



TITLE: Decreased Dosing of Bacillus Calmette-Guérin for Bladder Cancer: Clinical Effectiveness, Safety, and Guidelines

DATE: 24 September 2014

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of using one-third of the recommended dose of bacillus Calmette-Guérin for the treatment of adult patients with bladder cancer?
2. What are the evidence-based guidelines regarding the reconstitution of bacillus Calmette-Guérin?

KEY FINDINGS

Three randomized controlled trials, one non-randomized study, and one evidence-based guideline were identified regarding decreased dosing of bacillus Calmette-Guérin for the treatment of adult patients with bladder cancer. No evidence-based guidelines were identified regarding the reconstitution of bacillus Calmette-Guérin.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 9), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and September 21, 2014. Internet links were provided, where available.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

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Table 1: Selection Criteria

Population	Adult patients with bladder cancer
Intervention	Bacillus Calmette-Guérin (doses less than 81 mg)
Comparator	No comparator
Outcomes	Clinical benefit (cure rate, progression of cancer, recurrence of cancer, safety) Guidelines and recommendations (appropriate location to perform reconstitution of biohazard)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

Three randomized controlled trials, one non-randomized study, and one evidence-based guideline were identified regarding decreased dosing of bacillus Calmette-Guérin for the treatment of adult patients with bladder cancer. No evidence-based guidelines were identified regarding the reconstitution of bacillus Calmette-Guérin.

Additional references of potential interest are provided in the appendix.

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

1. Brausi M, Oddens J, Sylvester R, Bono A, van de Beek C, van Andel G, et al. Side effects of Bacillus Calmette-Guerin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. *Eur Urol.* 2014 Jan;65(1):69-76.
[PubMed: PM23910233](#)
2. Gontero P, Oderda M, Mehnert A, Gurioli A, Marson F, Lucca I, et al. The impact of intravesical gemcitabine and 1/3 dose Bacillus Calmette-Guerin instillation therapy on the quality of life in patients with nonmuscle invasive bladder cancer: results of a prospective, randomized, phase II trial. *J Urol.* 2013 Sep;190(3):857-62.
[PubMed: PM23545101](#)
3. Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary

bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur Urol.* 2013 Mar;63(3):462-72.
[PubMed: PM23141049](#)

Non-Randomized Studies

4. Bazarbashi S, Soudy H, Abdelsalam M, Al-Jubran A, Akhtar S, Memon M, et al. Co-administration of intravesical bacillus Calmette-Guerin and interferon alpha-2B as first line in treating superficial transitional cell carcinoma of the urinary bladder. *BJU Int.* 2011 Oct;108(7):1115-8.
[PubMed: PM21332904](#)

Guidelines and Recommendations

5. Babjuk M, Burger M, Zigeuner R, Shariat S, Van Rhijn B, Compérat E, et al. Guidelines on non-muscle-invasive bladder cancer (TaT1 and CIS) [Internet]. Arnhem (The Netherlands): European Association of Urology (EAU); 2013 Mar [cited 2014 Sep 23]. 42 p. Available from: http://www.uroweb.org/gls/pdf/05_TaT1_Bladder_Cancer_LR.pdf
See: 7.2.4 Optimal Dose of BCG, page 23

PREPARED BY:

Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

APPENDIX – FURTHER INFORMATION:**Randomized Controlled Trials***Other Quantity of Low Dose*

6. Inamoto T, Ubai T, Nishida T, Fujisue Y, Katsuoka Y, Azuma H. Comparable effect with minimal morbidity of low-dose Tokyo 172 strain compared with regular dose Connaught strain as an intravesical bacillus Calmette-Guerin prophylaxis in nonmuscle invasive bladder cancer: Results of a randomized prospective comparison. *Urol Ann* [Internet]. 2013 Jan [cited 2014 Sep 23];5(1):7-12. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3643329>
[PubMed: PM23662001](#)
7. Kamel AI, El Baz AG, bdel Salam WT, El Din Ryad ME, Mahena AA. Low dose BCG regimen in T1 transitional cell carcinoma of the bladder: long term results. *J Egypt Natl Canc Inst.* 2009 Jun;21(2):151-5.
[PubMed: PM21057566](#)

Review Articles

8. Brausi M, Olaru V. Management of high-risk non-muscle invasive bladder cancer. *Minerva Urol Nefrol.* 2012 Dec;64(4):255-60.
[PubMed: PM23288212](#)
9. Hilton WM, Ercole B, Parekh DJ, Sonpavde G, Ghosh R, Svatek RS. Efficacy of combined intravesical immunotherapy and chemotherapy for non-muscle invasive bladder cancer. *Expert Rev Anticancer Ther.* 2011 Jun;11(6):949-57.
[PubMed: PM21707292](#)
10. Sylvester RJ. Bacillus Calmette-Guerin treatment of non-muscle invasive bladder cancer. *Int J Urol.* 2011 Feb;18(2):113-20.
[PubMed: PM21091799](#)
11. Saad Aldousari, Wassim Kassouf. Update on the management of non-muscle invasive bladder cancer. *CUAJ* [Internet]. 2010 [cited 2014 Sep 23];4(1):56-64. Available from: <http://journals.sfu.ca/cuaj/index.php/journal/article/view/777/570>
See: Treatment schedules, page 60
12. Kenneth G. Nepple, MD; Michael A. O'Donnell. The optimal management of T1 high-grade bladder cancer. *CUAJ* [Internet]. 2009 [cited 2014 Sep 23];3(6 suppl. 4):s188-92. Available from: <http://journals.sfu.ca/cuaj/index.php/journal/article/view/1194/985>
See: Intravesical immunotherapy, page S190

Other Quantity of Low Dose

13. Zhu S, Tang Y, Li K, Shang Z, Jiang N, Nian X, et al. Optimal schedule of bacillus calmette-guerin for non-muscle-invasive bladder cancer: a meta-analysis of comparative studies. *BMC Cancer* [Internet]. 2013 [cited 2014 Sep 23];13:332. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3722001>

[PubMed: PM23829273](#)

Draft Recommendations

14. National Collaborating Centre for Cancer. Bladder cancer: diagnosis and management evidence review [draft on the Internet]. London: National Institute for Health and Care Excellence (NICE); September 2014 [cited 2014 Sep 23]. Available from: <http://www.nice.org.uk/guidance/qid-cqwave0600/resources/bladder-cancer-evidence-review2>
(NICE Guidance on bladder cancer is expect in Feb 2015)
See: Dose of BCG, page 263, 268, 269; Ojea study, page 333-334; Oddens study, page 335-336; Table 90, page 453; Brausi study, page 463