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Letter

Letter to the Editor: Bacillus Calmette-Guerin (BCG) Treatment Failures with Non-Muscle Invasive Bladder Cancer: A Data-Driven Definition for BCG Unresponsive Disease

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We would like to commend Steinberg et al. on their efforts to develop a data-driven sub-classification for an increasingly accepted disease state of non-muscle invasive bladder cancer – i.e. BCG unresponsive disease. The authors used data collected in the Phase II BCG-Interferon-α-2B trial originally published in 2006 [1] and performed subset analyses on the outcomes of patients who underwent additional intravesical therapy (in this case, combination BCG/IFNα therapy) [2]. Factors assessed included age, gender, number of prior BCG courses, BCG failure interval, BCG strain, number of prior TURBT's, and tumor size. Notably, most patients did not receive maintenance BCG, since the trial was initiated prior to acceptance of this as standard of care. Based on their analysis, for patients with CIS, the highest risk group was found to be those who had $\geq$2 episodes of BCG failure and disease-free interval of <12 months from BCG treatment (estimated RFS 14% at 24 months). For those with papillary tumors, risk factors for failure included $\geq$2 episodes of prior BCG failure, disease free interval of <6 months and multifocality on original diagnosis (estimated RFS 20% at 24 months). Using these data derived risk factors, the authors proposed separate subclasses for BCG-unresponsive-CIS and BCG-unresponsive-papillary disease.

The definition of BCG unresponsive disease is a relatively recent definition borne out of the need to better define patients who are unlikely to benefit from further intravesical therapy after BCG [3, 4] and has largely been based on expert consensus of both US (3) and US + European groups (4). While the time based differences proposed by Steinberg & O'Donnell [2] are certainly useful, we would like to point out that in their analysis, recurrence intervals were indexed from "the most recent prior BCG course completed by the patient" rather from the start of therapy (i.e. diagnosis of bladder tumor). Since the devil is in the details, these time calculations could cause readers/trial designs to underestimate disease free and time to recurrence intervals. For example, if a patient suffered tumor recurrence 3 months after completing induction and maintenance BCG according to the SWOG protocol, he would have a disease-free or time to recurrence interval of 3 months according to Steinberg et al. [2]. However, accounting for the duration

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of the SWOG maintenance BCG protocol [5], the patient would have been disease-free for 39 months from the time of starting induction BCG.

Previous prospective, randomized trials have indexed time to event endpoints from the time of randomization [5–7]. In the SWOG 8507 study examining the role of maintenance BCG, patients were randomized after deemed to be disease-free at 3 months after induction BCG [5]. In the two more recent EORTC studies comparing adjuvant intravesical BCG to epirubicin (EORTC 30911) and different dosing/duration of maintenance BCG therapy (EORTC 30962), randomization occurred soon after TURBT and prior to start of intravesical BCG [6, 7]. Internationally developed guidelines for reporting treatment results in solid tumors recommend using the date of starting treatment or the date of randomization as the starting point for calculating time to event endpoints [8–10]. Thus, while the data presented by Steinberg et al. are certainly useful in pointing out the temporal differences in the natural history of BCG unresponsive CIS and papillary disease, the time calculations should be tempered with the recognition that there is an inherent bias in how it was calculated and that this might confound results of trials powered for effect using these data. For prospective trials, we recommend that the timing of treatment endpoints be counted from the date of the first induction dose of therapy or randomization [4].

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