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Paper Alert

Salvage for BCG Unresponsive and Recurrent Disease

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So what does the patient with high grade, non-muscle invasive bladder cancer who has disease that is unresponsive to (or has quickly recurred after) adequate intravesical therapy with Bacillus Calmette Guerin (BCG) do, particularly if he (she) does not want to lose his (her) bladder? Two agents that received priority, fast track priority review by the Food and Drug Administration (FDA) for such patients, Vicinuim [1] and Nadofaragene (rAd-If Na/Syn 3) [2], which have efficacy in this circumstance have experienced production problems and are not available [3, 4]. In a non-randomized (single arm) phase 3 study, Vicinium, an antibody to the transmembrane cell adhesion molecule, EpCam, conjugated to Pseudomonas exotoxin A (which stops protein translation and induces apoptosis) there was a complete response (CR) rate of 39% at three months and 17% at 12 months [1], while Nadofaragene, an adenovirus mediated "gene therapy" producing interferon alpha [2] had 53% CRs at 3 months and 45% at 12 months in another single arm phase 3 study.

This leaves intravesical chemotherapy with one or two agents (usually gemcitabine and/or docetaxel) [5] or other drugs (e.g. mitomycin C or valrubicin), or intravenous infusions of Pembrolizumab (an anti-PD-1 antibody) [6] for these patients.

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Pembrolizumab, in the Keynote 057 single armed trial, had a three month CR rate of 38% and a two-year recurrence free survival rate of 15% [6] and also is FDA approved for this clinical scenario. While there are numerous agents in testing, including intravesical instillations of Coxsackievirus A21 [7] and a gemcitabine impregnated device placed in the bladder (TAR 200) [8], none are available currently and are unlikely to be until ongoing trials are completed.

Thus it is particularly disappointing that a recent publication indicates that even with its modest efficacy, Pembrolizumab (200 mg IV every three weeks until recurrence up to two years), is not cost-effective compared to intravesical chemotherapy (which has limited efficacy) or even the radical cystectomy (RC) that patients are trying to avoid [9].

In an elegant cost analysis study using a decision analysis Markov model, Wymer and colleagues authors found that at it's current cost (over $100,000 per year) [9], Pembrolizumab was far less cost-effective than either RC or sequential intravesical chemotherapy with gemcitabine-docetaxel (gem-doce) consisting of six weekly instillations and then monthly maintenance for two years [5, 9]. While the authors found RC most cost effective at the five year time horizon, the full five years was needed (this is a problem since assumptions about outcomes beyond two years had to be made for both gem-doce and Pembrolizumab). Moreover, in the analysis, the

expected rates of adverse events (especially for RC) were somewhat optimistic. For example, five year incidences of chronic bowel toxicity including bowel obstruction requiring hospitalization or surgery, of parastomal or incisional hernia warranting revision, and of stricture revision of the ureter were assumed to be 1% each (although the range for each tested in sensitivity analyses was 0–13%). Moreover if the rate of metastases at two years estimated for gem-doce dropped minimally, from 6.1% to 5.9% [5], then intravesical chemotherapy would be most cost effective.

That said, based purely upon one report of outcomes and complications, which appeared in abstract form, the cost of Pembrolizumab was so great, that even assuming no metastatic events at two years, a cost reduction of more than 90% was needed for Pembrolizumab to become cost effective with RC or gem-doce. While sensitivity analyses varying the incidences of adverse events was used for all the assumptions, Pembrolizumab was still not cost effective without drastic reductions in its price.

There are numerous limitations in this analysis, particularly a reliance on very few studies to estimate adverse events and outcomes (which the authors readily acknowledge), and that long term outcomes and adverse events were based on assumptions. However, the basic conclusion was that in treating BCG unresponsive or recurrent disease, RC or intravesical gem-doce were the best available options, and individual circumstances, including predicted five-year survival other than from bladder cancer, already present and likely future urinary symptoms, the perceived inconvenience and morbidity from further intravesical treatments, and, of course, the ability to withstand and willingness to undergo RC, must all be considered before the "best" approach is chosen.

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

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