Do we have all the facts to determine the impact of bacillus Calmette-Guérin therapy on bladder cancer?

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Patients with intermediate to high risk non-muscle invasive bladder cancer (NMIBC) as defined by the European Organization of Research and Treatment of Cancer (EORTC) risk tables have an increased risk of recurrence and progression (1). Intravesical bacillus Calmette-Guérin (BCG) immunotherapy is widely used to treat high risk NMIBC. This therapy has been in clinical practice for over 40 years (2). However, there is still debate on the dose, duration and strain of BCG that is best suited for clinical therapy (3,4). Several meta-analysis of BCG clinical trials have generally agreed that BCG immunotherapy reduces recurrence (5) but there are some doubts of its impact on progression and cancer specific death (6). The heterogeneity of study populations, BCG strains, dosage, frequency of therapy and staging of tumors place limitations on the conclusions drawn from these studies.

The manuscript by Thiel *et al.* (7), evaluates the long-term outcomes of BCG immunotherapy for bladder cancer and compares it to the outcomes for patients who did not receive BCG immunotherapy. This manuscript evaluates high-risk NMIBC patients [140] recruited between Jan 1995 to Dec 1996 from Stockholm County, 82 received BCG immunotherapy and 57 did not. Both groups were similar in terms of the number of tumors and size of tumors but the cohort that received BCG therapy were significantly younger and included cases with carcinoma in situ (CIS) and had more high-grade tumors. The authors had 15 years of follow-up data for these patients and used this to determine if BCG therapy is associated with reduced recurrence, progression and cancer specific mortality (CSM). The length of follow-up data is impressive but unfortunately, the issue of the type and duration of maintenance therapy was not available. This is an expected problem with retrospective studies where the information available is variable as there was no original plan to collect all required data.

The incidence of recurrence in the BCG treated cohort (42.7%) and in the non-BCG treated cohort (71.9%) was significantly different. In the cohort that did not receive BCG therapy all recurrences occurred early within a little over 3 years of diagnosis. Therefore, BCG did increase recurrence free survival. Similarly, for progression in the BCG treated cohort (25.6%) and in the non-BCG treated group (50.9%). After excluding patients with primary CIS there was still a significant difference in recurrence and progression. However, adjustments for age and stage resulted in an absence of significance for progression. There was reduced CSM in BCG treated (19.5%) versus non-BCG treated group (29.0%) but this difference was not significant when adjusting for age, stage, tumor size and number of tumors.

The long follow-up period means that it is possible to determine the validity of the EORTC risk tables. The EORTC guidelines state that 80–85% of high-risk patients will progress to muscle invasive disease within 48 months (1). Cancer specific death at 5 years was 21% and was similar to the data at 48 months. At 10 years it was 26.6% and at 15 years was 27%. So, most deaths related to bladder cancer occurred within the first 5 years.

Progression is broadly defined to include changes in stage and grade as well as muscle invasive and metastatic disease. Previous comparisons of cancer specific survival (CSS) have evaluated populations with disease progression versus those with muscle invasive bladder cancer (MIBC) (6). This comparison is based on the assumption that progression leads to the development of metastatic disease but MIBC does not always develop from NMIBC. In this manuscript by Thiel *et al.*, CSM was compared between two cohorts of patients with high risk NMIBC, one that received BCG and one that did not. However, there are differences in bladder cancer stage and grade and the majority of CIS patients received BCG therapy. This may have led to the lack of difference between the groups for CSM. However, it may be a true outcome that while BCG may reduce recurrence and progression it may not have an effect on CSM.

BCG induces both non-specific and specific effects. Non-specific effects would not protect against progression and CSM though they could induce the removal of remnant tumor cells, the proposed cause of recurrence. Specific responses may be effective against recurrence of the original tumor only. If BCG has an effect on progression, it should translate to reduced death from metastatic cancer. To have an impact on the development of metastatic disease BCG would have to induce long-term immunity to the tumor cells. This has been difficult to demonstrate in man primarily because of the absence of good tumor markers. Recent studies have identified a few markers associated with bladder tumors (8). Evaluating responses to these markers pre and post therapy would be useful. Another problem is that assays to confirm that BCG has induced effective immune activation in all patients are not routinely performed. Biot *et al.* showed that parenteral exposure to BCG could boost the host response to BCG in patients who do not respond to purified protein derivative (9). In the absence of data on immune parameters, it is uncertain if systemic immune activation is induced and if it is not induced then it is unlikely that BCG could reduce CSM.

Another possible reason that BCG could have an impact on progression and not CSM could be due to circulating tumor cells (CTC). All tumors release CTC even when they are not invasive. But only a very small proportion of released CTC are successful in developing a tumor at a secondary site. A study by Rink *et al.* showed that perioperative CTC were present even in patients with non-metastatic urothelial carcinomas and their presence was associated with the increased likelihood of reduced CSS (10). The tumor cells that develop at metastatic sites may have already implanted there before the patients received BCG therapy. Successful colonization of new sites would require further molecular changes in the tumor cells, which may result in the expression of different tumor antigens. Thus, immunity engendered against the original tumors would not be effective against the metastatic tumors even if systemic immune activation was induced.

Reappearance of tumors in initial responders to BCG therapy are taken to be recurrent disease even when recurrence happens after several years. In the absence of molecular markers, it cannot be determined if these are true recurrence of the original tumor or *de novo* tumors. Similarly for tumor progression. This adds another layer of uncertainty that makes it difficult to determine if BCG impacts recurrence, progression and CSM. Recent studies have identified tumor markers related to tumor types and these may in future help to ascertain the source of tumors. Several markers have been used to improve NMIBC risk analysis for disease progression (11). Gene signatures that correlate with disease stage, CIS and progression (12) have been validated. Besides their predictive value, these gene signatures could be used to determine whether the tumors that appear after therapy are true recurrence or *de novo* tumors. Bladder cancer is already one of the most expensive cancers to manage and additional assays may increase the cost further. But they may also reduce cost by identifying patients who would benefit from other novel therapies based on their gene signature.

Bladder cancer is most common in aged subjects. Thus, mortality could also be due to co-morbidities, which may temper the implementation of treatment such as maintenance schedules. Thus, not surprisingly BCG may not appear to have an impact on CSM. So, while long-term follow-up may not be able to determine the impact of BCG therapy on CSM it is still valuable as it highlights the benefits of BCG therapy in responders.

Acknowledgements

Footnote

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