Watchful Waiting Versus Intravesical BCG Therapy for High-grade pT1 Bladder Cancer with pT0 Histology After Second Transurethral Resection: Japan Clinical Oncology Group Study JCOG1019

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A Phase III clinical trial has been started in Japan to determine the optimal treatment strategy for patients with high-grade pT1 bladder cancer who have pT0 histology after second transurethral resection. The aim of this trial is to demonstrate the non-inferiority of relapse-free survival (excluding Tis or Ta intravesical recurrence) for watchful waiting compared with intravesical bacillus Calmette–Guérin therapy for pT0 after second transurethral resection. Patients with high-grade pT1 bladder cancer at the first registration and pT0 after second transurethral resection at the second registration are randomized to either a watchful waiting arm or an intravesical bacillus Calmette–Guérin therapy arm. A total of 575 patients at the first registration and 260 patients at the second registration will be accrued for this study from 38 institutions over 5 years. The primary endpoint is relapse-free survival (excluding Tis or Ta intravesical recurrence), and the secondary endpoints are overall survival, metastasis-free survival with bladder preserved, annual proportion of intravesical relapse-free survival, annual proportion of T2 or deeper relapse-free survival, adverse events and serious adverse events.

Key words: bladder cancer — second transurethral resection — BCG — watchful waiting — Phase III clinical trial

INTRODUCTION

Bladder cancer is a common disease in urologic oncology. Non-muscle invasive bladder cancer (NMIBC) comprises about 70% of all bladder cancers. NMIBC consists of Ta, Tis and T1 bladder cancers. The main problems with treatment for NMIBC are recurrence and progression after transurethral resection of bladder tumor (TURBT). Above all, high-grade pT1 bladder cancer has a high risk for progression. Sylvester et al. (1) published risk tables for predicting recurrence and progression in Stage Ta and T1 bladder cancers and showed that T1 category and high-grade disease were the predominant risk factors for progression. In fact, some researchers have demonstrated that the 3-year relapse-free survival (RFS) rate of watchful waiting after initial...
TURBT is approximately 40%, whereas that of intravesical bacillus Calmette–Guérin (BCG) therapy is approximately 70% for high-grade pT1 bladder cancer (2–5). The European Association of Urology (EAU) guidelines, therefore, advocate intravesical BCG therapy or total cystectomy as the standard treatments for bladder cancer in high-risk progression groups (6). Meanwhile, cystectomy is an invasive intervention and is generally considered to be a treatment option only for high-risk patients or poor BCG responders (6). Thus, intravesical BCG therapy is considered the first choice after TURBT for high-grade pT1 bladder cancer in clinical practice.

Jakse et al. (7) reported that residual tumors were observed in 27–62% of cases following second TUR after initial TURBT for high-grade Ta or T1 bladder cancer. It was recognized that one-time TURBT is insufficient for complete resection of bladder cancer and leads to an underdiagnosis of muscle invasive cancer. Based on this background, the practice of performing second TUR spreads widely. Actually, second TUR is the recommended therapy for high-grade Ta and T1 bladder cancers in the EAU guidelines (6). In addition, the National Comprehensive Cancer Network (NCCN) guidelines recommend repeat resection for any pT1 bladder cancers if the first TURBT does not allow adequate staging or if no muscle is observed in biopsy (8). Second TUR is currently recognized as the standard therapy for high-grade pT1 bladder cancer.

The diagnostic significance of second TUR is that it avoids the underdiagnosis of the first TURBT, but the treatment significance of second TUR is unknown. Before the concept of second TUR was proposed, the standard treatment for high-grade pT1 bladder cancer following TURBT was intravesical BCG therapy. A meta-analysis demonstrated the efficacy of intravesical BCG therapy in preventing recurrence and progression without second TUR (2). The recurrence rate of high-grade pT1 bladder cancer is 50–80% and the progression rate of high-grade pT1 bladder cancer is 30–60% when watchful waiting is selected after TURBT, but the recurrence rate of high-grade pT1 bladder cancer is 30–50% and the progression rate is 15–20% when intravesical BCG therapy is selected after TURBT (2–5,9–11). However, there is no evidence showing whether or not intravesical BCG therapy is necessary for patients with high-grade pT1 bladder cancer who have pT0 histology after second TUR. The current standard treatment for patients with high-grade pT1 bladder cancer who have pT0 histology after second TUR is intravesical BCG therapy. NCCN guidelines recommend intravesical BCG or mitomycin therapy when there is no residual tumor after second TUR. On the other hand, another opinion holds that pT0 status after second TUR carries minimal risk for recurrence or progression and that intravesical BCG therapy is overtreatment for these patients. It takes about 2 months to complete intravesical BCG therapy, and adverse events such as pollakisuria, macrohematuria and dysuria occur in almost all patients.

Based on this background, we began a multi-institutional Phase III trial (JCOG1019) to evaluate the non-inferiority in terms of RFS (excluding Tis or Ta intravesical recurrence) of a watchful waiting arm compared with an intravesical BCG therapy arm for patients with high-grade pT1 bladder cancer who have pT0 histology after second TUR.

The study protocol was designed by the Urologic Oncology Study Group (UOSG) of the Japan Clinical Oncology Group (JCOG), approved by the Protocol Review Committee of JCOG on September 2008 and activated on July 2011. This trial was registered at the UMIN Clinical Trials Registry as UMIN000006930.

**PROTOCOL DIGEST OF THE JCOG 1019**

**PURPOSE**

The aim of this study is to demonstrate the non-inferiority in terms of RFS (excluding Tis or Ta intravesical recurrence) of watchful waiting compared with intravesical BCG therapy for pT0 after second TUR after TURBT for high-grade pT1 bladder cancer.

**STUDY SETTING**

This study is a multi-institutional open-label randomized Phase III trial.

**RESOURCES**

This study is supported by a Health and Labour Sciences Research Grant for Clinical Cancer Research (H22-67) from the Ministry of Health, Labour and Welfare, Japan, and National Cancer Center Research and Development Funds (23-A-16 and 23-A-20).

**ENDPOINTS**

The primary endpoint is RFS (excluding Tis or Ta intravesical recurrence), which is defined as days from randomization to first evidence of either intravesical recurrence of pT1 or deeper, distant metastasis, cystectomy or death from any cause, and censored at the latest day without events. Tis and Ta intravesical recurrence were excluded from the primary endpoint because Ta intravesical recurrence can be treated by TURBT and these recurrences are not critical. We considered adopting ‘overall survival’ (OS) or ‘metastasis-free survival with bladder preserved’ as the primary endpoint, but the prognosis of the study subjects is too good to evaluate by OS and the adaptation of cystectomy depends on a patient’s preference or the general condition. Therefore, we selected ‘RFS (excluding Tis or Ta intravesical recurrence)’ as the primary endpoint because it is more objective and harder endpoint than ‘metastasis-free survival with bladder preserved’. 
The secondary endpoints are OS, metastasis-free survival with bladder preserved, annual proportion of intravesical RFS, annual proportion of T2 or deeper RFS, adverse events and serious adverse events. Tis or multiple Ta recurrence needs intravesical BCG therapy and survival without these recurrences might reflect a patient’s benefit. The event of ‘annual proportion of intravesical RFS’ includes even Tis or Ta recurrence, so the influence with Tis or Ta recurrence will be evaluated by this endpoint.

**Eligibility Criteria**

**Inclusion Criteria**

Patients are included in this trial if they fulfill all of the following first registration criteria:

(i) Complete eradication of all visible tumors in the bladder by TURBT
   (a) Depth of TURBT: muscularis propria or deeper
   (b) Surgical specimens must contain muscularis propria
(ii) Histopathological diagnosis: Stage T1, high-grade urothelial carcinoma of the bladder
(iii) Aged between 20 and 85 years
(iv) Within 56 days from the date of TURBT
(v) ECOG performance status of 0 or 1
(vi) No history of administration of cyclophosphamide or methotrexate
(vii) No history of pelvic irradiation
(viii) No history of BCG intravesical therapy
(ix) No history of either bladder cancer (except for Tis Ta bladder cancer) or upper urinary tract cancer (ureteral cancer and/or renal pelvic cancer)
(x) Sufficient organ function
(xi) No strongly positive tuberculin reaction
(xii) Written informed consent

Patients receive second TUR after the first registration and are enrolled in the second registration if they fulfill all of the following second registration criteria:

(i) Histologically proven pT0 after second TUR
(ii) Negative or suspected positive urine cytology in two consecutive examinations (The classification of urine cytology is defined as negative, suspected positive and positive according to the General Rule for Clinical and Pathological Studies on Renal Pelvic, Ureteral and Bladder Cancer, first edition. Classes I and II are defined as negative, Class III is defined as suspected positive and Classes IV and V are defined as positive in the five-step evaluation.)
(iii) Within 28 days from the date of second TUR
(iv) Sufficient bone marrow function

**Exclusion Criteria**

Patients are excluded from the first registration if they meet any of the following criteria:

(i) Simultaneous or metachronous (within 5 years) double cancers
(ii) Infectious disease (including tuberculosis) to be treated
(iii) Body temperature of 38°C or higher
(iv) Positive anti-HIV antibody
(v) Women during pregnancy or breastfeeding
(vi) Psychiatric disease
(vii) Systemic and continuous steroid medication
(viii) History of severe brain ischemia or myocardial infarction within 6 months
(ix) History of systemic anaphylactoid reaction to BCG

There are no exclusion criteria at the second registration.

**Randomization**

After confirming the eligibility criteria, the first and second registrations are completed by telephone or fax or via the JCOG Data Center web site. At the second registration, patients are randomized to either the watchful waiting arm or the intravesical BCG injection arm by a minimization method that balance the arms in terms of institution, number of occurrences (initial or recurrence) and number of tumors (single or multiple).

**Treatment Methods**

**Second TUR**

Second TUR is performed from days 21 to 56 after the latest TURBT. Day 0 is defined as the day of the latest TURBT before the first registration. The resection area must include the entire scar from the latest TURBT as well as the surrounding area. The ureteral orifice and the internal urethral orifice are excluded from the resection area.

**Intravesical BCG Therapy**

Intravesical BCG therapy is initiated within 28 days of the second registration. For the intravesical BCG therapy arm, Immunobladder® (80 mg/body) or Immucyst® (81 mg/body) is administered intravesically once a week for 8 weeks. Neither the change of the drug after the start of BCG therapy nor the dose reduction in BCG is permitted. After intravesical BCG therapy, patients are observed without any treatment until recurrence is observed.

**Watchful Waiting**

Patients allocated to the watchful waiting arm at the second registration are observed without any treatment until
recurrence is observed. Protocol completion is defined at the date of the second registration.

**Follow-up**

All enrolled patients are followed for at least 5 years. Blood and urine examinations are evaluated at least in the fourth and eighth courses during intravesical BCG therapy. For both arms, cystoscopy and urine cytology examinations are conducted every 3 months for the first 3 years, every 6 months for the next 2 years and every year after the 5th year. Abdominal computed tomography or magnetic resonance imaging is performed every year for the first 3 years and once during the 5th year.

Adverse events resulting from second TUR are evaluated for 30 days after the procedure. Adverse events related to BCG are evaluated every week during intravesical BCG therapy and every 3 months for the first 6 months. All adverse events are evaluated using Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0.

Protocol treatment is continued until progression, unacceptable toxicity or patient refusal.

**Study Design and Statistical Analysis**

This study is designed as a randomized Phase III trial to determine the non-inferiority of the watchful waiting arm in terms of RFS (excluding Tis or Ta intravesical recurrence) compared with the intravesical BCG therapy arm for patients with high-grade pT1 bladder cancer and pT0 after second TUR.

This study is designed with a two-stage registration. High-grade pT1 bladder cancer patients are registered at the first registration, while the second registration is performed when patients are diagnosed as pT0 at the time of second TUR. Patients enrolled at the first registration who do not proceed to the second registration will also be followed up for at least 5 years because there are few data for this population about the prevalence of residual tumors after first TURBT, adverse events, prognosis and clinical course after second TUR procedures.

The planned accrual period is 5 years, and the follow-up period is 5 years after the completion of accrual. The primary analysis is carried out at 3 years after accrual completion. The hazard ratio between treatment arms and its confidence interval, estimated by the Cox proportional hazard model stratified by number of tumors and number of occurrences, is used to test the non-inferiority of the watchful waiting arm in terms of RFS (excluding Tis or Ta intravesical recurrence). The significance level is set at 0.05 in a one-sided test because of the non-inferiority design of the study. Eighty-five events would be required to demonstrate, with a statistical power of 70%, that the watchful waiting arm is not inferior to the intravesical BCG therapy arm in terms of RFS (excluding Tis or Ta intravesical recurrence), with a non-inferiority margin of 10% in terms of 3-year RFS. Non-inferiority will be concluded if the upper limit of the confidence interval of the hazard ratio does not exceed the limit of 1.60, which is in accord with the non-inferiority margin. A sample size of 258 patients at the second registration is necessary to observe 85 events, considering the accrual and follow-up periods and an estimated 3-year RFS (excluding Tis or Ta intravesical recurrence) of 80% in both arms. We estimated that the number of T0 patients after second TUR would be 50% of the patients at the first registration, and there would be 10% ineligible patients at the second registration. Thus, the target sample size is set at 575 patients at the first registration and 260 patients (130 patients in each treatment arm) at the second registration.

**Interim Analysis and Monitoring**

We plan to conduct interim analyses twice during this study. The study might be terminated for futility, but not for efficacy, because the watchful waiting arm is unlikely to be superior to the intravesical BCG injection arm in terms of RFS. If the hazard ratio exceeds the non-inferiority margin of 1.60 (indicating that the watchful waiting arm is unexpectedly inferior to the intravesical BCG injection arm), the study will be terminated early for futility. In addition, if the 1-year intravesical RFS in the watchful waiting arm is ≤60%, if the 1-year T2 or deeper intravesical RFS in the watchful waiting arm is ≤90% or if the safety and/or efficacy of the intravesical BCG injection arm is much worse than expected, we will consider early termination of the study.

In-house monitoring will be performed every 6 months by the JOCG Data Center to evaluate study progress and to improve study quality.

**Participating Institutions**

The participating institutions (from north to south) are as follows: Hokkaido University Hospital, Sapporo Medical University Hospital, Hirosaki University Hospital, Tohoku University Hospital, Miyagi Cancer Center, Akita University Hospital, Yamagata University Hospital, Tsukuba University Hospital, Tochigi Cancer Center, National Defense Medical College Hospital, Chiba University Hospital, National Cancer Center Hospital, Keio University Hospital, Tokyo Jikei University School of Medicine, Teikyo University, Kitasato University, Niigata Cancer Center Hospital, Niigata University Hospital, Yamanashi University, Shinniku University, Shizuoka Cancer Center, Hamamatsu University School of Medicine, Nagoya University, Mie University, Kyoto University Hospital, Osaka Prefectural Hospital Organization Osaka Medical Center for Cancer and Cardiovascular Diseases, Kobe University, Nara Prefectural University, Tottori University, Shimane University, Yamaguchi University Hospital, Kagawa University, Shikoku Cancer Center, Kurume University, Kyushu University, etc.
University Hospital, Harasanshin Hospital, Kumamoto University and Kagoshima University Hospital.

Conflict of interest statement
None declared.

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