It is an expected effect, which occurs as a result of the location of the radio frequency (RF) antenna in the bladder. The dissipated heat around the antenna causes a small localized superficial reaction, which resolves spontaneously.

The most common adverse events were pain during treatment (7.8%) followed by hematuria and irritative symptoms (~2% each). These side effects are mild and temporary and frequently disappear within 48–72 h after treatment.

Three prophylactic patients were reported with urethral stenosis. Two of them are highly recurrent patients that underwent multiple procedures and previous instillations and had a known and documented urethral stenosis prior to Synergo treatment. One patient underwent internal urethrotomy and the other required dilatations. This patient was treated with Synergo as a last treatment resort. The third patient (following two mapping TURs and 12 Synergo treatments) required internal urethrotomy. No data of pre-inclusion status is available. All the patients completed their treatments and are recurrence free.

Mild skin allergy was reported in two prophylactic patients (4.3%). This is a known and anticipated reaction to MMC that may also be attributed in prophylactic patients to the yet unhealed scars in the bladder post-TUR-T. Skin allergy resolved in both patients and enabled treatment to continue as scheduled. One patient required antihistamine treatment. The distribution of the other adverse events was similar among patients from both treatment groups. This should be noted in light of the fact that the ablative patients received a higher dose of MMC than the prophylactic patients (two instillations of 40 mg instead of 20 mg MMC) [4, 8, 9]

Discussion

The recurrence rate of Ta/T1 bladder cancer within 5 years after TUR-T followed by bladder instillation is about 50–70%. In addition, 5–20% of the cases show pathologically progressive disease [10, 11].

Table 2. Adverse events by treatment group (per patient and per treatment)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Total population</th>
<th>Prophylactic group</th>
<th>Ablative group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td>n=47</td>
<td>n=33</td>
<td>n=14</td>
</tr>
<tr>
<td>Cystitis</td>
<td>2 (4.3)</td>
<td>2 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Posterior wall thermal reaction (cystoscopy)</td>
<td>9 (19.2)</td>
<td>7 (21.2)</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Skin allergy</td>
<td>2 (4.3)</td>
<td>2 (6)</td>
<td>–</td>
</tr>
<tr>
<td>Urethral stenosis</td>
<td>3 (6.4)</td>
<td>3 (9)</td>
<td>–</td>
</tr>
<tr>
<td>Per treatment</td>
<td>n=398</td>
<td>n=289</td>
<td>n=109</td>
</tr>
<tr>
<td>Dysuria</td>
<td>1 (0.3)</td>
<td>–</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>8 (2)</td>
<td>5 (1.7)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Pain during treatment</td>
<td>31 (7.8)</td>
<td>15 (5.2)</td>
<td>16 (14.7)</td>
</tr>
<tr>
<td>Difficult catheter insertion</td>
<td>4 (1)</td>
<td>4 (1.4)</td>
<td>–</td>
</tr>
<tr>
<td>Urge and/or incontinence during session (spasms)</td>
<td>8 (2)</td>
<td>7 (2.4)</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

Data in parentheses are percentages.
Intermediate and high-risk recurrent patients, known to have a more aggressive tumour behaviour, recur within 2–3 years, with 20% progressing in stage within 5 years and ∼10–25% eventually will die of their disease. Therefore, the primary goal of treatment in bladder cancer, especially in this group of patients, is to prevent recurrence and progression to an incurable stage.

One of the main reasons for the unsatisfactory results in treating patients with bladder cancer is the residual tumour cells at the base of the resected lesions. Indeed, several studies describe extremely high rates of positive biopsy obtained shortly after TUR-T. Mersdorf et al. [12] found early residual disease in 31% of cases with Ta tumours and 58% for those having T1 disease. Similar data was reported by Klan et al. [13], who studied 69 patients with T1 bladder cancer and detected cancer cells in the resected areas in 43.5% of the cases. The limited penetration of the intravesical agents that are given following the removal of the tumour accounts for the relatively high failure rate.

Hyperthermia causes inhibition of DNA, RNA and protein synthesis by blocking the cells in S phase. Limited results are obtained when hyperthermia is used as a monotherapy approach [6, 14, 15].

New approaches have been used in order to enhance the antitumoural effect of intravesical chemotherapy as an alternative strategy or complementary regimen to TUR-T. Microwave-induced hyperthermia has been shown to have a synergistic antitumour cell killing effect when used in combination with selected cytostatic agents for the treatment of many solid tumours, including transitional cell carcinoma [16–19].

Recently the Synergo system (SB–TS101) designed for thermo-chemotherapy has been used for patients with STCCB. This system delivers local bladder hyperthermia concomitant with intravesical instillation of MMC. In addition to the antineoplastic effect the Synergo system improves drug penetration into the deep bladder wall [3, 6]. It enables adequate treatment of the residual cancer cells that potentially could give rise to disease recurrence. Paroni et al. [3] studied patients with superficial bladder cancer managed by intravesical MMC with and without hyperthermia following the surgical procedure. Both in the 20mg group and the 40mg group hyperthermia enhanced the passage of the drug through the bladder wall. This phenomenon is attributed to the modification of urothelial permeability induced by the thermotherapy.

In the present study we investigated the efficacy and safety of 47 patients with intermediate and high-risk recurrent TCC who received a combined thermo-chemotherapy treatment regimen in our institution.

Both prophylactic and ablative treatment arms showed encouraging results in avoiding disease recurrence or progression. Among the patients treated with the prophylactic protocol a 91% recurrence-free rate was achieved during a mean follow-up period of 289 days.

The results confirm those of a recently published randomised controlled study comparing combined chemothermotherapy with intravesical chemotherapy alone. Tumour recurrence was significantly sooner and more frequent in the intravesical chemotherapy alone group (58%) compared to the Synergo group (17%) [7]. The results are also comparable to those published for a similar patient population [20] and for high grade TCC patients treated with hyperthermia and intravesical chemotherapy [8]. This combined thermo-chemotherapy was also successful in ablating visible tumours in all patients with 80% CR after a mean period of 104.5 days, with mean follow-up time of 169.4 days.

This technology has been also used by other groups. Colombo et al. [4] studied microwave-induced hyperthermia and intravesical chemotherapy as a neoadjuvant therapy in 52 patients with recurrent disease. A complete response was seen in 19 cases (66%) and a partial response in 10 (34%). Afterwards the same group published their results with combined chemo-thermotherapy as a salvage approach in 19 patients with recurrent refractory bladder tumours considered for radical cystectomy [9]. After eight weekly sessions, TUR appeared to be feasible and curative in 16 patients (84%). Forty-seven percent had a complete response and 37% had a partial response. After a median follow up time of 33 months, 42% had a disease recurrence that was easily eradicated by TUR-T or transurethral fulguration in patients in whom the bladder have been saved.

Gofrit et al. [8] have used this treatment modality for the treatment of high-grade superficial bladder cancer. No stage progression to T2 occurred. At the prophylactic protocol, after a mean follow-up of 35.3 months, 15 patients (62.5%) were recurrence free and the bladder preservation rate was 95.8%. Initial complete ablation of the tumour was accomplished in 21 patients (75%). After a mean follow-up period of 20 months, 80.9% of these patients remained recurrence free and bladder preservation rate was 78.6%.

The outcome of our patients is encouraging considering that most of them are at a considerably greater risk for tumour progression and disease-related mortality because of their prior failed intravesical therapy. Seventy-seven percent in the prophylactic group and 100% in the ablative group were classified as high-risk patients according to the EAU risk criteria [21]. The clinical outcome, though of relatively short follow-up time, is valuable considering the mean time between previous occurrences in this subset group of patients. The combined treatment is more expensive and time consuming compared to the routine chemotherapeutic or immunotherapeutics instillations. However, the reduction in recurrence rate in patients belonging to the intermediate or high-risk categories favours the thermo-chemotherapy as it reduces the need for repeated procedures and instillations.

Almost all patients tolerated this combined treatment well. Most of the adverse events were identical in both treatment groups and were localised and transient. The thermal reaction of the posterior bladder wall found on cystoscopy in about two-thirds of the patients appeared as a small, superficial, dark
discoloration patch surrounded by hyperemia, which spontaneously resolved. The location of this thermal reaction corresponds to the location of the tip of the microwave antenna in the bladder.

Allergic reaction to MMC was witnessed only in the prophylactic patients, although they received a lower MMC dose than the ablative patients. This may be attributed to the yet unhealed scars in the bladder post-TUR-T.

The appearance of systemic reaction was rare, as expected from the low absorption rate of MMC from the bladder into the blood. The maximal concentration of 69 ng/ml documented by Paroni et al. [3] using ablative MMC dosage (80 mg), is below the threshold concentration for myelosuppression (400 ng/ml).

The present study suggests that microwave-induced local hyperthermia combined with MMC appears to be a safe and efficient treatment modality for both prophylactic and ablative patients. The technology has a potential additional value for the prevention of recurrence of superficial bladder cancer, particularly when other treatments have failed. Synergo ablative treatment offers an alternative therapy for a patient population for whom no other treatment option exists.

These encouraging results in a relatively short follow-up time deserve to be confirmed with many more patients and study protocols.

References