BC Cancer Protocol Summary for Therapy for High or Intermediate Risk Non-Muscle Invasive Bladder Cancer using BCG

Protocol Code	*GUBCG*
Tumour Group	*Genitourinary*
Contact Physician	*Dr. Peter Black*

ELIGIBILITY:

- Urothelial carcinoma of the bladder
  - Squamous differentiation, glandular differentiation and nested variant should be treated the same as conventional urothelial carcinoma
- Any of the following uses:
  - Carcinoma in situ (CIS)
  - Therapy of truly unresectable Ta (papillary urothelial carcinoma)
  - Prevention of recurrence/progression of resected T1 disease (superficial invasion of submucosa)
  - Prevention of recurrence/progression of resected high grade Ta
  - Prevention of recurrence of resected multifocal or recurrent or large (>3cm) low grade Ta tumour

Note:
- Brand selection based on product availability and physician's discretion
- Treatment is permitted for relapse:
  - After previous chemotherapy
  - After previous BCG if the patient does NOT meet criteria for BCG-unresponsive high-risk non-muscle bladder cancer (i.e. "BCG-exposed").
  - BCG-unresponsive is defined as:
    - Recurrent/persistent high-grade Ta tumour within 6 months of last dose of BCG after induction and at least one round of maintenance BCG;
    - Recurrent/persistent CIS within 12 months of last dose of BCG after induction and at least one round of maintenance BCG;
    - Recurrent/persistent high-grade T1 tumour within 6 months of last dose of BCG after induction BCG.

EXCLUSIONS:

Any of the following:
- Presence of non-urothelial histology including small cell/neuroendocrine carcinoma, squamous cell carcinoma or adenocarcinoma
- Micropapillary, sarcomatoid or plasmacytoid histology (patients should be considered for immediate cystectomy)

- Urothelial carcinoma of the prostatic urethra (patients should be considered for immediate cystectomy)
- Muscle invasive bladder cancer
- BCG-unresponsive high-risk non-muscle invasive bladder cancer as defined above
  - Note: positive urine cytology alone may be originating in the upper tracts or prostatic urethra and does not necessarily constitute failure but requires specific management
- Ongoing gross hematuria
- TURBT or urethral trauma within 2 weeks
- Concurrent systemic corticosteroids or a specific immunodeficiency syndrome
- Inability to hold BCG in the bladder for one hour

TESTS:

- Pre-treatment:
  - Urine cytology
  - Cystoscopy with biopsy or resection to confirm histologic diagnosis
  - Resection of all visible papillary disease if possible
  - Upper tract assessment (CT-IVP, MR-Urogram or retrograde ureteropyelogram)
- Post-treatment:
  - Cystoscopy and urine cytology 4-6 weeks after the last dose of BCG and at regular intervals thereafter

TREATMENT:

Induction:
Select one of the following BCG strains based on availability:

Drug*	Dose**	BC Cancer Administration Guideline
BCG (ONCOTICE)	50 mg (1 vial)	Intravesically diluted in normal saline up to 45 mL Administer instillation into bladder via catheter (dwell time of 1-2 hours)
BCG (VERITY-BCG)	80 mg (2 vials)	Intravesically diluted in normal saline up to 45 mL Administer instillation into bladder via catheter (dwell time of 1-2 hours)

*BCG strain: The reimbursable strain and supplier may change from time to time. Contact a BC Cancer Centre pharmacy, if necessary. BCG (ONCOTICE) = Tice strain; BCG (VERITY-BCG) = Russian BCG-I strain. A patient would ideally receive all induction and maintenance therapy with the same strain, but switching strains is recommended if necessary to ensure administration of full dose according to conventional dosing schedule.

**The full dose (mg) will depend on the reimbursable product and is supplied in vials - i.e. BCG (ONCOTICE) 50 mg (1 vial); BCG (VERITY-BCG) 80 mg (2 vials).

- **Induction:** weekly for 6 doses

- Patients with recurrent or persistent Ta tumour or CIS after induction BCG should receive the first cycle of maintenance BCG or a second 6-week induction course after resection of all visible papillary tumour.

Maintenance:

Select one of the following BCG strains based on availability:

Drug*	Dose**	BC Cancer Administration Guideline
BCG (ONCOTICE)	50 mg (1 vial)	Intravesically diluted in normal saline up to 45 mL Administer instillation into bladder via catheter (dwell time of 1-2 hours)
BCG (VERITY-BCG)	80 mg (2 vials)	Intravesically diluted in normal saline up to 45 mL Administer instillation into bladder via catheter (dwell time of 1-2 hours)

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- **Maintenance:**
  - High risk: weekly for 3 consecutive weeks at 3, 6, 12, 18, 24, 30, 36 months
  - Intermediate risk: weekly for 3 consecutive weeks at 3, 6,12 months

DOSE MODIFICATION:

- Some symptoms of cystitis are to be expected. If these are severe, exclude non-BCG bacterial infection and wait 1-4 weeks until symptoms improve, then continue with a dose reduction
  - BCG (ONCOTICE): 1/3 vial (17 mg)
  - BCG (VERITY-BCG): 1 vial (40 mg)
- The dose-response relationship of BCG is unclear. The dose should never be increased beyond full dose.

PRECAUTIONS:

1. Patients should be advised to minimise oral fluids (especially those containing caffeine) for 6-8 hours before each treatment to minimise dilution of drug in the bladder.

2. Patient may experience some bladder irritation, with more frequent or painful urination, urination at night and some blood or tissue in the urine
3. BCG is a live bacterial preparation. If patients experience persistent fever with or without a pulmonary infiltrate, systemic BCG infection, should be suspected.[6]

Call tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Alexandroff AB et al. BCG immunotherapy of bladder cancer: 20 years on. Lancet 1999;353:1689-94.
2. Herr HW et al. Intravesical BCG therapy prevents progression and death from superficial bladder cancer. J Clin Oncol 1995;13:1404-8.
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4. Lamm DL et al. Maintenance BCG of superficial bladder cancer: a randomized prospective SWOG study. Proc ASCO 1992;11:203, A627.
5. Lamm DL et al. Megadose vitamins in bladder cancer: a double-blind clinical trial. J Urol 1994;151:21-6.
6. Lamm DL, et al. Maintenance BCG immunotherapy for recurrent Ta, T1 and CIS transitional cell carcinoma of the bladder: a randomized SWOG study. J Urol 2000; 163: 1124-9.
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8. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancer 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 maintenance. Eur Urol 2013;63:462–72.
9. Pagano F, Fair WR (eds). Superficial bladder cancer. Isis (Oxford) 1997. 228 pp.