What to do after failure of BCG?

Ashish M. Kamat, MD, MBBS, FACS
Professor of Urologic Oncology
Wayne B. Duddlesten Professor of Cancer Research
President, International Bladder Cancer Group
Associate Cancer Center Director, RFHNH
Why is this important?

~ 1.2 Million Doses of BCG used globally for Bladder Cancer
How common is BCG failure?

![Graph showing recurrence-free survival over time for BCG and Epi/Inf arms.]

**Figure 3.** RFS according to randomization arm ($p = 0.001$)

Hemdan et al. J Urol 2014; 191: 1244
Definition of BCG Failure

• Must include clear definition of **ADEQUATE** prior BCG therapy

• BCG Induction (6 weeks) plus at least one course of Maintenance BCG (3 weeks)

• Persistent disease at/after 6 month time point after initiation of therapy
  o Exception Ta/Tis -> T1 at 3 mos

Martin and Kamat, Exp Reviews 2010
Why decision timing is important

260 CIS Patients

114 Induction
6 week BCG

116 Maintenance
6 week BCG

Adapted from Lamm, JU 2000
Why decision timing is important

260 CIS Patients

114 Induction
- 6 week BCG
- 3 month eval
- 58% CR

116 Maintenance
- 6 week BCG
- 55% CR

Adapted from Lamm, JU 2000
Why decision timing is important

Adapted from Lamm, JU 2000

- 260 CIS Patients
  - 114 Induction
    - 58% CR
    - 69% CR (Observation)
  - 116 Maintenance
    - 55% CR

6 week BCG

P=0.7
Why decision timing is important

260 CIS Patients

114 Induction
- 6 week BCG
- 58% CR (P=0.7)
- Observation
- 69% CR

116 Maintenance
- 6 week BCG
- 55% CR (P=0.01)
- 3 week BCG
- 84% CR

6 month eval

Adapted from Lamm, JU 2000
Why decision timing is important

64% of ‘failures’ salvaged with 3 weeks of BCG

Adapted from Lamm, JU 2000
BCG unresponsive NMIBC

- Persistent high grade disease at 6 months cysto after BCG-Unresponsive Nonmuscle Invasive Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment Guidance for Industry
- Progression of disease from Ta/Tis > T1 at 3 mos cysto after BCG alone
- Recurrence of HG disease while on maintenance therapy

Kamat et al, JCO, 2016; Lerner et al, Bladder Cancer, 2016
Definitions, End Points, and Clinical Trial Designs for Non–Muscle-Invasive Bladder Cancer: Recommendations From the International Bladder Cancer Group

Ashish M. Kamat, Richard J. Sylvester, Andreas Böhle, Joan Palou, Donald L. Lamm, Maurizio Brausi, Mark Soloway, Raj Persad, Roger Buckley, Marc Colombel, and J. Alfred Witjes

BCG Unresponsive CIS

- Initial complete response (CR) of **50% at 6 months**; durable response rate of at least **30% at 12 months** and **25% at 18 months**

BCG Unresponsive papillary disease

- Recurrence free rate of **30% at 12 months** and **25% at 18 months**
BCG Unresponsive Non-muscle Invasive Bladder Cancer: Definition, Treatment Options and Management Recommendations from the IBCG

Ashish Kamat¹, Marc Colombel², Debasish Sundi¹, Donald Lamm³, Andreas Boehle⁴, Maurizio Brausi⁵, Roger Buckley⁶, Raj Persad⁷, Joan Palou⁸, Mark Soloway⁹, J. Alfred Witjes¹⁰
High risk NMIBC after TUR (or re-TUR when indicated) → BCG Induction → Tumor recurrence

LG

- ‘Non-event’
- Continue maintenance BCG/surveillance

HG

- Evaluate with axial imaging, consider adjunctive imaging modalities (blue light or narrow band) at cystoscopy, consider prostatic urethral biopsies

Was recurrence at 3 months?

Yes →

No →
Was recurrence at 3 months?

Yes

CIS
Continue BCG (1st maintenance course), re-evaluate at 6 months

TaHG
Discuss option of RC, continue BCG (1st maintenance course), re-evaluate at 6 months

T1HG
Exposure to BCG ≤6 months?

BCG Unresponsive

RC is the only recommended option

If refuses RC, consider clinical trial

If refuses trial, consider enhanced MMC or off-label use of intravesical chemotherapy

No

Received ≥1 BCG maintenance course?

Did not receive maintenance BCG?

Consider repeat induction BCG if >12 months since last exposure or start maintenance if <12 months since last BCG exposure

Early recurrence last exposure to BCG ≤12 months
Intermediate recurrence last exposure to BCG 12-24 months
Late recurrence last exposure to BCG >24 months

Consider repeat induction BCG
Options for Intravesical Therapy after BCG
What About Repeat BCG?
BCG plus interferon-α (INF-α)

Gallagher BL et al, Urology, 2008
Valrubicin

- **FDA approved** in 1998 for BCG-refractory CIS in those who are not candidates for cystectomy

- **CR** at 6 months in **18%** of patients

- **2-year DFS** only **4%**

SWOG S0353 Phase II Gemcitabine

- Minimum of 2 courses of BCG
- Tis, T1, Ta high-grade, or Ta low-grade with >2 lesions
- 2gm Gem weekly x6, monthly to 12 months

2-year DFS only 21%
Sequential Doublet Chemotherapy with Gemcitabine – Mitomycin for HG BCG Refractory Patients (n=47)

Induction weekly X 6 then monthly X 12

≥ 2 prior BCG: 69% CR
RFS: 50% 1yr, 32% 2yr

Independent validation 37% NED at 22 months; n = 27 (Cockerill, BJUI 2015)

Lightfoot, O’Donnell, Urol Oncol 2014
Sequential Gemcitabine-Docetaxel

Patient Characteristics (n =45)
64% CIS; 91% HG
38% BCG Fx1; 53% BCG

Induction weekly X 6 then monthly X 12

BCG naive
1 BCG Failure
≥2 Prior BCG Failures

Percent success
Months

54%
34%
Gemcitabine Docetaxel Regimen

- **Gemcitabine**: 1 g in 50 ml of sterile water via catheter, plugged, and retained for 90 minutes.
- **Docetaxel**: drain bladder, then 37.5 mg of docetaxel in 50 mL of saline is instilled.
- **Catheter removed**, patients are instructed to not urinate for 2 hrs.

1300 mg oral sodium bicarbonate evening prior and morning of treatment to alkalinize their urine.

Prevent some side effects of acidic gemcitabine (pH 2.5); modify for sicker patients with sodium load.

Oral ondansetron prophylactically to patients who report nausea after their first instillation.
Hyperthermic MMC post BCG

- 111 patients with recurrent papillary NMIBC after BCG

DFS estimates:
- 85% and 56% after 1 and 2 years, respectively.
- 38% were BCG refractory and 17% relapsed within 12 mos of BCG

Mycobacterium cell wall-DNA complex

- Reanalysis of subset that was BCG Unresponsive
- 1 yr DFS: 35% in BCG unresponsive vs. 25% overall
  - Papillary: 61% and 51% at 1 & 2 yrs, respectively

Plenary Session EAU 2016; Li & Kamat, Bladder Cancer. 2017;3(1):65
At 12 months: 40 patients (35%) free of high grade disease
- No grade 4/5 AE
- No treatment discontinuation due to AE

Intravesical rAd–IFNα/Syn3 for Patients With High-Grade, Bacillus Calmette-Guerin–Refractory or Relapsed Non–Muscle-Invasive Bladder Cancer: A Phase II Randomized Study


J Clin Oncol, Epub, 2017
Pembrolizumab in Patients With Bacillus Calmette Guérin (BCG)–Unresponsive, High-Risk Non–Muscle-Invasive Bladder Cancer (NMIBC): Phase 2 KEYNOTE-057 Study

Ashish M. Kamat,1 Ronald de Wit,2 Joaquim Bellmunt,3 Toni K. Choueiri,4 Kijoeng Nam,5 Maria De Santis,6 Robert Dreicer,7 Noah M. Hahn,8 Rodolfo Perini,5 Arlene Siefker-Radtke,2 Guru Sonpavde,9 J. Alfred Witjes,10 Stephen Keefe,5 Dean Bajorin11

1The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 2Erasmus MC Cancer Institute, Rotterdam, Netherlands; 3Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; 4Dana-Farber Cancer Institute/Brigham and Women’s Hospital, Boston, MA, USA; 5Merck & Co., Inc., Kenilworth, NJ, USA; 6University of Warwick, Coventry, United Kingdom; 7University of Virginia School of Medicine, Charlottesville, VA, USA; 8Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; 9University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL, USA; 10Radboud University, Nijmegen, Netherlands; 11Memorial Sloan Kettering Cancer Center, New York, NY, USA
Localized UC Registration Trials

NMIBC

- S1602 BCG-prime (TICE/Tokyo +/- SQ BCG) (n=969)
- BCG +/- BC-819 BCG-relapsing (n=470)
- KEYNOTE-057 Pembrolizumab BCG-unresponsive (n=260)
- S1605 Atezolizumab BCG-unresponsive (n=148)
- CG0070 BCG-unresponsive (n=122)
- BC-819 BCG-unresponsive (n=120)
- Instiladrin BCG-unresponsive (n=135)
- Vicinium BCG-unresponsive (n=134)

Slide: Noah Hahn, JHU, Feb 2018
BCG Failure - Summary

• Make sure patient is truly BCG Unresponsive

• Radical Cystectomy treatment of choice
  o recommended by AUA, EAU, IBCG guidelines

• Options for intravesical therapy
  o Combination chemotherapy
  o Hyperthermic chemotherapy

• Enroll in clinical trials!
Thank you!

Ashish M. Kamat, MD, MBBS, FACS
akamat@mdanderson.org
@UroDocAsh