An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus Bacillus Calmette-Guerin for non-muscle-invasive bladder cancer


CRD summary
This individual patient data meta-analysis concluded that maintenance BCG was superior to mitomycin C in reducing recurrence of bladder cancer. Overall, the results appear reliable although they were based on studies with differing patient characteristics, treatment regimens and follow-up schedules.

Authors' objectives
To compare the effectiveness of bacillus Calmette-Guérin (BCG) and mitomycin C as adjuvant intravesical therapy after surgery in patients with non-muscle invasive bladder cancer.

Searching
PubMed and CancerLit were searched. Search terms and dates were not specified. Meeting abstracts and proceedings were handsearched. Trial investigators and unspecified organisations were contacted.

Study selection
Randomised trials that compared transurethral resection and mitomycin C to transurethral resection and BCG in patients with non-muscle invasive bladder cancer were eligible for inclusion. The primary end point was time to first recurrence in the bladder irrespective of stage or grade. Secondary end points were time to progression to muscle-invasive disease, duration of overall survival and cancer-specific survival.

Seventy-one per cent of included patients had primary bladder cancer, 54% had carcinoma in situ (Ta), 43% had early stage cancer (T1), 25% were low grade (G1), 58% were moderately differentiated (G2) and 16% were high grade (G3). Median follow-up was 4.4 years. Seven per cent of patients had prior intravesical chemotherapy. Doses and duration of treatment varied.

The authors did not report how many reviewers performed the study selection.

Assessment of study quality
Individual patient data were compared to data abstracted from the most recent publications and checked for consistency. Discrepancies were resolved after discussion with the trialists.

The authors did not report how many reviewers performed the study validity assessment.

Data extraction
Individual patient data were collated for each primary and secondary end point based on time to event. It was unclear whether or not data were compiled based on intention-to-treat. It was unclear how any missing data were handled.

Methods of synthesis
Two stage common effect analyses were used to combine time to event data for time to first recurrence based on Kaplan-Meier or cumulative incidence functions. Exploratory subgroup analyses were undertaken on seven subgroups. These included BCG maintenance and BCG maintenance with and without prior chemotherapy, which were tested for interaction with treatment effects.

Results of the review
Nine trials (2,820 patients) were included in the analyses of recurrence.
There was no overall difference in the risk of time to first recurrence between BCG and mitomycin C. Exploratory subgroup analysis illustrated a 32% (95% CI 25% to 39%) reduction in risk with BCG compared to mitomycin C. No maintenance resulted in a 28% (95% CI 18% to 38%) increase in risk with BCG compared to mitomycin C (test for interaction, $X^2 = 28.1, p<0.0001$). BCG with maintenance was more effective than mitomycin C irrespective of previous chemotherapy regimen (prior chemotherapy $p=0.026$ and no prior chemotherapy $p=0.0003$).

Seven trials (1,880 patients) included data on time to progression to muscle-invasive disease, duration of overall survival and cancer-specific survival.

Twelve per cent of patients progressed to muscle-invasive disease (median follow up 4.8 years) with 24% mortality. Death was due to bladder cancer in 30% of patients. No statistically significant results between treatments were found for these long-term end points.

**Authors' conclusions**

Maintenance BCG was more effective than mitomycin C for prevention of bladder cancer recurrence. There were no statistically significant differences between BCG and mitomycin C regarding progression, overall survival and cancer-specific survival.

**CRD commentary**

The authors of this individual patient data meta-analysis used a range of search methods to identify studies. Exact search terms and dates were not reported. The authors did not report how many reviewers performed the study selection, so the possibility of error and bias could not be discounted. Individual patient data were obtained for all eligible trials, which reduced the risk that reporting biases might result in discrepancies between analyses based on aggregate data and analyses based on individual patient data.

Analyses were conducted appropriately. Overall, the results appear reliable although they were based on studies with differing patient characteristics, treatment regimens and follow-up schedules. As noted by the authors, the analysis was likely to be underpowered to detect differences in the outcomes of progression, overall survival and cancer-specific survival.

**Implications of the review for practice and research**

**Practice**: Maintenance BCG should be standard treatment for high-risk populations. Intermediate risk groups should consider treatment based on mitomycin C with failures switched to BCG.

**Research**: Optimal strain, dosing volume and duration of maintenance of BCG deserved further study.

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