

Intravesical Therapy for Bladder Cancer

**Norm D. Smith, M.D.
Chief of Urologic Oncology
Department of Urology
Northwestern University
Feinberg School of Medicine**

The Problem

- **Bladder cancer**

- **Superficial disease – 60-80% chance of recurrence at 5 years with surgery alone**
- **Exception – first time, solitary, small, TaG1 papillary tumors**

(Millan-Rodriguez et al. JUrol 2000)

The Bigger Problem

- **Aside from recurrent disease**
 - T1
 - High grade
 - Carcinoma-in-situ (CIS)
- **Progression to Muscle Invasive Bladder Cancer**

Initial Management

- TURBT – complete endoscopic resection with sampling of muscle (2nd look procedures for T1 disease)
- Perioperative intravesical cytotoxic chemotherapy (within 6 hours)
 - Low-risk patients – 40% decreased odds of recurrence
 - Multiple tumors – 56% decrease
(Sylvester et al. JUrol 2004)

Perioperative intravesical cytotoxic chemotherapy

- Mitomycin C
- Doxorubicin
- Epirubicin
- Pirarubicin
 - Seem equally effective
- Not Thiotepa, IFN or BCG
- Treatment not safe with suspected perforation, large resection beds and bleeding

Perioperative Intravesical Mitomycin C

- **Within 6 hours but best immediately**
- **Side Effects (roughly 5%)**
 - Severe reactive cystitis
 - Skin rash
 - Calcified scar at large resection site
- **Significantly Underutilized**
 - multifactorial

Choices For Adjuvant Intravesical Therapy

- **Chemotherapy – reasonable for low-to-intermediate risk groups (not T1, G3 or CIS)**
 - Fewer side effects
 - Much more popular in Europe
 - Failure does not affect future response to BCG
 - Usually 6-8 weekly treatments
 - Optimization strategies can double tumor-free rate (Au et al. JNCI, 2001)

Choices For Adjuvant Intravesical Therapy

- Immunotherapy – reasonable for low-to-intermediate risk, superior for high-risk groups
- Bacillus Calmette-Guerin (BCG)
 - Developed as vaccine to Mycobacterium bovis, an organism similar to the one that causes TB
- Induces immune response
 - Exact reason for this is unclear

BCG Immunotherapy

- Usually 6 weekly treatments starting 2-4 weeks after endoscopic resection
- Optimization strategies
- Repeat 6-week course for non-progressing patients with first failure
- 1 year of maintenance therapy

BCG Immunotherapy

- 70% response rate with CIS
- Especially effective versus chemo in chemotherapy failures
- Overall, BCG twice as effective as chemotherapy regarding recurrence, also prevents progression (2 meta-analyses)
- No proof of survival advantage (O'Donnell, Urol Clin N Am, 2005)

Contraindications for BCG Immunotherapy

- Blood in urine – may lead to BCG sepsis
- Traumatic catheterization
- High fever
- UTI
- Immunosuppression
- Previous bad reaction to BCG

BCG Immunotherapy

- **Common Side Effects – resolve in 24-48 hr**
 - Burning with urination
 - Blood in urine
 - Flu like symptoms
 - Low grade fever
- **Rare side effects**
 - High Fever
 - Systemic infection (0.4%)

Maintenance Therapy Intravesical Chemotherapy

- **Additional treatments when in complete clinical remission**
- **Attempt to prevent new cancers and get rid of cancers too small for detection**
- **Usually monthly therapy**
- **Controversial with conflicting studies**

Maintenance Therapy

Intravesical BCG

- Various regimens but maintenance BCG clearly superior to non-maintenance (Lamm et al. JUrol, 2000)
- Problems
 - 25% with grade 3 toxicity
 - Less than half had more than 3 cycles
 - 16% completed the maintenance regimen
 - No proof of survival advantage

Intravesical Failures

- **Chemotherapy failures - BCG**
- **BCG failures – controversial**
 - **2nd course of BCG – more than 2 with very low success rates**
 - **Early cystectomy – high-risk patient (multifocal T1G3 or CIS)**
 - **Intravesical chemotherapy – poor results**
 - **Salvage intravesical therapy**

Salvage Intravesical Therapy

- **IFN**
 - well tolerated, dose-dependent with 12-20% response rates
- **BCG + IFN**
 - 1-2 year success rates of 50-60%, improved with 2nd course and maintenance
- **New intravesical chemotherapeutics**
 - Valrubicin – 8% durable response, 90% side effects
 - Gemcitabine – promising data, not FDA approved
 - Taxanes (Paclitaxel and Docetaxel)

Emerging Intravesical Therapies

- Chemothermotherapy – Mitomycin C with local hyperthermia using microwave antennae on Foley catheter
- Electromotive Mitomycin C – with 20 mA of electric current
- Photodynamic therapy – using 5-aminoleulinic acid or the newer hypericin
- All are investigational

Take Home Messages

- Complete TURBT with 2nd resection for T1 disease if bladder sparing strategy
- One dose of perioperative Mitomycin C
- Adjuvant Induction BCG for intermediate and high-risk groups
- 1 year of maintenance BCG
- 2nd course of BCG for non-progressing failures
- Consider salvage intravesical therapy for non-progressing recurrent failures
- Early cystectomy for high-risk failures (T1G3, CIS)