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Intra-arterial Combination Chemotherapy with Maximum Transurethral Resection of Bladder Tumour for T1 Grade 3 and T2--3N0M0 Bladder Cancers

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Abstract

Purpose: We evaluated the clinical outcomes following intra-arterial chemotherapy with maximum transurethral resection of bladder tumour (TURBT) for patients with T1 grade 3 (G3) and T2--3N0M0 bladder cancers.

Material and methods: Patients were 27 males and 7 females with a median age of 63.6 years. With the cooperation of an interventional radiologist, cisplatin (100 mg/m^2), methotrexate (30 mg/m^2) and adriamycin (20 mg/body) were administered via a catheter in 2 cycles every 4 weeks.

Results: The 5-year cancer-specific survival rate in T1 G3, T2 and T3 was 100.0%, 57.3% and 50.0%, respectively. In T2--3N0M0 cases, complete response (CR) and non-CR were seen in 13 (46.4%) and 15 cases (53.6%), respectively. Response to treatment proved to be the most significant prognostic predictor of cancer-specific survival by multivariate analysis in T2--3N0M0 cases. T2--3N0M0 cases with ≥2 prognostic predictors at staging TURBT (age >70 years, male, size >3 cm and the presence of hydronephrosis) had an unfavourable outcome. There was a statistical association between the number of prognostic predictors at staging TURBT and response to treatment.

Conclusion: These results suggest that our protocol prevents disease progression in T1 G3 cases, but that it is not suitable for T2--3N0M0 cases with ≥2 prognostic predictors at staging TURBT.

Keywords: Bladder cancer; Intra-arterial chemotherapy; Maximum TURBT; Bladder preservation

Introduction

Radical cystectomy is the standard therapy for muscle-invasive bladder cancer. Recently, it has also been suggested that T1 grade 3 (G3) bladder cancer is an indication for early radical cystectomy because of the high likelihood of recurrence and disease progression [1,2]. Survival outcome following radical cystectomy has gradually improved with more modern techniques (e.g. the mortality rate for extended lymphadenectomy) has decreased by 50% over the past 20 years [3-6]. On the other hand, around 15% of patients with muscle-invasive bladder cancer had no residual tumour following radical cystectomy on pathological examination. These data suggest that selected patients with muscle-invasive bladder cancer benefit from bladder preservation therapy. Some patients with muscle-invasive bladder cancer may opt for bladder preservation therapy given the choice. Bladder preservation therapy for muscle-invasive bladder cancer has been available for more than 20 years, and many protocols have been reported to date [7,8]. Most multimodality bladder preservation therapies show a similar treatment efficacy when compared to radical cystectomy [7,8].

Intra-arterial chemotherapy, which can deliver a high concentration of the selected drug(s) to the target organ, is one method of bladder preservation therapy [9-13]. The response rate when treating the same type of tumour with intra-arterial cisplatin infusion was found to be 2--10 times that for intravenous administration [14,15]. Since 1998, we have been performing intra-arterial combination chemotherapy with maximum transurethral resection of bladder tumour (TURBT) for T1 G3 and T2--3N0M0 bladder cases at Nippon Medical School, Chiba Hokusoh Hospital. In the present study, we evaluated the safety and efficacy of our bladder preservation therapy at long-term follow-up.

Material and Methods

Patient characteristics

We conducted our retrospective study at Nippon MedicalSchool, Chiba Hokusoh Hospital, between December 1998 and March 2008. The clinical stage was determined by TURBT, computed tomography (CT), chest radiography and/or bone scintigraphy. Tumours were staged and graded according to the 1997 TNM classification. After evaluation of clinical staging, we informed patients that the efficacy of intra-arterial chemotherapy was currently under investigation and that they were registered with the intention of performing this procedure. A total of 42 patients with pathologically confirmed T1 G3 bladder cancer and T2 or T3 muscle-invasive bladder cancer with performance

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status 0 or 1 were treated as per our protocol. In this study, we excluded patients with pelvic lymph node metastasis, distant metastasis, non-transitional cell carcinoma histology, any previous treatments and other active malignancy. Finally, we selected 34 of the 42 patients as being eligible. The median age of the subjects (male = 27, female= 7) was 63.6 years (range, 47--82 years), and the median follow-up period was 57.9 ± 34.9 months (range, 9--116 months).

Treatment schedule

In staging of TURBT, we resected all visible tumours as widely and deeply as possible. Two-layer TUR biopsies of tumour bases (superficial and deep muscle layers) were taken to include a representative thickness of the underlying detrusor muscle down to the perivesical fat. Intravesical therapy was performed for 12 cases [Bacille de Calmette et Guérin (BCG), 10 cases; mitomycin C, 2 cases] with multiple superficial tumours and/or carcinoma in situ before intra-arterial chemotherapy.

Two balloon catheters were inserted through both contralateral femoral arteries by Seldinger's technique under local anaesthesia. To prevent a high concentration of anti-cancer drugs from flowing into the gluteal region, the catheters were advanced to the superior gluteal artery, and temporarily occluded. For intra-arterial chemotherapy, a third catheter was introduced from the femoral artery to the terminal abdominal aorta. To establish the pelvic circulation, the thighs were bilaterally bound with tourniquets (pressure 200--300 mmHg) while confirming a pulse for the dorsalis pedis artery. Cisplatin (100 mg/m^2), methotrexate (30 mg/m^2) and adriamycin (20 mg/body) were administered via the catheter in 2 cycles every 4 weeks. The dose of cisplatin was reduced to 70% of the full dose when creatinine clearance was <70 ml/min. Patients were given a continuous infusion to maintain hydration and routinely received 5 hydroxytryptamine-3 receptor inhibitor as an antiemetic. Adverse event data were collected and evaluated by the Common Terminology Criteria for Adverse Events version 4.0.

Approximately one month after the final intra-arterial chemotherapy, restaging of TURBT was performed to evaluate residual tumours. Residual tumours assessed histologically indicated complete response (CR) as microscopically complete TUR, and non-CR as superficial or muscle-invasive residual microscopic tumour. After restaging of TURBT, all patients were followed every 3 months by urinary cytology and cystoscopy, and every 6 months by abdominal and chest CT scans.

Statistical analysis

Statistical analysis was performed using StatMate IV (ATMS Co., Ltd., Tokyo, Japan). The Kaplan--Meier method was used for calculation of survival rates. The clinical parameters were subjected to the log-rank test. Multivariate risk analysis was performed by Cox proportional hazard model; p-values <0.05 were considered significant.

Results

Patient characteristics are detailed in Table 1. Two courses of intra-arterial chemotherapy were completed in 32 cases (94.1%). Thirty cases (88.2%) received the full dose of intra-arterial chemotherapy.

Treatment response and survival

The 5-year cancer-specific survival rate for T1 G3, T2 and T3 was 100.0%, 57.3% and 50.0%, respectively (Figure 1). No progression or metastases were observed in T1 G3 cases. With regard to response

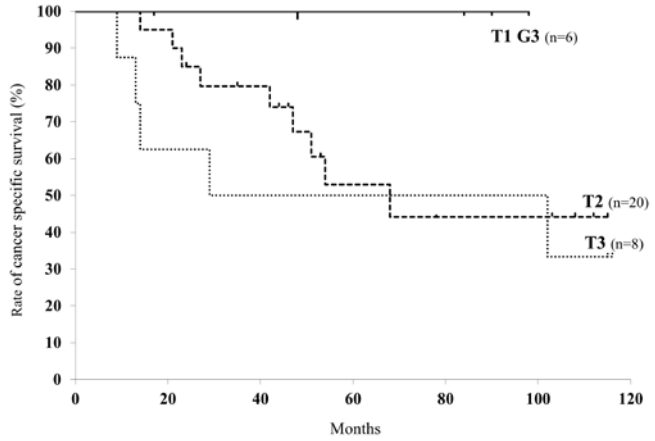

Figure 1: Kaplan-Meier curves showing cancer-specific survival according to T stage.

	T1 G3 (n = 6)	T2 (n = 20)	T3 (n = 8)	Total (n = 34)
Age				
≤70 years	5	14	5	24
>70 years	1	6	3	10
Gender				
Male	3	16	8	27
Female	3	4	0	7
Size				
≤3 cm	5	10	2	17
>3 cm	1	10	6	17
Multiplicity				
solitary	0	8	4	12
multiple	6	12	4	22
Hydronephrosis				
presence	0	2	5	7
absence	6	18	3	27
Grade				
Grade 2	0	14	3	17
Grade 3	6	6	5	17
β	6	16	4	26
γ	0	4	4	8
Lymphovascular invasion				
positive	3	16	8	27
negative	3	4	0	7

Table 1. Patient characteristics.

to treatment, 16 CR (47.1%) and 18 non-CR (52.9%) cases showed positive results. In T2--3N0M0 cases, CR and non-CR were seen in 13 (46.4%) and 15 cases (53.6%), respectively. All T1 G3 cases and the CR cases in T2--3N0M0 underwent no other salvage therapy. Nine non-CR cases in T2--3N0M0 received salvage therapy, 3 underwent systemic chemotherapy, 3 underwent extra intra-arterial chemotherapy, 2 underwent radical cystectomy and 1 underwent radiation therapy with systemic chemotherapy. Another 9 non-CR cases in T2--3N0M0 did not request further treatment. In T2--3N0M0 cases, disease recurrence developed in 14 (CR, 3 cases; non-CR, 11 cases) at a median of 26.6 months after restaging of TURBT. Of these, 9 cases (64.3%) had recurrence in the intrapelvic lymph node and 5 cases (35.7%) developed recurrence within 6 months.

	Univariate				Multivariate		
	Hazards ratio	95%CI	p-value		Hazards ratio	95% CI	p-value
Age	0.33	0.12--0.94	0.037		3.81	1.03--14.08	0.045
Gender	3.32	1.21-37.1	0.029		0.38	0.08--1.71	0.210
Multiplicity	0.626	0.21--1.94	0.427				
Size	0.298	0.11--0.99	0.049		3.00	0.57--15.65	0.191
Hydronephrosis	0.251	0.09--0.68	0.006		1.81	0.44--7.38	0.407
Grade	0.573	0.16--2.03	0.389				
Infiltration	0.588	0.19--1.76	0.343				
Lymphovascular invasion	0.02	0.07--1.16	0.081				
Response	0.22	0.07--0.69	0.014		2.89	1.26--6.62	0.012

Table 2. Univariate and multivariate analyses of prognostic predictors in T2--3N0M0 cases. CI, confidence interval.

On multivariate analysis, age >70 years and response to treatment proved to be independent prognostic factors of disease-specific survival in T2--3N0M0 cases (Table 2, Figure 2). In T2--3N0M0 cases, univariate analysis using the log-rank test revealed that the 4 significant prognostic predictors of survival at staging TURBT were age >70 years, male gender, size >3 cm and presence of hydronephrosis (Table 2). Using these 4 prognostic predictors at staging TURBT in T2--3N0M0, we classified our cases into 3 groups: 9 with 1 prognostic predictor, 11 with 2 prognostic predictors and 8 with 3 or 4 prognostic predictors. There were significant differences in cancer-specific survival rates (Figure 3, $p = 0.007$). Cases with ≥2 prognostic predictors at staging TURBT in T2--3N0M0 had an unfavourable outcome. There was a statistical association between the number of prognostic predictors at staging TURBT and response to treatment ($p = 0.035$).

Toxicity

Common adverse reactions were gastrointestinal complications and general fatigue. Although 26 cases (76.4%) showed gastrointestinal complications, vomiting in G3 was seen in only one case. Haematological toxicities were relatively mild, with 10 cases (29.4%) showing the same type, although only one case occurred in G3. There were no treatment-related deaths. Six cases showed abnormal urinary frequency and/or micturition pain during treatment. In regard to long-term complications, contraction of the bladder was not reported and numbness of the lower extremities was found in only two cases. In all long-term survivors with bladder preservation, patient satisfaction was obtained.

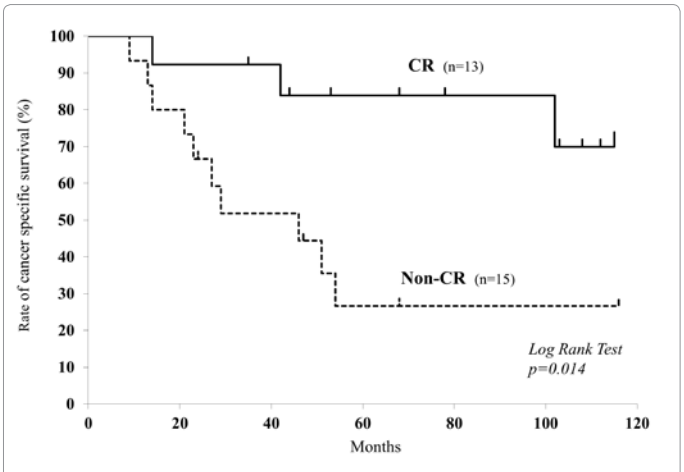

Figure 2: Kaplan-Meier curves showing cancer-specific survival according to response to treatment in T2-3N0M0 cases.

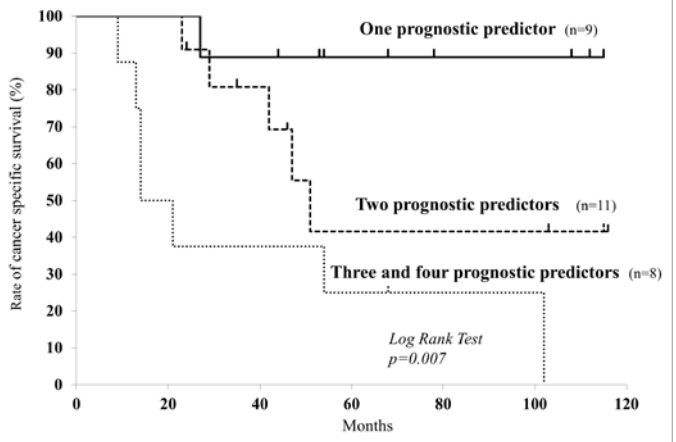

Figure 3: Kaplan-Meier curves showing cancer-specific survival according to prognostic predictors of survival at staging TUR-BT in T2-3N0M0 cases.

Discussion

For T1 G3 bladder cancer, intravesicular BCG therapy is the standard treatment for prevention of recurrence and disease progression; however, disease progression following this method occurs in around 20% of cases [1,16]. Thus, several groups of workers have recommended early radical cystectomy for T1 G3 bladder cancer. However, this carries the potential of over-treatment for many such cases. In this study, we performed intra-arterial chemotherapy for T1 G3 bladder cancer in order to reduce disease progression, and no disease progression was found. In addition, our protocol includes a second TURBT procedure, which is the recommended therapy for T1 G3 bladder cancer. However, because our study was based on a small number of patients, additional studies will be required before any clinical benefit can be reliably established in regard to our protocol for this type of cancer.

Several studies have evaluated the predictive factors for recurrence

and survival in muscle-invasive bladder cancer therapy [7,8,17-20]. In our study, 4 predictive factors were found by univariate analysis in T2--3N0M0 cases. Because the prognosis of patients with ≥2 prognostic predictors in T2--3N0M0 cases was unfavourable, our protocol proved inadequate for those patients. From our findings, it is obvious that reducing lymph node recurrence is key to improvement in treatment efficacy. The most commonly performed bladder preservation therapy is trimodal, including radiotherapy. We chose a protocol excluding radiotherapy to avoid adhesion formation following radiation therapy for total cystectomy in the refractory case. However, the recent literature on bladder preservation therapy does not mention this side effect in radiation therapy [9-13,21,22]. Compared with the results of protocols that include radiotherapy, we consider that our results suggest the necessity of radiotherapy in bladder preservation therapy for high-risk T2--3N0M0 cases.

The possibility of bladder preservation therapy is mentioned in recent guidelines from an evidence-based algorithm [20]. In contrast, the presence of local lymph node micrometastasis and understaging at TUR are typical reasons given for the non-acceptance of bladder preservation therapy for muscle-invasive bladder cancer. It is likely that because of micrometastases, there has been no mention in recent guidelines of intra-arterial infusion as a method for administration of anti-cancer drugs. However, the treatment outcome following bladder preservation therapy using intra-arterial infusion bears comparison with that of radical cystectomy. On the other hand, with regard to TUR, we cannot deny that there are technical differences among institutions. We consider maximum TUR the most suitable technique for bladder preservation therapy, particularly bearing in mind technical factors. In addition, apart from the high level of patient compliance, successful bladder preservation requires a multidisciplinary team with specialized skills in radiation and medical oncology. Our aim is to develop a better protocol for bladder preservation therapy by incorporating new improvements and ideas.

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