Results of a Phase 1 Dose Escalation Study of Intravesical TMX-101 in Patients with Nonmuscle Invasive Bladder Cancer

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Purpose: Imiquimod, a toll like receptor 7 (TLR-7) agonist, is effective as a topical treatment for skin malignancies. TMX-101 is a liquid formulation of imiquimod. In this study we establish a safety profile of TMX-101 in patients with nonmuscle invasive bladder cancer.

Materials and Methods: We conducted a multicenter phase 1 dose escalation study in patients with nonmuscle invasive bladder cancer. Patients were included in 1 of 4 dose groups (0.05%, 0.1%, 0.2% or 0.4%) and treated with 6 weekly instillations of TMX-101, starting 2 weeks after transurethral resection of bladder tumor. Patients were evaluated weekly, and pharmacokinetic and pharmacodynamic parameters were measured.

Results: A total of 16 patients were included in the study with 4 per dose group. Two patients dropped out after instillation 2 in dose groups 1 and 2. Overall, 88 instillations were administered without serious adverse events. There were 118 adverse events, of which 84 were related to the study drug. All adverse events were mild or moderate and number or severity was not correlated with dose group. Of the related adverse events 70% were confined to the genitourinary tract and resolved without intervention. There was a dose dependent systemic uptake with low plasma levels up to dose group 3 (0.2%, 100 mg). Maximum plasma concentration in dose group 4 (0.4%, 200 mg) was 71.7 ng/ml. This is below plasma concentrations of 123 and 128 ng/ml without significant side effects measured in healthy volunteers after subcutaneous (30 mg) or oral intake (100 mg) of imiquimod, respectively.

Conclusions: Intravesical treatment with TMX-101 is safe. The side effects are common but mild and mostly limited to the genitourinary tract. There is a low systemic uptake.

Key Words: imiquimod; immunotherapy; administration, intravesical; urinary bladder neoplasms; toll-like receptor 7

Abbreviations and Acronyms

AE = adverse event
BCG = bacillus Calmette-Guérin
C_{max} = maximum plasma concentration of TMX-101
CTCAE = Common Terminology Criteria for Adverse Events
DLT = dose limiting toxicity
IL = interleukin
INF = interferon
NMIBC = nonmuscle invasive bladder cancer
TLR = toll like receptor
TURBT = transurethral resection of bladder tumor

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BLADDER cancer causes a considerable burden for patients and seems to be the most expensive cancer.[1] Therefore, bladder cancer is an important health care problem with approximately 2.7 million patients worldwide.[2,3] Approximately 75% of bladder cancer is nonmuscle invasive.[4,5] According to EAU (European Association of Urology) guidelines, the choice of treatment depends on the risk group to which the patient belongs.[4,5] All patients should undergo TURBT followed by an immediate intravesical instillation of chemotherapy,

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which has been shown to significantly reduce recurrence rates.[6] This treatment is sufficient for low risk patients, but intermediate and high risk patients should receive additional treatment. The EAU and American Urological Association guidelines advise maintenance intravesical chemotherapy for intermediate risk patients, whereas patients with high risk NMIBC should receive intravesical BCG, which is considered the optimal adjuvant treatment.[4,7,8] Despite having been the most widely used intravesical treatment for more than 35 years,[9] BCG is associated with local and systemic side effects in a significant proportion of patients.[10–12] Moreover, in about a third of patients, bladder cancer recurs,[5,13] stressing the need for better and safer treatments.

Toll like receptors are proteins with a critical role in antimicrobial immunity and are key components of the innate immune system. Activation of the receptor results in an efficient antigen presentation by mature dendritic cells and enhanced production of antigen specific T cells.[14] Evidence also suggests that this TLR pathway, and especially TLR-7, may be crucial in antitumor immunity.[15] In the family of imidazoquinolines, the synthetic drug imiquimod (1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine) is a TLR-7 agonist and acts as an immune modulator via the MyD88 dependent pathway, with a potent antiviral and antitumor effect. Imiquimod is the active ingredient of Aldara™ cream, which is used for the treatment of genital warts, basal cell carcinoma and actinic keratosis,[16] as well as carcinoma in situ of the glans penis.[17] TMX-101 is an optimized formulation of imiquimod, suitable for intravesical instillation.[18,19] Previous preclinical research showed that imiquimod has an antiproliferative effect against urothelial carcinoma in vitro,[20] as well as an antitumor effect[20] and a good safety profile in vivo.[18] In this study we established a safety profile of TMX-101 in patients with low and intermediate risk NMIBC. Therefore, we conducted a phase 1 dose escalation study in which patients were treated with 6 consecutive instillations of TMX-101 after TURBT.

MATERIALS AND METHODS

After approval from the ethical committee, patients were included in this open label, multicenter, prospective phase 1 trial from June 2010 until November 2011. In this study 16 patients were treated at 4 Dutch hospitals.

Patient Selection

Patients with a bladder tumor judged to be a Ta–T1 low grade tumor were asked to participate before undergoing TURBT. Written informed consent was obtained before screening. Patients were eligible if they had pathology confirmed pTa–pT1 low grade (WHO 2004) urothelial carcinoma, if they were 18 years old or older, had an Eastern Cooperative Oncology Group performance score of 0 to 1, and if they had adequate renal, hepatic and hematological function. Women of childbearing potential and sexually active men had to agree to use contraception during the study. Exclusion criteria were pT1 high grade bladder cancer, carcinoma in situ, high grade cytology, muscle invasive urothelial carcinoma, inability to retain an intravesical instillation for 1 hour, uncontrollable infections, history of upper urinary tract disease, immune compromised patients, active malignancies other than urothelial carcinoma and basal cell carcinoma, previous or present radiotherapy or brachytherapy, suspicion of hypersensitivity to the study drug, pregnant or breastfeeding women, participation in other studies with investigational drugs, intravesical chemotherapy within 6 months before study entry and intravesical immunotherapy within 24 months before study entry.

Treatment and Study Design

Treatment consisted of a macroscopically complete TURBT followed by 6 intravesical instillations with TMX-101 once a week for 6 weeks. The study drug TMX-101 is a 50 ml sterile liquid solution applied intravesically and retained for 1 hour. Included patients did not receive a single postoperative instillation with chemotherapy.

The study was designed as a dose escalation study with 3 to 6 patients per dose group. Dose escalation and/or patients per dose group were per protocol defined based on dose limiting toxicities and maximum tolerated dose. DLT was defined as any CTCAE grade 3 or more toxicity related to the trial medication, and/or any treatment delay of 21 days or more due to drug related adverse events. Maximum tolerated dose was defined as the highest dose level at which less than 33% of patients experienced DLT, with a minimum number of 6 patients. The schedule consisted of dose groups 1 through 4 with doubling concentrations of TMX-101 of 0.05%, 0.1%, 0.2% and 0.4%, respectively.

Patient Evaluation

The presence, severity and frequency of adverse events were assessed in the weeks after treatment, and defined according to CTCAE version 4.2. Patients were monitored routinely every week with the assessment of vital signs, blood analysis (hematology, chemistry, immunoglobulin) and urinalysis (culture, macroscopic and microscopic).

Pharmacokinetics and Pharmacodynamics

Urine samples for pharmacokinetic and pharmacodynamic investigations were obtained from all patients predose and 1 hour after instillation. Furthermore, blood and urine sampling for pharmacokinetic and pharmacodynamic investigation was performed in 1 patient per dose group at points pre-dose, 0.5, 1, 1.5, 3, 4.5 and 6 hours, at treatment numbers 1 and 6. For these patients an additional written informed consent was required. Blood samples were collected in lithium-heparin tubes, transported on ice, centrifuged at 2,500 rpm for 15 minutes at 4C within 30 minutes after collection. Aliquoted plasma was stored and shipped at -20C upon analysis.

Plasma samples were analyzed for concentrations of the study drug and 2 of its main metabolites by liquid chromatography-mass spectroscopy with a detection range of 0.025 to 10 ng/ml. Urine samples were analyzed for TMX-101 with a detection range of 5 to 2,500 μg/ml. ELISA kits