Mistletoe Plant Extract in Patients with Nonmuscle Invasive Bladder Cancer: Results of a Phase Ib/IIa Single Group Dose Escalation Study

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Purpose: We determined the maximum tolerated dose, safety and effectiveness of intravesical instillation of mistletoe extract after transurethral resection of nonmuscle invasive bladder cancer.

Materials and Methods: In this single group dose escalation study patients with nonmuscle invasive bladder cancer were treated with weekly instillations of mistletoe extract for 6 weeks. Four weeks before instillation therapy all patients underwent transurethral resection of bladder tumors. During this procedure a marker tumor was left. At 12 weeks after the start of instillation therapy transurethral resection of the marker tumor or biopsy of the former marker tumor location was done so that patients were tumor free when entering followup until week 48. During the followup clinical assessment laboratory tests for safety and cystoscopy were done every 12 weeks.

Results: A total of 36 patients were treated with increasing doses of mistletoe extract. We found no dose limiting toxicity up to a dose of 675 mg of plant extract. Besides local reactions we saw hints that pyrexia may develop. All adverse events were well manageable. At 12 weeks a marker tumor remission rate of 55.6% (95% CI 38.1 to 72.1) was achieved. At 1 year a recurrence rate of 26.3% (95% CI 9.1 to 51.2) was observed.

Conclusions: In this study intravesical instillation of mistletoe extract as treatment in patients with nonmuscle invasive bladder cancer was shown to be safe and well tolerated. Promising data on efficacy were observed and will be further investigated in a phase III study.

Key Words: urinary bladder neoplasms; mistletoe; abnoba viscum; administration, intravesical; treatment outcome

Abbreviations and Acronyms

AVF2 = Abnoba viscum Fraxini 2

BCG = bacillus Calmette-Guérin

MMC = mitomycin-C

TURB = transurethral bladder resection

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BLADDER cancer is the most common malignancy of the urinary tract. The global mortality rate is 4/100,000 men and 1.1/100,000 women. In Europe bladder cancer mortality rates have decreased in the last decade to about 16% in men and 12% in women. Approximately 75% to 85% of patients present with nonmuscle invasive bladder cancer confined to the mucosa (Ta—noninvasive papillary carcinoma, carcinoma in situ or T1—submucosa with tumor invading subepithelial connective tissue).[1]

Despite complete primary TURB nonmuscle invasive bladder cancer

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shows a recurrence rate of 50% to 70% accompanied by tumor progression in approximately 20% of cases. The frequency of recurrence correlates with the depth of infiltration and the grade of tumor differentiation.

Currently the most effective adjuvant treatment to reduce the risk of tumor recurrence after transurethral resection is intravesical chemotherapy or immunotherapy. Results of meta-analyses have shown that 1 immediate intravesical instillation of chemotherapy after TURB significantly decreased tumor recurrence compared with TURB alone.[2,3] An adjuvant intravesical treatment with cytostatic substances such as doxorubicin, mitomycin and thiotepa or immunotherapeutic BCG decreases the recurrence rate in about a quarter of patients with nonmuscle invasive tumors.[4–8] However, to our knowledge the frequency and duration of adjuvant treatment in patients at intermediate risk is not yet determined. In addition, BCG therapy has a high rate of side effects, including cystitis disorders and fever. Single cases of miliary tuberculosis and subsequent death have also been observed.[9–12]

The untoward effects of established treatments have promoted the use of unconventional therapies such as mistletoe extracts, among others. Mistletoe is a semiparasitic green shrub with more than 1,000 species that belong mainly to 2 families, that is Viscacea and Loranthaceae. The active agents are mainly proteins such as mistletoe lectins and viscotoxins but polysaccharides and liposomal structures also contribute to the overall effect. Of all of the different species the Viscum album subspecies album contains the highest amounts of active mistletoe ingredients.

Goebell et al evaluated subcutaneously applied mistletoe lectin after TURB for bladder tumor but found no influence on the frequency of or time to recurrence.[13] Preclinical in vitro studies showed a dose dependent antiproliferative effect of mistletoe extracts on bladder cancer cell lines.[14,15] Further studies demonstrated that intravesically applied mistletoe lectins have the potency to induce antitumor activity in different bladder cancer models in the rat.[16,17] Luboldt et al intravesically instilled recombinant mistletoe lectin.[18] Complete remission of a marker lesion was found in 3 of 17 patients and no treatment related side effects were reported.

An alternative to the use of recombinant mistletoe lectin is the administration of mistletoe plant extracts, which contain a high concentration of mistletoe lectin and other active ingredients of the European mistletoe that support an antitumor effect. Since little is known about intravesical instillation of mistletoe plant extracts in patients with bladder cancer, we performed this study to establish the maximum tolerated dose and gain more insight into the efficacy and tolerability of this drug. In this study we used AVF2 mistletoe plant extract (Abnoba, Pforzheim, Germany). It is an injectable solution obtained from the European mistletoe species Viscum album L. for the treatment of malignant tumors, tumor recurrences and defined precancerous conditions.

MATERIALS AND METHODS

Patients with histologically proven, nonmuscle invasive bladder cancer (Ta G1/G2 or T1 G1/G2) were enrolled in this open label, single group phase Ib/IIa study. Sample size was fixed without power considerations in accordance with current EMA/CHMP (European Medicines Agency/Committee for Medicinal Products for Human use) guidelines for clinical phase I studies. To assess the maximum tolerable concentration of AVF2 for intravesical instillation a common 3 + 3 design was applied, which stipulates a first cohort of 3 patients at the lowest dose level. If no WHO grade III toxicity is observed, the next dose level can be tested in another cohort of 3 patients. If 1 of 3 patient experiences grade III toxicity at a certain dose level, another cohort of 3 patients is included at the same dose level. If no grade III toxicity develops in this cohort, one can proceed to the next dose level. Dose escalation is stopped when at least 2 grade III toxicities occur at 1 level. The maximum tolerated dose is defined as the next lower dose level. This design is well established in phase I cancer trials.[19]

Dose levels administered in the dose finding stage of this study ranged from 45 to 675 mg plant extract, that is 3 to 45 ampoules for a total of 34,500 to 517,500 ng mistletoe lectin.

Patients were excluded from study if they had muscle invasive bladder carcinoma or carcinoma in situ. Intravesical instillation therapy within 6 months before study enrollment and radiotherapy of the bladder were further exclusion criteria. Patients with a contracted bladder, untreated acute or chronic urinary tract infection, or subvesical obstruction were also excluded from participation.

All patients underwent TURB in the screening phase (week −2). To judge the ability of AVF2 to induce complete remission a 0.5 to 1.0 cm marker tumor was left behind in the patient bladder after initial transurethral resection. This marker tumor concept is generally accepted to evaluate the efficacy of bladder cancer treatments in patients at up to intermediate risk and it is also deemed safe and ethically justified in this patient cohort.[20–23] Starting at week 0 instillations were performed weekly for a total of 6 weeks. At week 12 (14 weeks after initial resection) cystoscopy was performed to assess marker tumor remission. All remaining residual tumor was resected. In case of no visible tumor biopsy was obtained at the site of the former marker lesion so that all patients were tumor free when entering the additional followup period, which lasted until week 48. After this period the recurrence rate was assessed.

Safety assessments included adverse event recording, laboratory tests for safety and global judgment of tolerability by patients and investigators.