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Paper Alert

Bladder Sparing Therapy for BCG Failures – I – Intravesical Immunotherapy

Edward M. Messing*
University of Rochester Medical Center, Rochester, NY, USA

Between 15 and 20% of patients with newly diagnosed urothelial cancer (UC) of the bladder will have high grade (HG) non-muscle invasive (NMI) disease including carcinoma-*in-situ* (CIS) and stage Ta and T1 tumors [1]. After transurethral resection of the cancer (TURBT), patients may undergo re-TURBT, but if no muscle invasive (MI) cancer is found most will receive an induction course of 6 weekly intravesical instillations of Bacillus Calmette Guerin (BCG). If at the first post BCG surveillance cystoscopy no cancer is found, they usually receive 3 weekly instillations of BCG every 6 months for 3 years [2]. If persistent or recurrent NMI cancer is found, they will usually receive another 6 week re-induction course of BCG without [3] or with alpha interferon [4].

Persistence or recurrence of any HG cancer at 6 months after the initial TURBT (termed "BCG unresponsive or resistant" disease) is generally an indication for cystectomy. However, bladder cancer is a disease of the elderly, and usually arises in patients with numerous comorbidities [5]. Thus, some UC patients are not candidates for cystectomy, and some patients who are medical "candidates" decline to undergo it. Treatment options for these patients are limited. Only Valrubicin has been approved by the US Food and Drug Administration (FDA) for salvage intravesical therapy for patients with CIS after BCG, even though 20% or fewer patients so treated remained recurrence-free by 12 months [6]. Studies of bladder preservation therapies for BCG unresponsive or "relapsing" (recurrence of HG NMI UC after a tumor free interval of less than 12 months after the index TURBT) cancer [7] have reported that courses of intravesical instillations of a variety of single agents including chemotherapies and biological preparations effect <25% two year recurrence free survival (RFS), and combination chemotherapies, usually gemcitabine with either mitomycin C or docetaxel provide $\leq$35% two year RFS [7]. Phase II studies with other novel agents, [8] radiation therapy with systemic chemotherapy, and systemic checkpoint inhibitors are also underway, but not completed.

Two recent articles report novel immunotherapies for BCG unresponsive and relapsing HG NMI UC [9, 10].

Shore and co-workers in the Society of Urologic Oncology Clinical Trials Consortium, building upon a phase 1b trial reported from the MD Anderson Cancer Center, [11] randomized 40 patients with primarily BCG unresponsive HG NMI UC to receive 75 ml of 10^{11} viral particles (VP)/ml or 3×10^{11} vp/ml of rAd-INFα -Syn 3. Over 90% of participants had at least two prior induction courses of BCG.

rAd-INFα is a replication deficient recombinant adenovirus encoding the human INFα 2b gene, which was administered with Syn3, a polyamide surfactant which enhances adenoviral transduction of the urothelium. rAd-INFα-Syn 3 was instilled intravesically one time several weeks after the index TURBT, and one month after negative cystoscopy, cytology and biopsy (if clinically indicated) at months 3, 6 and 9 after the index TURBT. 33% of patients receiving the lower dose and 36.8% receiving the higher dose of rAd-INFα-Syn 3 were free of recurrence at 12 months. While these results may seem modest, it should be noted that over half the patients at each

*Correspondence to: Edward M. Messing, University of Rochester Medical Center, Rochester, NY, USA. Tel.: +1 585 275 3345; E-mail: Edward.messing@urmc.rochester.edu.

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dose level had BCG unresponsive disease, indicating that they were at very high risk of recurrence. All patients had elevated urinary interferon levels 2 and 4 days after each instillation, but interferon level did not correlate with response. Over 70% of those who were recurrence-free at 12 months had positive anti-adenoviral antibody titers (>4 times pre-dose titers), while only 24% of those who experienced a recurrence did.

Urinary urgency, frequency, dysuria and fatigue occurred in 32.5–40% of patients, but almost 80% of adverse events (AE) were transient and primarily not severe. Grade 3 AEs occurred in 22% and most were not drug related. There were no grade 4 or 5 AEs.

Interferon α has anti-angiogenic and pro-apoptotic properties, and induces dendritic cell maturation promoting tumor cell recognition by T cells and NK cells; but how it helps prevent bladder tumor recurrence is not precisely known. Because interferon α induces programmed death ligand 1 (PD-L1) expression, it is possible that combining rAd-INFα-Syn 3 with a systemic PD-L1 inhibitor would have additive or even synergistic efficacy.

Steinberg and colleagues described an intravesical combination of 1/3 strength BCG, 50 million units of interferon alpha, 22 million units of interleukin-2 and 250 mcg of subcutaneously injected granulocyte-macrophage colony stimulating factor (quadruple immunotherapy = QIT) [10]. QIT was given weekly for 3 weeks, and then, after a two week hiatus, another 3 weekly treatments were administered. This was done primarily, for BCG relapsing disease. Complete responders underwent repeat 3 weekly QIT treatments at months 3, 9, and 15 using lower doses of BCG.

Forty-seven of 52 patients (90%) had some side effect, mostly urinary frequency, urgency and dysuria, and fatigue. In 9 (17.5%) a delay in treatment was required. Three patients (6%) could not tolerate the full induction course. However 55% of patients were disease free at 12 months, and 53% at 24 months. Presence of CIS or age >80 years did not affect results.

Thirteen patients underwent cystectomy and 5 patients who recurred were deemed not to be cystectomy candidates. However, of the patients who underwent cystectomy, while 2 had pT3 disease, none had positive surgical margins or positive lymph nodes, implying there was a window of time after initial BCG relapse where patients could undergo bladder salvage therapy and still have curative surgery if needed.

In future Paper Alerts other bladder sparing approaches to BCG resistant and relapsing HG NMI UC will be discussed, as study results are published. However, the FDA recognizes the great need in this patient subgroup, and is trying to find mechanisms to rapidly approve agents for these patients.

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