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Paper Alert

BCG versus Cystectomy for High Risk, High Grade Non Muscle Invasive Bladder Cancer

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Patients with newly diagnosed high risk (see below), high grade (HG) non-muscle invasive bladder cancer (NMIBC) have a significant likelihood of disease recurrence, progression and eventual death from BC [1, 2]. The two standard treatments for this disease in relativity healthy individuals are induction and maintenance courses of Bacillus Calmette Guerin (BCG) Intravesical therapy (combined with surveillance cystoscopies/cytologies and transurethral resection of bladder tumors [TURBTs] versus radical cystectomy. Given that BC is a disease of the elderly and often occurs in patients with significant comorbidities, treatment choice is not always an option. However, in patients healthy enough, and willing to undergo cystectomy, the "correct" approach requires considerable counseling, and, in the absence of randomized trial data, remains uncertain. It is for this reason that the conduct and publication of a randomized controlled feasibility trial is of great interest [3]. The goal of this trial was to see if carrying out an appropriately sized clinical trial to answer the question definitively was feasible.

Patients with newly diagnosed HG NMIBC were considered to be at "high risk" if their tumors had one or more of the following characteristics: carcinoma in *situ* (CIS), lymphovascular invasion (LVI), residual HG urothelial cancer (UC) on re-TURBT,>3 tumors, initial largest tumor > 3cm, or lamina propria Invasion (T1). Patients were stratified by age (<75 and > 75 years), gender, highest stage, presence of CIS, and a history of previous low-grade (LG) UC. Re-resection was required for all patients with stage T1 disease, or Ta/CIS disease without muscularis propria in the initial specimen. Successful BCG treatment was considered completion of at least four induction instillations and three weekly maintenance instillations every six months for a minimum of one year. Maintenance BCG could continue if there was HG NMIBC at the first three-month cystoscopy or LG NMIBC at any time.

After screening 407 patients, 215 (52.8%) were considered suitable for participation, of whom 185 were approached to take part and counselled; 51 (27.6% of the approached patients–12.6% of those screened), were consented and one subsequently declined participation. Five patients randomized to cystectomy refused their assignment, as did two assigned to BCG. All in all, 20 underwent radical cystectomy and 23 BCG treatment. Six percent of randomized patients had prior LG UC, 74% were current or former smokers, and 84% had some exposure to industrial or other bladder carcinogens. After the first TURBT, or if needed, re-resection, 32% of patients

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had stage T1 cancers, 62% had some CIS (20% CIS alone), and 24% had stage Ta disease.

Quality of life (QOL) questionnaires were completed at baseline, three, six, and 12 months, and "decision regret" questionnaires were filled out at 12 months.

Of those who started BCG, five permanently discontinued treatment and four had unplanned hospital admissions related to treatment. In general, however, BCG was well tolerated; most adverse events were grade 2. In the cystectomy group 85% had open surgery and, 85% had ileal conduit diversions performed. Five cystectomy patients (25%) experienced surgical complications including bleeding, small bowel injury, and nerve injury; one (5%), required a transfusion, and six (30%), experienced postoperative complications (chest and wound infections, urine leak, and constipation–some multiple). Four patients (20%) had a prolonged length of stay (not defined), and four required readmission.

OUTCOMES

In the cystectomy group, five (25%) tumors were pT0, 13 were NMI UC (65%), and two (10%) were pT2. Three (15%) had positive urethral margins, but none had positive lymph nodes. All patients were alive at 12 months without evidence of recurrence. In the BCG group, four had tumor persistence/recurrence after induction BCG (two LG and two HG), and at the second cystoscopy one had LG and two HG T1 disease. Five patients discontinued BCG; one for unrelated reasons, two for symptoms, and two for disease persistence/progression. Two BCG patients underwent cystectomy, one for HG T1 disease and one for persistent CIS at the second cystoscopy; one had pT3 N1 disease at cystectomy. Another patient, who did not undergo cystectomy, progressed to distant metastatic disease.

Thus at diagnosis at least 10% had potentially lethal disease (pT2) and over the next six months (in the BCG arm) at least two (9%) developed metastases. The QOL surveys revealed that at three months after randomization, the BCG group had a non-significantly superior QOL, but differences disappeared by six and 12 months. Conversely, by 12 months there was slightly more decision regret and lower emotional function scores in the BCG group.

This study does not pretend to offer a definitive answer about which treatment is superior, and, indeed, even the questionnaires were greatly underpowered to show significant differences between the groups. However the study reinforces that high risk, HG NMIBC is a life threatening disease in at least 10% of patients and this becomes manifest quickly (although possibly too late to intervene successfully). Importantly, cystectomy patients eventually accommodate to their equality of life. On the other hand most patients do well with BCG and removing the bladder in the 25% of cystectomy patients who were pTO after TURBT/reTURBT may be over-treatment. This is important information for us to use in counseling our patients, but performing a definitive randomized clinical trial based on only 27% of approached patients participating and 14% of randomized patients withdrawing because of not accepting randomization assignment, will make a much larger randomized study very challenging to conduct. Perhaps, getting nurses involved with solicitation and retention, as they were for another extremely difficult-to-accrue-study, ProtecT (randomization to monitoring vs definitive treatment for localized prostate cancer), could provide some guidance for such an undertaking [4].

CONFLICTS OF INTEREST

The author has no conflicts of interest to report.

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