Bladder Cancer 2 (2016) 279–282
DOI 10.3233/BLC-169006
IOS Press

Clinical Trials Corner

Dear Readers,

The Clinical Trials Corner of the Bladder Cancer Journal is a new section devoted towards highlighting ongoing trials or recently completed trials in urothelial cancer. Our hope is to encourage accrual for ongoing trials and to educate readers on the results of completed trials. If you feel that you would like to draw attention to a specific trial, please feel free to email us at: piyush.agarwal@nih.gov and/or cnsternberg@corasternberg.com.

Non-muscle invasive bladder cancer (NMIBC) accounts for the majority of presenting bladder tumors. As a community, we abandoned the term "superficial" to describe these tumors with the increasing realization of not only the extent of these tumors but also the cost (both financial and emotional) of managing these tumors. In patients with recurrent high grade NMIBC after BCG therapy, there is a real risk of tumor progression and consideration for definitive therapy with radical cystectomy is paramount. However, patients are reluctant to proceed to surgery and so patients with recurrent high grade NMIBC who are truly BCG-refractory and/or unresponsive have several clinical trial options. We highlight a few of the trials below.

Sincerely,

Piyush K. Agarwal, MD
Associate Editor, *Bladder Cancer*
Head, Bladder Cancer Section
Urologic Oncology Branch
National Cancer Institute
Bethesda, MD, USA

Cora N. Sternberg, MD, FACP
Associate Editor, *Bladder Cancer*
Chair, Department of Medical Oncology
San Camillo Forlanini Hospital
Rome, Italy

Completed Trials With Results

Study Title: Mycobacterial Cell Wall-DNA Complex in Treatment of BCG-refractory Patients With Non-muscle Invasive Bladder Cancer

Clinicaltrials.gov identifier: NCT00406068

Sponsor: Bioniche Life Sciences Inc.

Enrollment: 129

Study Design: Phase II/III, single arm trial of mycobacterium phlei cell wall – nucleic acid complex (MCNA) in patients with non-muscle invasive bladder cancer (high grade papillary tumors and/or CIS) who are refractory to BCG therapy. Patients treated with an induction course followed by maintenance therapy up to 2 years. The primary endpoint was 1-year DFS and secondary endpoints were duration of disease-free survival (DFS), progression-free survival (PFS), and overall survival.

Rationale: MCNA is a nonpathogenic and nonviable strain of mycobacterium that may potentially offer the benefits of BCG without the potential toxicity. Furthermore, it may be a viable substitute for BCG shortages.

Results: Overall DFS was 25% at 1 year and 19% at 2 years. PFS was 87.3% at 1 year. The median time to cystectomy was 263 days in MCNA responders vs. 174 days in non-responders. Overall, 15 patients (11.6%) developed metastatic bladder cancer.

ISSN 2352-3727/16/€27.50/$35.00

Comments: After publishing the results, the drug was presented to a FDA panel for a biologics license application and voted down 18-6. Unfortunately the primary endpoint fell short of the intended result (1 year DFS ≥ 40%). Furthermore, the FDA calculated the true DFS to be 20.9% at 1 year. In the FDA analysis, DFS in CIS-containing patients was also evaluated separately as the absence of tumor in these patients is unlikely to result from bladder biopsy/TURBTs (as opposed to papillary tumors). By looking at only CIS containing tumors, DFS did not appear as robust (18.8% DFS at 1 year). Finally, we now know that the intended endpoint of improvement in DFS was much higher than it needed to be as an absolute improvement of 10-15% in BCG-unresponsive patients may be clinically significant. The two main learning points were a) that studies should enrich their population with CIS-containing patients and b) that studies should aim for an absolute improvement of 10-15% over historical controls in endpoints even though this will require the enrollment of more patients.

Study Title: Maximum Tolerable Concentration of Abnoba viscum Fraxini 2 (AVF2) Intravesically in Patients With Superficial Bladder Cancer

Clinicaltrials.gov identifier: NCT02007005

Sponsor: Abnoba Gmbh

Enrollment: 36

Study Design: Phase Ib/IIa, single arm dose escalation trial of mistletoe plant extract (AVF2) in patients with Ta G1/G2 or T1 G1/G2 non-muscle invasive bladder cancer who had a marker lesion left in bladder after TURBT. A weekly instillation of AVF2 was started 2 weeks after TURBT. Instillations were performed weekly for 6 weeks and then patients assessed for a response 6 weeks after completion of therapy (14 weeks from TURBT).

Rationale: Pre-clinical work demonstrated that mistletoe extracts have an antiproliferative effect on bladder cancer cell lines and anti-tumor activity in rodent bladder tumor models. This trial sought to establish safety with intravesical administration of mistletoe plant extracts specifically using AVF2 in the setting of a marker lesion. The primary endpoint was safety with dose escalation and the secondary endpoint was tumor remission rate of the marker lesion.

Results: No grade III toxicity attributable to AVF2 was noted and so dose safely increased to 45 ampules (675 mg AVF2 extract). 30 patients available for assessment of marker lesion and 20 (~67%) had no visible lesion and a negative biopsy at 14 weeks from TURBT. Only 19 of the original patients had follow-up at 1 year and 14 of these patients (73.7%) remained tumor-free.

Comments: AVF2 was well-tolerated and may have activity against intermediate risk papillary tumors (12 patients had T1 G1/G2 and 9 patients had Ta G2 disease). This study did not use the revised 2004 WHO Pathologic staging criteria and so it is unclear what the true pathology is for the T1G1 patients. This trial excluded CIS patients and so appropriately a marker lesion design was performed which more accurately assesses response of papillary tumors to treatment alone. However, 3 months and 12 months are not sufficient durations of follow-up to clearly establish efficacy of AVF2. Furthermore, it is unclear whether patients would have done equally well if they had been given perioperative mitomycin C.

Completed Trials Pending Results

Study Title: Genetic Susceptibility to Tumor Recurrence and Progression in Patients With Non-Muscle Invasive Bladder Cancer

Clinicaltrials.gov identifier: NCT00582387

Sponsor: Memorial Sloan Kettering Cancer Center

Participating Centers: New York, NY

Accrual: 116

Study Design: Observational cohort study of patients with non-muscle invasive bladder cancer that includes genetic assessment of tumors and behavioral questionnaires to establish whether they can enhance the ability to predict tumor recurrence and progression over tumor grade and stage.

Rationale: Tumor and grade are not adequate predictors of recurrence and progression in NMIBC and so by identifying behavioral risk factors from questionnaires and genetic susceptibility genes in DNA repair, cell cycle, and detoxifying pathways; perhaps, better prediction of NMIBC outcomes can occur.

Comments: Samples will be obtained from blood, urine, and tumor tissue. The study hopes to predict the 40% of patients with NMIBC that may never recur or progress with tumor. The study has accrued 116 patients and analysis is pending. One concern is that often very little tumor tissue is present in NMIBC specimens and instrumented urine may not contain enough urothelial cancer cells for analysis.

Study Title: Intravesical Administration of rAd-IFN/Syn3 in Patients With BCG-Refractory or Relapsed Bladder Cancer

Clinicaltrials.gov identifier: NCT01687244

Sponsor: FKD Therapies Oy

Enrollment: 40

Study Design: Phase II, randomized trial comparing two different doses of rAd-IFN (Instiladrin) in high grade BCG-refractory or BCG-relapsing NMIBC patients. The primary endpoint is RFS at 12 months following four instillations. The secondary endpoint is toxicity and adverse event evaluation. This trial has been completed but results are pending.

Rationale: Interferon (IFN) is postulated to be important in BCG-responsive tumors but intravesical IFN ineffective due to short exposure to urothelium. Intravesical IFN production is facilitated by co-administration of recombinant adenovirus (rAd)-mediated IFN-α2b protein, with the excipient Syn3 which improves viral mediated transduction of the urothelium. In a phase I trial of 17 patients, rAd-IFN was well tolerated and 43% (6/13) of patients with detectable IFN-α in the urine achieved complete remission at 3 months that lasted on average for 31 months.

Results: Preliminary results were presented at the 2015 AUA Annual Meeting. Of 34 evaluable patients at the time of the abstract, 10 patients (29%) had achieved a complete remission at 12 months. Tolerability in these patients was excellent with some minor urinary urgency post-instillation that was managed with oral anticholinergics.

Comments: IFN is a logical next step in immunotherapy and adenoviral mediation transduction may improve significantly upon intravesical administration. The impressive complete remission rates in the phase I and II trials are very encouraging. Also it will be interesting to see the duration of IFN detection in the urine post-treatment to establish adequate dosing of Instiladrin. A phase III single-arm registration trial is planned with activation expected in 2016.

Recruiting

Study Title: Phase 1/2 Study of ABI-009 in Non-muscle Invasive Bladder Cancer

Clinicaltrials.gov identifier: NCT02009332

Sponsor: Aadi, LLC

Participating Centers: New York and Nashville

Accrual: estimated 40

Study Design: A Phase 1/2, Single Arm Open-Label Study to Determine the Efficacy and the Safety of Albumin-bound rapamycin nanoparticles (ABI-009) in recurrent or BCG-refractory NMIBC patients.

Rationale: Rapamycin is an MTOR inhibitor that has demonstrated activity against bladder cancer in preclinical models. Intravesical administration, however, is not practical for most targeted therapies. Nanoparticles may allow for increased delivery of therapeutic agents across the urothelium and has been demonstrated to be active with agents such as paclitaxel. Therefore, now rapamycin is being evaluated in this trial.

Comments: Nanotechnology allows delivery of a variety of therapeutics intravesically and has been successfully done with paclitaxel. Therefore, this trial has a lot of potential.

Study Title: Study of Bacillus Calmette-Guerin (BCG) Combined With PANVAC Versus BCG Alone in Adults With High Grade Non-Muscle Invasive Bladder Cancer Who Failed At Least 1 Course of BCG

Clinicaltrials.gov identifier: NCT02015104

Sponsor: National Cancer Institute

Participating Centers: Bethesda and New Brunswick

Accrual: 54

Study Design: Phase 2, randomized trial comparing BCG alone to BCG and PANVAC in high-grade BCG-refractory NMIBC patients. The primary endpoint is 12 month DFS rate. The secondary endpoints are time to recurrence, progression-free survival, and immunologic correlates.

Rationale: PANVAC is a vaccine with transgenes for CEA and MUC-1. These tumor antigens are overexpressed on the surface of high-grade urothelial tumors. Also PANVAC contains three co-stimulatory molecules that can augment a T-cell immune response. In theory, the vaccine should augment a T-cell response against cells expressing CEA and MUC-1. Therefore, it is postulated that it will augment the response to BCG when combined with BCG.

Comments: An immune response can be triggered either by inhibiting blockade or augmenting T-cell stimulation. PANVAC attempts the latter with three co-stimulatory molecules. By using a systemic vaccine with a local immunotherapeutic agent, this trial attempts to establish greater efficacy than BCG alone.