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Original article

A phase 2 study of TMX-101, intravesical imiquimod, for the treatment of carcinoma in situ bladder cancer

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Abstract

Purpose: Imiquimod is a toll-like receptor agonist with proven antitumor activity as a topical treatment for skin cancer. TMX-101 (Vesimune) is a novel liquid formulation of imiquimod optimized for intravesical delivery. The agent demonstrated safety as an intravesical treatment for non–muscle-invasive bladder cancer in a phase 1 clinical trial. We report the results of a phase 2 prospective multicenter clinical trial assessing the safety and activity of TMX-101.

Materials and methods: Patients with non–muscle-invasive bladder cancer containing carcinoma in situ were eligible for inclusion. Enrolled patients received 6 weekly intravesical administrations of 200 mg/50 ml TMX-101 0.4%. End points included rate of adverse events, changes in urinary cytokine levels following treatment, and clinical response at 6 weeks following final instillation, defined as negative posttreatment bladder biopsy and urine cytology results.

Results: A total of 12 patients were enrolled, with 10 available for efficacy analysis. Half of the patients (6/12) had received $\geq$2 prior induction courses of bacillus Calmette-Guerin. All patients received all 6 doses of TMX-101 per protocol. Overall, 75% of patients experienced treatment-related adverse events, only 1 of which was >grade 2 (urinary tract infection). Furthermore, 2 patients demonstrated a negative cytology and biopsy result at 6 weeks following treatment. Significant increases in urinary cytokines, including IL-6 and IL-18, were seen following treatment.

Conclusion: In this phase 2 pilot study in patients with carcinoma in situ bladder cancer, intravesical TMX-101 was safe and well tolerated with common, mild genitourinary adverse effects. Clinical activity was suggested by the increase in posttreatment urinary cytokines. Complete responders were seen. Further investigation of the agent is warranted.

Keywords: Imiquimod; Urinary bladder neoplasms; Carcinoma in situ; Administrations, intravesical drug; Immunotherapy

1. Introduction

Bladder cancer is a common malignancy, representing 429,800 new cases and 165,100 deaths annually worldwide [1]. Approximately 80% of these patients present with

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non–muscle-invasive bladder cancer (NMIBC), which exists in 2 phenotypic forms: discrete papillary tumors that are generally well demarcated and can be removed via endoscopic resection and carcinoma in situ (CIS), a high-grade multifocal entity with a tendency toward frequent recurrences and progression to muscle-invasive disease [2]. Intravesical bacillus Calmette-Guerin (BCG) is an effective treatment for CIS [3], demonstrating consistent initial response rates of 70% [4]. Unfortunately, BCG fails in a significant proportion of patients, owing to either intolerable adverse effects, serious infections, or refractory disease [5–7]. Patients in whom BCG fails are at high risk for disease progression [8]. Many of these patients may not be candidates for radical cystectomy owing to underlying health status. As such, there is a clinical need for alternative treatments for patients with CIS bladder cancer.

Toll-like receptors (TLRs) are a family of highly conserved transmembrane receptors that function in innate and adaptive immunity [9]. Activation of TLR pathways results in expression of various proinflammatory cytokines including chemokines and other inflammatory mediators [10]. These mediators, in turn, result in efficient antigen presentation by mature dendritic cells and enhance production of antigen-specific T cells. Imiquimod is a small molecule of the imidazoquinoline family that acts via agonism toward TLR7 [11,12]. Imiquimod has been successfully used as the active ingredient in Aldara as a topical treatment for various benign and malignant skin conditions. This has prompted interest in imiquimod as a potential intravesical bladder cancer treatment. TMX-101 is a novel liquid formulation of imiquimod that is optimized for intravesical delivery. Intravesical TMX-101 induces local immunological activation, resulting in significant reductions in tumor burden in an orthotopic bladder cancer model [11,13]. A phase 1 dose-escalation study demonstrated doses up to 200 mg (0.4%) were safe, with low systemic uptake and common, mild, adverse effects and no reported grade 3 adverse events (AEs) [14]. Herein, we present the results of a phase 2 single-arm study evaluating the tolerability, safety, and activity of intravesical TMX-101 in patients with NMIBC containing CIS.

2. Materials and methods

2.1. Study design

We performed a prospective, nonrandomized, open-label, fixed-dose, phase 2 trial investigating the safety, tolerability, and biological activity of intravesical TMX-101 0.4% in patients with CIS bladder cancer at 4 centers in the United States. End points included clinical response at 6 weeks following the final instillation, safety, and the tolerability of TMX-101, as well as biological activity of TMX-101, as measured by pharmacodynamic markers in predosing and postdosing urine specimens. After informed consent, patients were evaluated for study eligibility during the screening period (days -28 to -1). Screening evaluations included a medical history, physical examination, vital signs, Eastern Cooperative Oncology Group performance status determination, complete blood count, serum chemistry, microscopic urinalysis, urine culture, and urine sampling for pharmacodynamic parameters. Screening procedures also included cystoscopic examination of the bladder with mapping and biopsies of all suspicious areas between days-28 and days-14, followed by bladder washing for cytology. Patients who had undergone such examinations as part of their treatment outside of the study protocol were not required to repeat the procedures, provided that examinations took place during the specified timeframe, and pathologic samples were available for central review. Patients with histologically confirmed CIS and who fulfilled all other eligibility criteria were enrolled in the study. The study planned to enroll up to 12 patients to obtain 6 evaluable patients (patients with confirmed positive CIS on screening histology who received all 6 TMX-101 doses and underwent 6-week evaluation with cystoscopy with interpretable histologic and cytologic sampling). Patients provided informed written consent. Institutional review board approval was obtained at each participating site.

2.2. Patient inclusion

Inclusion criteria included age $\geq$18 years, Eastern Cooperative Oncology Group performance status 0 to 2, with adequate bone marrow, hepatic, and renal function, and with histologically proven CIS. CIS lesions could be primary, secondary, or recurrent and could be concomitant to Ta or T1 lesions, provided that these lesions had been fully resected. BCG-naive patients were allowed to enroll in the study, provided they undergo close follow-up after the end of the study period and were allowed to undergo additional treatments following treatment with TMX-101, as dictated by their referring urologist. Women of childbearing age were required to have a negative pregnancy test result at screening and to avoid pregnancy by use of adequate contraceptive methods.

Exclusion criteria included the inability to maintain intravesical treatments within the bladder, a history of pelvic radiation, perioperative intravesical chemotherapy, a history of either muscle-invasive urothelial carcinoma of the bladder or urothelial carcinoma of the ureter or renal pelvis, immunocompromised state, an active infection at the time of screening, a history of hypersensitivity to any of the study drug components, or participation in any other investigational trials in the 3 months before screening. Patients who had received any intravesical therapy in the 3 months before screening were also excluded.

2.3. Study drug

Intravesical TMX-101(Vesimune) is a sterile liquid dosage form of imiquimod, suitable for intravesical