REVIEW

Is participation in a clinical trial associated with a survival benefit in patients with bladder cancer?

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Abstract

Bladder cancer that is unresponsive to intravesical therapies is difficult to treat. Patients with this disease usually have to try salvage therapies, partial cystectomy, or radical cystectomy. Unfortunately, the population afflicted by bladder cancer is older and frailer than those afflicted by other cancers with mortality approaching 1.5% and readmission rates approaching 64%. These patients are left with no other options aside from participating in a clinical trial to delay or avoid surgery. We hypothesized that participation in a clinical trial provides survival benefits when controlling for tumor stage and pathology in the case of non-muscle invasive bladder cancer that is refractory to intravesical Bacillus Calmette-Guérin (BCG). Using our Institutional Review Board (IRB) approved Columbia Urologic Oncology Database, 55 patients with BCG-refractory NMIBC (29 clinical trial patients, 26 non-clinical trial patients) were identified between 2008 and 2012. Clinical characteristics, demographics, and outcomes were obtained from the medical records. Non-clinical trial patients had fewer mean BCG instillations than their clinical trial counterparts (7.8 versus 11.5 doses, $p < .01$). Kaplan Meier (KP) curves for Overall Survival (OS) and Cancer Specific Survival (CSS) indicate an increased survival benefit for patients enrolled in a clinical trial (OS: $\chi^2 = 8.802$, $p< 0.01$, median of 6.68 years versus 3.15 years; CSS: $\chi^2 = 10.205$, $p < 0.01$, mean 5.6 years versus 2.65 years). The data support the notion that there may be an inherent survival benefit gained by virtue of being included in a clinical trial. The drivers of this survival benefit may include more interactions with the hospitals and clinics, greater patient involvement in their health care, and increased surveillance by clinicians.

Introduction

Among cancers in the United States, bladder cancer is the 4th most common cancer in males and the 12th most common cancer in females.[1] There will be around 74,960 new cases overall accompanied by an estimated 15,580 deaths for the year 2015. However, bladder cancer is highly neglected in terms of funding and public attention, which is not concomitant to its incidence and burden on society. It is likely to appear as the 11th most mentioned cancer in the media despite the fact that its actual incidence in the world is 6th.[2] Moreover, when people are asked about its perceived incidence, it ranks 15th in comparison to other more rare cancers like brain, thyroid, stomach, bone/muscle, kidney, pancreatic, and blood/leukemia.[3] This has dramatic consequence for funding as bladder cancer receives less funding than other cancers relative to its incidence; the National Cancer Institute reports state that $23.4 million is spent on bladder cancer, while other more rare entities like brain cancer have much more funding to the tune of 171 million.[4] This lack of awareness and funding makes it very difficult to recruit patients for clinical trials and limits the amount of clinical trials available to patients.

Within bladder cancer, there are two clinical entities that are treated separately given their clinical management and outcomes. Muscle invasive bladder cancer (MIBC) is defined by invasion of the malignant cells past the detrusor muscle. For patients with this disease, radical cystectomy (RC) and urinary diversion is warranted with neoadjuvent chemotherapy in the form of platinum based agents.[5] There is also non-muscle invasive bladder cancer (NMIBC), which is defined by malignant cells that are on the urothelial lining of the bladder but that do not invade into the musuclaris propria of the detrusor muscle.

At diagnosis, usually done by endoscopy with biopsy, around 75% of cases are NMIBC; these patients are at high risk of recurrence once treated with a transurethral urinary resection of the bladder, which involves removing the suspicious mass or cauterizing any suspicious areas to kill malignant cells.[6] For this group, bladder-preserving strategies are employed afterward. These may involve intravesical immunotherapy or chemotherapy. In select cases and where all else fails, salvage therapies are attempted such as partial cystectomy and other intravesical treatments. All of these attempt to prolong a patient's time with their natural bladder function and avoid the prospect of RC, which is a highly morbid surgery with over 64% complication rate in 90 days post-surgery and 1.5% mortality rate 30 days post-surgery.[7] However, those patients who undergo salvage strategies and refuse RC after failing primary therapies are at high risk of recurrence, their risk varying according to their tumor stage, high or low grade, and/or presence of carcinoma-in-situ with other histological tumor subtype.[8]

Existing options for these patients at high risk of recurrence and/or progression include the gold line intravesical treatment for bladder cancer, which is Bacillus Calmette-Guérin (BCG). This treatment is specifically for high-risk tumors defined as high-grade Ta, T1, and Tis, as it reduces disease recurrence while remaining superior to other intravesical chemotherapeutic agents like adriamycin, mitomycin C, or epirubicin.[9] Moreover, in this high risk group, a meta-analysis of mitomycin C showed that patients receiving a single dose within 24 hours of a transurethral resection of the tumor have up to 39% lower risk of recurrence, independent of chemotherapeutic agent received afterward.[10]

Bacillus Calmette Guerin (BCG) – refractory NMIBC is a disease in a subset of patients defined as either failing to respond to BCG, recurring after being cancer free, intolerant to BCG due to side effects, or not receiving adequate amounts of BCG instillations. This population has worse outcomes than those who permanently respond to BCG, and those who are at high risk usually are recommended to undergo neoadjuvant platinum-based chemotherapy followed by radical cystectomy.[8] The salvage intravesical therapies available to these patients yield variable and inconsistent response results with rates of remission in 19-21% of the time using mitomycin C, valrubicin, docetaxel, and paclitaxel.[11] At this point, after these salvage therapies, patients are considered multi-drug resistant and again are recommended to undergo radical cystectomy; alternatively, a partial cystectomy may be attempted. However, in both cases of BCG refractory disease and MDR NMIBC bladder cancer, these patients are either not good surgical candidates or decline to have a radical cystectomy. This is the population for whom clinical trials may offer a glimmer of hope for patients to retain their bladder. However, one must balance the risk of delaying curative surgery with the possibility of a cure that a clinical trial can provide to patients who may not survive the surgery.

At the J. Bentley Squier Urologic Clinic at Columbia-Presbyterian Medical Center, our department has enrolled patients across various studies at in phase I and phase II trials for agents like intravesical albumin-bound docetaxal, intravesical albumin-bound sirolimus, intravesical cisplatin, gemcitabine,

cabazitaxel, oral mTOR inhibitor with intravesical gemcitabine, adenovirus carrying GM-CSF coding gene aiming for stimulation of interferon production, and other medications aimed at trying to help this population of patients who do not have other options besides surgery. Nevertheless, a clinical concern for this special population is that many of them forgo the decision of having surgery with the hope of preserving their bladder but compromising their outcomes. Some of these patients may theoretically have progression while receiving experimental treatments. Hence, we wanted to know whether clinical trial participation affords any survival advantages or disadvantages in comparison to patients who do not enroll in a clinical trial. Moreover, we wanted to investigate the clinical and demographical characteristics of patients who enroll in clinical trials at Columbia to find ways to optimize clinical trial enrollment.

Artwork by Hannah Singer

Materials and Methods

The Institutional Review Board (IRB) Columbia Urologic Oncology Database was queried for patients who participated in a clinical trial at Columbia from 2008 to 2012 for a total of 77 patients. A second query was done for all patients refractory to BCG and who were given the choice of receiving salvage intravesical treatment (interferon and BCG, paclitaxel, or docetaxel), radical cystectomy, or enrolling in a clinical trial for a total of 158 patients. We included only patients who had a visible tumor T1 high grade or higher and with or without carcinoma in situ in order to control for stage, grade, and baseline risk. We also excluded those with only carcinoma in situ, as they represent a higher risk population. This led to a total of 29 clinical trial patients and 26 non-clinical trial patients who had all of their care at Columbia and matched for disease severity. Demographic variables recorded through chart review included age, sex, marital status, religion, race, ethnicity, health insurance, driving distance, public transportation time, education, urban/rural neighborhood, and zip code. Incomes and driving distances were estimated using the United Census Bureau zip code income look up and Google Maps, respectively. Other clinical variables recorded via chart review included time to recurrence from last intravesical treatment, Charlson Comorbidity Index (CCI) adjusted for age, pathological and histological characteristics of recurrence, type of BCG failure, number of BCG instillations, and rates of radical/partial cystectomy (RC/PC) between the groups.

A Chi-square or Fisher's Exact Test was performed for categorical variables. A Mann Whitney Test was performed for non-parametric data and comparisons. A Student T-test was performed for analysis and comparisons of continuous variables. Kaplan Meier (KM) methods were used to compare overall survival (OS), cancer

specific survival (CSS), and disease free survival (DFS).

Results

Increased education (Fisher's Exact Test, $p < 0.013$), rural-suburban living (Fisher's Exact Test, $p < 0.011$), and increased distance from our institution (52.85 miles versus 23 miles, Mann Whitney U-test, $p < 0.01$) were associated with enrollment in a clinical trial compared with patients who did not enroll. With regards to other demographics, there were no associations between clinical trial participation and mean yearly incomes, age of recurrence, sex, religion, marital status, number of children, transportation time, smoking history, or insurance status (Supplementary Table 1).

With regards to clinical characteristics, there were no differences in CCI at diagnosis, pathology at recurrence, BCG failure type, or RC/PC rates between the two groups (Supplementary Table 2). There were no differences in median age at bladder cancer recurrence. However, clinical trial patients received more BCG instillations in their lifetime than their non-clinical trial counterparts (11.85 versus 7.83 doses, Student T-test, $p < .0007$). KM curves for OS and CSS indicate an increased survival benefit for patients enrolled in a clinical trial (OS: $\chi^2 = 8.802$, $p< 0.01$, median of 6 .68 years versus 3.15 years; CSS: $\chi^2 = 10.205$, $p < 0.01$, mean 5.6 years versus 2.65 years, Figures 1, 2). These survival benefits were seen despite the fact that DFS were not different between groups ($\chi^2 = 1.569$, $p=0.210$, 3.57 years for clinical trial patients versus 1.22 years for non-clinical trial patients, Figure 3).

Discussion

This retrospective study looked at whether a clinical trial affords clinical benefits for patients who decide to participate in these trials. We looked at both overall survival and cancer specific survival. We showed that patients in a clinical trial might have a survival advantage compared with those who do not participate in a clinical trial, with a median survival of two times higher than non-clinical trial patients with similar disease stages. Moreover, with regards to demographic analysis of the cohorts, patients on a clinical trial were more educated, lived in rural/suburban areas, and lived at an increased distance from our institution. This may suggest that patients who are recruited to enroll are an educated, motivated group that seeks inclusion into a clinical trial. The clinical trial information is available in the public domain via the National Cancer Institute website and other sources. However, this finding also suggests a possible selection bias in the Phase I and II clinical trials held at our institution for NMIBC, as we may unknowingly choose a more educated patient population for enrollment.

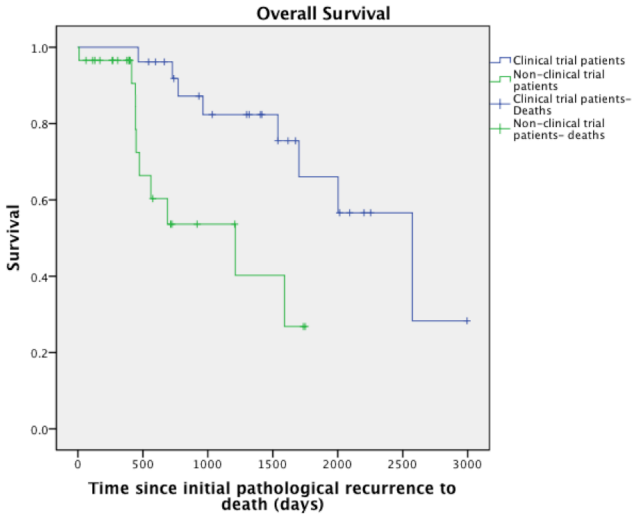

Figure 1. Kaplan-Meier curve plotting overall survival since initial pathological recurrence in days with patients censored at death ($\chi^2 = 8.802$, $p< 0.01$, median of 6 .68 years versus 3.15 years).

With regards to clinical characteristics, patients that enroll in clinical trials do not differ significantly from those who do not with regards to their comorbidities as assessed by the comparison of their CCI. This was unexpected given that usually these trials tend to include patients who are not surgical candidates. Moreover, of interest was the fact that patients who

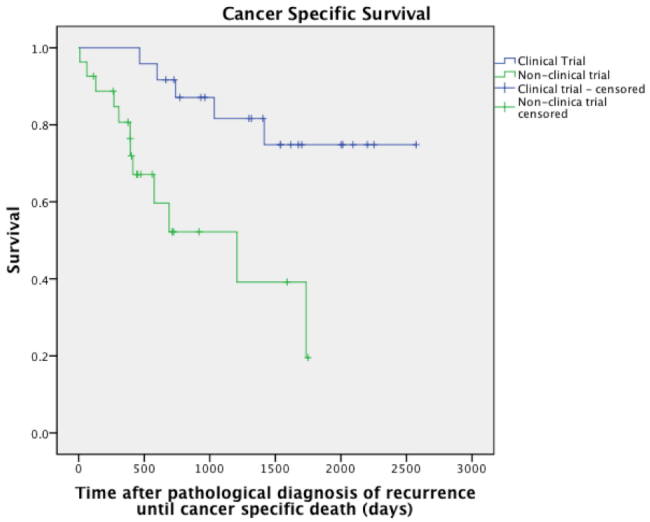

Figure 2. Kaplan-Meier curve plotting cancer specific survival since initial pathological recurrence in days with patients censored at death due to bladder cancer ($\chi^2 = 10.205$, $p < 0.01$, mean 5.6 years versus 2.65 years).

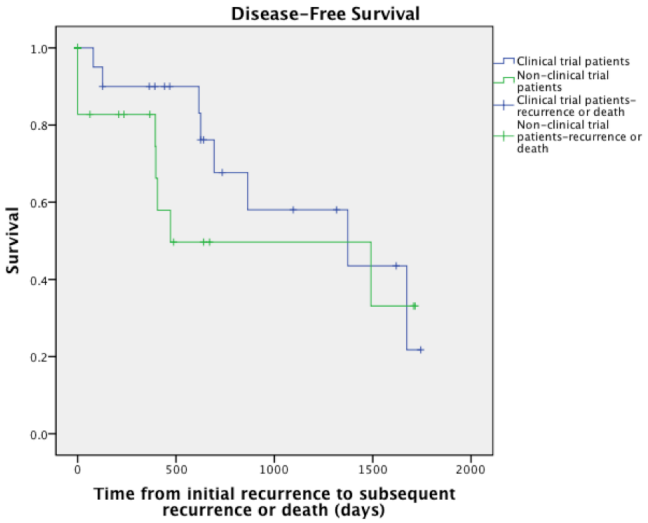

Figure 3. Kaplan-Meier curves plotting patients that after the clinical trial or other treatments undergo disease free period and censored for when they have subsequent recurrence or death ($\chi^2 = 1.569$, $p=0.210$, 3.57 yrs for clinical trial patients vs 1.22 yrs for non-clinical trial patients).

did enroll in a clinical trial were a much higher risk subgroup of BCG refractory disease than the non-clinical trial group. Previous research at our institution has shown that increasing amounts of intravesical therapies including BCG instillations prior to radical cystectomy leads to worse outcomes and decreased survival after surgery.[12] Hence, the clinical trial patients appear to be a much higher risk group, yet this group still maintains an overall survival benefit in comparison to the non-clinical trial patients.

This is an unexpected result and should be interpreted cautiously. There are many instances of patients who are wary of enrolling in clinical trials given the delay to ultimate curative treatment for those who do have the option. In other cases, the providers sometimes weigh the benefits of a clinical trial for patients who may benefit from immediate radical cystectomy. Although these results may offer some relief to providers, they need to be tempered with existing studies indicating that longer wait times for surgery predict worse outcomes.[13]

In the literature, a similar analysis has been done with a large Cancer Registry with stage I to IV solid organ tumors, where enrollment into clinical trials predicted lower overall and cancer-specific mortality among cancer sites.[14] However, on multivariate analysis, only lung, colon, and breast cancers were statistically significant, indicating that patients enrolling in a clinical trial tend to have more favorable and lower risk characteristics than the broader population of patients with the given disease. This paper neither included the urological cancers nor looked at the individual risk factors of the patients for a given disease as we have done with our analysis of patients enrolled in a clinical trial for BCG refractory bladder cancer.

Some reasons why clinical trial enrollment itself may afford survival benefits include more consistent clinical follow up, more interventions and surveillance by the medical team, and increased engagement of patients with their health. Nevertheless, this reason may be confounded by the fact that patients who enroll in clinical trials tend to be more educated and live in areas that are associated with high socioeconomic status enclaves in suburban communities.[15] Contrary to other studies, there were no differences in insurance status or income among

the groups; nevertheless, it is possible that the study was underpowered to detect those differences. Moreover, underinsured and uninsured status has also been implicated in under-enrollment in clinical trials, although the best study investigating this relationship showed results that were trending toward significance but did not meet the threshold.[16] We did not find any association between insurance status and clinical trial enrollment.

Of greatest concern in our study is the potential for selection biases seen in Phase I and Phase 2 trials that have taken place in our institution during the time of the retrospective study. Although, patient selection is a less important factor in these cases given that first toxicity and then efficacy tend to be the endpoints analyzed, this does lead to questions about how well we are recruiting patients and how well we will be able to do so in the future. The data we have so far suggest that we have to increase the emphasis on recruiting patients who may not have a college degree or graduate degree, actively improve enrollment people within the community of Washington Heights, increase the number of minorities enrolled including Hispanics and African Americans, and increase outreach to segments of the population with less access to information on clinical trials. All of these actions may help overcome this potential bias. This is especially important for bladder cancer as incidence will only increase in the future in the contexts of an ever- expanding minority population and a more chronically ill, aging population.[17]

Our study has several limitations. First, patients were matched by disease severity but not for other variables given the low case numbers. The patients selected as a group for comparison were patients who were similar in terms of disease burden (no Tis on pathology and clinically met criteria for enrolling in any trial dealing with BCG refractory) and for whom we had enough follow up to longitudinally track across our database. This may have created a lead-time bias, as we selected patients who may have survived instead of recruiting a representative group across all risk groups. Moreover, we excluded those who had low-grade disease and those who had only carcinoma in situ on pathology. The latter cases were excluded from analysis because they represented a unique population for whom endoscopic surveillance and biopsy tends to be unreliable, making progression or recurrence harder to measure in comparison with those who have a tumor and visible growth at recurrence. However, we did include those who have mixed Tis and visible tumors in our retrospective analysis.

Moreover, we could not assess all pathological and demographic data for patients who received their diagnosis or long-term follow up outside of our institution. In addition, everyone referred to Columbia in the clinical trial group was from an outside clinic. Hence, it was hard to collect reliable information regarding the total number of BCG instillations and the exact point at which patients failed or the type of BCG failure experienced. Furthermore, many of the trials that were recruiting at the time enrolled patients who had a specific high functional status, and each clinical trial had different follow-ups and protocols. Hence, these protocols might have created a selection bias for patients who overall were less frail than those not enrolled in a clinical trial. However, there were no differences in CCI or age between the groups, indicating that frailty was not a difference between the populations.

Conclusion

Clinical trials are important for the advancement of medicine and treating diseases like BCG refractory bladder cancer for which we have few treatments or for which the consequences of said treatments are too risky to implement. We show here that our patients benefitted from clinical trial enrollment in terms of cancer specific survival and overall survival but did not differ with regards to time to disease recurrence. Nevertheless, caution must be exerted as these findings may not be applicable to other institutions,

and they need to be investigated with more patients over a much longer time span across the country.

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Conflicts of Interest
This author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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