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 Satistical 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 secondary 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 $\leq$60%, if the 1-year T2 or deeper intravesical RFS in the watchful waiting arm is $\leq$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 JCOG 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, Shinshu 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 Hospital, Harasanshin Hospital, Kumamoto University and Kagoshima University Hospital.

Conflict of interest statement

None declared.

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