BCG-Refractory NMIBC Treatment: Present and Future

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Outline

• Definitions
• Evaluation
• Treatment
  • Surgery
  • Chemoradiation
  • Chemotherapy
  • Immunotherapy
• Future Directions
BCG

• First reported by Morales et al. in 1976

• Superior to chemotherapy in both recurrence and progression
Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline

Intravesical Therapy; BCG/Maintenance; Chemotherapy/BCG Combinations

15. In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

16. In a low-risk patient, a clinician should not administer induction intravesical therapy. (Moderate Recommendation; Evidence Strength: Grade C)

17. In an intermediate-risk patient a clinician should consider administration of a six-week course of induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

18. In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should administer a six-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)

19. In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)

20. In an intermediate-risk patient who completely responds to induction BCG, a clinician should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)

21. In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)
63yo M with history of HGT1. He undergoes BCG induction. During his first surveillance, a bladder tumor is noted and found to be HGTa. How would you describe this patient?

A. Inadequate BCG
B. BCG intolerant
C. BCG refractory
D. BCG relapsing
E. BCG unresponsive
Adequate BCG
Adequate BCG

- 6 week induction + 3 week maintenance
  - SWOG protocol: 3, 6, 12, 18, 24, 30, 36 months
- “Adequate BCG” clinical trial design standpoint
  - At least 5 of 6 intended weekly induction treatments (one induction course) +
  - At least 2 additional weekly maintenance treatments or a second re-induction in a 6-month time period

Kamat et al, 2016 J Clin Oncol 34: 1935-1944
• Intolerant
• Refractory
• Relapsing
• Unresponsive
BCG Terminology

• BCG Intolerant
  • Cannot receive due to treatment-related adverse effects

• BCG Refractory
  • Persistent high grade cancer 6 months after start of induction therapy OR
  • Progresses grade/stage 3 months after start of induction

• BCG Relapsing
  • Recurrence after achieving disease-free state at 6 months

• BCG Unresponsive
  • Combination of BCG refractory + BCG relapsing whose tumors recur within 6 months of last BCG exposure (early)

Kamat et al, 2016 J Clin Oncol 34: 1935-1944
Cystectomy preferred option
Repeat BCG induction or intravesical chemo viable option for intermediate risk disease

Best option might be repeat induction BCG but cystectomy also indicated

Radical cystectomy
No additional BCG
Consider clinical trials
• Optimally stage
• Evaluate sanctuary sites
  • Prostatic urethra
  • Upper urinary tract
Surgical Options for BCG-Refractory NMIBC

When?
Why?
Surgical Options

DOES EARLY CYSTECTOMY IMPROVE THE SURVIVAL OF PATIENTS WITH HIGH RISK SUPERFICIAL BLADDER TUMORS?

HARRY W. HERR AND PRAMOD C. SOGANI

From the Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York
Group 1 (n=61): BCG with or without IFN
Group 2 (n=56): At least 1 additional salvage IVC after BCG

Risk Factors for ACM:
- Upstaging to T1
- LN invasion
- + Prostatic urethral
Immediate cystectomy not mandatory if expeditious cystectomy after salvage attempt

Staging is critical
Chemo-Radiation
A Randomized Trial of Radical Radiotherapy for the Management of pT1G3 NXM0 Transitional Cell Carcinoma of the Bladder


From the Institute of Urology and Department of Oncology, University College London (SJH) and Cancer Group, Medical Research Council Clinical Trials Unit (SC, TB, MKBP, GOG), London, Department of Urology, University Hospital of Wales, Heath Park, Cardiff (HK), Department of Pathology, Western General Hospital, Edinburgh (KG), Department of Urology, Queen Elizabeth Hospital, Birmingham (DMW), Department of Urology, Royal Shrewsbury Hospital, Shrewsbury (CB), and Department of Urology, Leicester General Hospital, Leicester (RK)

• Group 1: New HGT1, no CIS
  - Observation vs. radiotherapy

• Group 2: CIS
  - Intravesical therapy vs. radiotherapy

No difference between radiotherapy and conservative management in progression, recurrence or survival
Non-randomized CR achieved in 88%
70% “pleased” or “delighted” with urinary function
80% preserved bladder
RTOG 0926: A PHASE II PROTOCOL FOR PATIENTS WITH STAGE T1 BLADDER CANCER TO EVALUATE SELECTIVE BLADDER PRESERVING TREATMENT BY RADIATION THERAPY CONCURRENT WITH RADIOSENSITIZING CHEMOTHERAPY FOLLOWING A THOROUGH TRANSURETHRAL SURGICAL RE-STAGING

- Single arm study to evaluate chemoradiation in patients with HGT1 UCC bladder
- Primary endpoint: Radical cystectomy rate at 3 years
- Accrual is closed, estimated completion 2023
Chemo after BCG Failure
Valrubicin

- Only approved intravesical agent for BCG-Refractory CIS when cystectomy not an option
- Single-arm study of patients with BCG Failure
  - 70% with >=2 prior BCG courses
  - 81% with 3-24mo interval between last tx and valrubicin
  - Unclear % BCG unresponsive
- Primary outcomes DFR 6 months = 21%
- Suboptimal salvage therapy for BCG failure

Steinberg et al, J Urol, 2000
• Single arm study, 55 patients
• 2g gemcitabine/100cc NS
  • Weekly x 6
  • Maintenance: monthly x 1
  • Dwell time: 1hr

BCG Failure: Gemcitabine
Intravesical gemcitabine may be better than BCG for Refractory NMIBC
BCG Failure: Nab-Paclitaxel

- Prospective single institution: 28 patients
- Regimen:
  - Nab-Paclitaxel 500mg/100ml NS
  - Induction weekly x 6
  - Maintenance monthly x 6
RFS
3mo: 36%
12mo: 36%
Mean f/u: 21mo

Toxicity
9/28 (32%) grade 1-2
NO discontinuation of therapy

McKiernan et al. J Urol 2014:1633
BCG Failure: Combo Chemo

- Retrospective case series: 45 patients
- Regimen:
  - Gemcitabine 1g/50cc NS x 90min
  - Followed by docetaxel 37.7mg/50ml NS x 2hrs
  - Induction weekly x 6
  - Maintenance monthly x 24
Sequential Intravesical Gemcitabine and Docetaxel for the Salvage Treatment of Non-Muscle Invasive Bladder Cancer

40/45 (89%) tolerated full induction
28/45 (62%) with symptoms during induction
7/45 (16%) impacted treatment schedule

RFS
3mo: 66%
12mo: 54%
24mo: 34%
BCG Failure: Combo Chemo

Multi-institutional retrospective series: 47 patients

Regimen:
- Gemcitabine 1g/50cc NS x 90min
- Followed by MMC 40mg/20ml NS x 90min
- Induction weekly x 6
- Maintenance monthly x 12
• 87% high grade
• Median # prior tx: 2
  • 55% ≥ 2 prior tx
• 30% grade 1-2 toxicity
  • 4/47 (9%) discontinued induction

Lightfoot et al. Urol Oncol 2014:35.e15
Immunotherapy

- BCG
- Interferon
- Emerging Therapies
Repeat BCG

• Persistent disease after single induction course, repeat induction
  • 43-63% response rate
• Additional \( \geq 3 \) courses not recommended
  • 20% response rate
  • 80% rate of progression/metastasis
  • Increased toxicity

Bui, *Urology* 1997:49
BCG + Interferon

- Large non-randomized phase 2
  - Group 1- BCG Failure (n=467)
    - 1/3D BCG + 50m u INF-α (+maintenance)
  - Group 2- BCG Naive (n=536)
    - FD BCG + 50m u INF-α (+maintenance)

Joudi et al. Urol Oncol 2006:344
BCG + Interferon

- Consideration for BCG failure after 1 course (HR 1.5 for failure after ≥2 courses)
- Not directly compared to BCG re-induction alone
- Multiple design concerns (BCG naïve patients)

Joudi et al. Urol Oncol 2006:344
BCG + Interferon

• Further data demonstrate that BCG-IFN no more effective than BCG alone\(^1\)

• Response rate at 24 months 23% for truly BCG unresponsive disease\(^2\)
  • Similar to historic BCG rates

• Bottom line: **BCG+IFN has a limited role** in treatment of BCG refractory NMIBC

\(^1\) Nepple, J Urol 2010; 184.
\(^2\) Roseveat, J Urol 2011; 186
Emerging Immunotherapies
SWOG S1602 (PRIME)
PI: Rob Svatek

- Intradermal injection to augment BCG response
- Leads to BCG-specific memory T cell response → increased bladder infiltration by cytotoxic CD8+ T cells upon repeated BCG exposure

Randomize CIS, HG TA, or HG T1 bladder cancer

PPD

Prime: intradermal BCG (Tokyo strain 100 µl at 0.5 mg /ml) + Intravesical BCG (Tokyo strain 80 mg/dose)
SWOG 1605
Phase 2 trial of Atezolizumab in BCG-unresponsive NMIBC

- Single agent IV Atezolizumab
  - Antibody targets PD-L1
- BCG unresponsive population
- Building on success seen in metastatic UCC
- Opened first quarter 2017

PI: Peter Black

IMvigor 210: Overall Survival in mUC

- Median OS (95% CI):
  - IC2/3: 11.4 mo (9.0, NE)
  - IC0/1: 6.7 mo (5.4, 8.0)
- 12-month OS (95% CI):
  - IC2/3: 48% (38, 58)
  - IC0/1: 30% (23, 36)
- All: 36% (30, 41)

Median follow up: 11.7 mo (range, 0.2+ to 15.2 mo)
- mOS appears to be longer in patients with higher PD-L1 IC expression
- 12-month OS compares favorably to previous estimates of ≈ 20% in a 2L setting

Hoffman-Censits et al. IMvigor 210, 2016

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Viral Gene Therapy: CG00700

- CG0070 – oncolytic adenovirus
  - Expresses GMCSF transgene
  - Selectively replicates in Rb-deficient cells

- Phase I: 49% RR at 10.4 months
- Phase III: Single arm study, RR at 18 months
  - NCT02365818
  - PD-1 and PD-L1 immunohistochemistry scores of tumor cells and infiltrating immune cells
• Adenovirus vector harboring human IFN alpha2b gene
• Gene incorporated into bladder lining → expression of large amount of protein
• 40 patients
• 35% high-grade 12mo RFS
• No grade 4/5 AE or tx discontinuation
• Phase III trial now completed accrual (n=157)
Future Directions

• Targeted therapy
  • VEGFR3-FGFR3 inhibitor (dovitinib) (NCT01732107)
  • mTOR inhibitor (everolimus) + gemcitabine (NCT01259063)
  • Vicinium (EpCam Ab conjugate)
  • Oral su tinib (NCT 01118351)
  • ALT-801 + gemcitabine (NCT 01625260)

• Drug delivery
  • MitoGel – thermosensitive hydrogel MMC
  • Taris GemRIS
## Ongoing Trials: BCG-Refractory NMIBC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Sponsor</th>
<th>Phase</th>
<th>NCT#</th>
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Take-Home Points

• BCG + maintenance remains first-line standard of care therapy for high risk NMIBC
• Defining BCG unresponsive disease *consistently* is paramount
• Cystectomy is standard of care for BCG unresponsive disease *for now*
• Bladder-preserving regimens available - including intravesical chemo, immunotherapy and radiation
• Large amount of clinical investigation ongoing for improving outcomes for BCG unresponsive patients