Updates for NMIBC During the BCG Shortage Era

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Country Music Hall of Fame
The Ryman Auditorium
The World Has Changed

RESPONSIBLE RECREATION
COVID-19

KEEP YOUR DISTANCE
Practice proper social distancing with people outside your household.

STAY HOME IF SICK
If you have a fever, respiratory symptoms or are just not feeling well, please stay home.

WEAR A MASK
When entering an indoor space or interacting with others, wear a face covering.

OBSERVE GUIDELINES
When visiting new locations, respect established capacity and safety guidelines.

VANDERBILT DEPARTMENT OF UROLOGIC SURGERY
BCG Shortage: Latest from Merck (Oct 4, 2020)

Merck Announces Plans to Construct New Facility in the United States to Expand Manufacturing Capacity for TICE® BCG

KENILWORTH, N.J., Oct. 14, 2020 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced it will construct a new manufacturing facility to significantly expand its production capacity for TICE® BCG (BCG Live For Intravesical Use), a

“...will triple current production... [this will] take approximately 5-6 years...[there will be a] gradual increase over time...”
“This guideline provides a risk-stratified clinical framework for the management of NMIBC.”

2020 – 2021 update

https://www.auanet.org/guidelines/bladder-cancer-non-muscle-invasive-guideline
For Every NMIBC Patient: Management Strategies

• Perform quality TURBT
• Risk stratify to individualize care
  – Ration our BCG supplies and use appropriately
  – Utilize current intravesical treatments
  – Proceed to initial radical cystectomy when appropriate
  – Utilize systemic immunotherapy when appropriate
• Look for and enroll in clinical trials
My Key Points To Perform Quality TURBT

– Enhanced techniques are helpful and should be considered
  • Cysview “blue light”
  • Narrow Band Imaging (NBI)
– Separate pathologic specimens for better evaluation
  • Tumor
  • Deep margin with tumor
– Bi-polar resection for larger, more extensive tumors
– Consider cold cup specimens to avoid electrocautery artifact
– Repeat TURBT within 3-6 weeks for T1 and high-volume, high-risk Ta
– Pathologic communication/experienced review
– Realize no substitute for experience

– In the future: need to find a better technique for tumor removal and staging
BCG Is Standard of Care: Guidelines from the AUA and EAU

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>AUA</th>
<th>EAU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recommendation: BCG induction + maintenance (SWOG protocol 3 years)</td>
<td>Recommendation: BCG induction + maintenance 1-3 years OR radical cystectomy</td>
</tr>
</tbody>
</table>
When NO BCG is Available—What Are Current and Novel Options?
No single agent intravesical chemotherapy has been FDA approved in decades for bladder cancer treatment.
Combination Chemotherapy: Gem + Docetaxel

- **65 BCG-Naïve patients, although 6/65 had received previous intravesical chemotherapy**
  - 50/65 (75%) had high grade disease.
  - 26/65 (40%) had pure CIS or papillary disease with concomitant CIS
- Received sequential for 90-120 min each q week x 6 weeks
  - Gemcitabine 1 g in 50 ml of water or NS
  - Docetaxel 37.5 mg in 50 mL of NS
  - If disease-free, monthly maintenance depending on institution

RFS at 6 months = 82%
RFS at 12 months = 76%
RFS at 24 months = 66%

Institutions involved:
- University of Iowa
- Johns Hopkins
- Iowa City VA
- BCG-Oncology University of Arizona
- University of Calgary
- MD Anderson

Courtesy of M. O’Donnell, in press, Bladder Ca Jrl, 2021
Cystectomy Can Be Curative

- Survival outcomes are excellent
  - 92% overall survival rate for pathologic T1 disease.\(^1\)
    - Found 27% were upstaged at cystectomy
    - 12% had nodal disease
    - Stein et al reported a 5 year recurrence-free rate of 83% for pT1\(^2\)
  - Five-year survival is better with early compared to delayed cystectomy timing
    - 90% for early cystectomy (within 3 months of diagnosis) \(^1\)
    - 50-60% if cystectomy delayed

- Disease High Risk Factors:
  - +LVI
  - variant histology
  - >3 cm
  - multi-focal T1
  - CIS

\(^1\)Bianco et al Urol Oncol 2004
\(^2\)Stein et al JCO 2001
What Therapy Alternative Should Be Used When BCG Not Available?

• High-risk disease: Balancing risk of disease, patient desires, and success of treatment
  – Intravesical: combination chemo seems to have efficacy
    • Gemcitabine and Mitomycin C
    • Gemcitabine and Docetaxel
  – Always need to consider initial, timely cystectomy, especially for T1 bladder cancer

• Chemo-hyperthermia = effective therapy but not available in US
Many Patients Still Receive BCG; What Do We Do If BCG Has Not Worked?
# Treatment Options for BCG unresponsive NMIBC

<table>
<thead>
<tr>
<th>OPTIONS</th>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical Cystectomy with LND and diversion</td>
<td>Definitive LUTS addressed</td>
<td>Morbidity (competing risks, frailty for this pt)</td>
</tr>
<tr>
<td>Intravesical Chemotherapy</td>
<td>Avoid major surgery, doublet preferred (Gem/Docetaxel: 42% 2yr RFS)</td>
<td>Already has severe LUTS (? Tolerability) Efficacy/durability</td>
</tr>
<tr>
<td>Systemic therapy Pembrolizumab: FDA approved 2020</td>
<td>Not intravesical therapy ie minimize LUTS , Avoid major surgery</td>
<td>Efficacy/durability Rare, but severe side effects Cost</td>
</tr>
<tr>
<td>Intravesical therapy e.g. nadofaragene, vicineum *Clinical trial</td>
<td>Avoid major surgery, early phase data good!</td>
<td>Already has severe LUTS (? Tolerability) Efficacy/durability</td>
</tr>
</tbody>
</table>
AUA 2020

• In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy.

• In a patient with persistent or recurrent intermediate- or high-risk NMIBC within 12 months of completion of adequate BCG therapy (two induction courses or one induction course plus one maintenance cycle) who is unwilling or unfit for cystectomy, a clinician may recommend clinical trial enrollment or offer alternative intravesical therapy (e.g., valrubicin, gemcitabine, docetaxel, combination chemotherapy) when clinical trials are unavailable. A clinician may also offer systemic immunotherapy with pembrolizumab to a patient with CIS within 12 months of completion of adequate BCG therapy.
## Intravesical “Salvage” Chemotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Study</th>
<th>#</th>
<th>Schedule</th>
<th>1 yr CRR</th>
<th>2 yr CRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valrubicin</td>
<td>Steinberg 2000</td>
<td>90</td>
<td>6 weekly</td>
<td>14%</td>
<td>(8%-30 months)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Skinner 2013</td>
<td>47</td>
<td>6 weekly, monthly x12</td>
<td>28%</td>
<td>21%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Barlow 2013</td>
<td>54</td>
<td>6 weekly, monthly x 9</td>
<td>40%</td>
<td>--</td>
</tr>
<tr>
<td>Nab-Paclitaxel</td>
<td>McKiernan 2014</td>
<td>28</td>
<td>6 weekly, monthly x6</td>
<td>36%</td>
<td>--</td>
</tr>
<tr>
<td>Gemcitabine/Docetaxel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breyer 2010, Lightfoot 2014,</td>
<td>10-47</td>
<td>6 weekly, monthly x 12 (or no maintenance)</td>
<td>48-70%</td>
<td>38-41%</td>
</tr>
<tr>
<td>Gem/Mito</td>
<td>Cockerill 2016</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine/Docetaxel</td>
<td>Steinberg 2015, Milbar 2017</td>
<td>45</td>
<td>6 weekly</td>
<td>54-56%</td>
<td>34-42%</td>
</tr>
<tr>
<td>BCG/IFN/IL2/GM-CSF</td>
<td>Steinberg 2017</td>
<td>52</td>
<td>6 weekly</td>
<td>55%</td>
<td>53%</td>
</tr>
<tr>
<td>Cab/Gem/Cis</td>
<td>McKiernan 2019</td>
<td>18</td>
<td>6 weekly, maintenance</td>
<td>78%</td>
<td>--</td>
</tr>
</tbody>
</table>

Not FDA Approved aside from Valrubicin
Adapted from Li et al, EU 2018
Combination Intravesical Chemotherapy: Cabazitaxel + Gemcitabine + Cisplatin (CGC)

• Recurrence Free Survival Rates (RFS)
• 17/18 (94%) tumor free at 3 month f/u
  – 12 months = 83%
  – 24 months = 78%

• Received treatment Mon, Wed, every other Fri x 6 weeks, then q month maintenance up to 24 months
• 2/4 recurrences in prostatic urethra if excluded, 2 year *intravesical* RFS 89%

DeCastro J, McKiernan J et al, J Urol, 2020
Systemic Immunotherapy for BCG Unresponsive Disease
Systemic Therapy: KEYNOTE-057—EMUC 2019
Single-arm, Open-label Phase II Study (NCT02625961)
Pembrolizumab

Patients
- HR NMIBC patients unresponsive to BCG who refuse or are ineligible for cystectomy
- Patients with papillary disease must have fully resected disease at study entry
- Two cohorts
  - Cohort A (n=130)—CIS with or without papillary disease (high-grade Ta or T1)
  - Cohort B (n=130)—papillary disease (high-grade TA or any T1) without CIS

Pembrolizumab
- 200 mg Q3W
- Evaluations with cystoscopy, cytology, ± biopsy Q12 weeks x 2 years and once yearly thereafter
- CT urogram Q24 weeks x 2 years or more frequently as clinically indicated

Continue assessments and pembrolizumab until recurrence of HR NMIBC, PD, or 24 months of treatment complete
Discontinue treatment, enter survival follow-up

Primary End Points
- CR (absence of HR NMIBC) in Cohort A
- DFS in Cohort B

Secondary End Points
- CR (absence of any disease—high-risk or low-risk NMIBC) in Cohort A
- DOR in Cohort A
- Safety/tolerability

If no persistence or recurrence of HR NMIBC at any assessment
If HR NMIBC present at any assessment

KEYNOTE-057
BCG Unresponsive CIS Patients Achieving CR with Pembrolizumab

CR, complete response.

- 1 month = 30.4367 days.
- Month 0 = time point when initial CR was achieved.

Best response n (%) 95% CI

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>39 (40.6)</td>
<td>30.7, 51.1</td>
</tr>
<tr>
<td>Non-CR</td>
<td>56 (58.3)</td>
<td>47.8, 68.3</td>
</tr>
<tr>
<td>Progression to T2</td>
<td>0</td>
<td>NA, NA</td>
</tr>
<tr>
<td>Non-evaluable</td>
<td>1 (1.0)</td>
<td>0, 5.7</td>
</tr>
</tbody>
</table>

Median CR duration, mo (range) 16.2 (0.0+ - 26.8+)

- Upstaging to ≥pT2 in 8.3% patients
- Number of patients with observed DOR ≥12 mo was 19% of all treated patients (n = 96)

@ 3 months

No progression to T2 disease
As a result:
FDA Approved IV Pembrolizumab

January, 2020

Pembrolizumab is approved for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for, or who have elected not to undergo, cystectomy
Intravesical therapy: What’s Next?

Intravesical Nadofaragene Firadenovec Gene Therapy for BCG-unresponsive Non-muscle-invasive Bladder Cancer: A Single-arm, Open-label, Repeat-dose Clinical Trial
Single-Arm, Open-Label Study Evaluating Nadofaragene Firadenovec in High-Grade, BCG-Unresponsive NMIBC

replication-deficient recombinant adenovirus that delivers human interferon alfa-2b cDNA into the bladder epithelium

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-Grade</strong></td>
<td>Nadofaragene firadenovec 3 x 10^{11} vp/mL (75 mL) intravesically every 3 months with a planned 1-hour dwell time</td>
<td><strong>Primary:</strong> CR in patients with CIS ± Ta/T1 at any time after the first instillation</td>
</tr>
<tr>
<td><strong>BCG-unresponsive NMIBC</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td><strong>Key Secondary:</strong></td>
</tr>
<tr>
<td><strong>N=157</strong></td>
<td></td>
<td>• Durability of CR in patients with CIS ± Ta/T1 who achieved a CR</td>
</tr>
<tr>
<td><strong>Cohorts:</strong></td>
<td></td>
<td>• HGRFS rate in patients with High-Grade Ta/T1</td>
</tr>
<tr>
<td>1</td>
<td>CIS ± Ta/T1</td>
<td>• Durability of HGRF survival in patients with High-Grade Ta/T1</td>
</tr>
<tr>
<td>2</td>
<td>High-Grade Ta/T1</td>
<td>• Time to cystectomy&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>• Overall survival&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Key Inclusion Criteria**
- High-grade BCG-unresponsive NMIBC patients ≥18 years:
  1. CIS ± Ta/T1 (CIS with or without high-grade Ta/T1)
  2. High-Grade Ta/T1 (without concomitant CIS)

**Key Exclusion Criteria**
- Current or previous evidence of muscle invasive (muscularis propria) or metastatic disease
- Intravesical therapy within 8 weeks prior to beginning study treatment

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<sup>a</sup> BCG-unresponsive NMIBC is defined as: (1) persistent high-grade T1 recurrence ≤12 months after BCG initiation; (2) relapse with CIS after initial complete response ≤12 months after last BCG treatment; or (3) relapse with high-grade Ta/T1 NMIBC ≤6 months after last BCG treatment.<sup>b</sup> Results for time to cystectomy and overall survival are not, yet, presented due to insufficient follow-up as of this data cut off.

Primary endpoint:
Incidence of CR at any time in CIS±Ta/T1 cohort

<table>
<thead>
<tr>
<th>Patients Who Have Achieved a CR (n, %)</th>
<th>CIS±Ta/T1 (N=103)</th>
<th>% of CR (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>By 3 months</td>
<td>55 (53.4)</td>
<td>100%</td>
</tr>
<tr>
<td>During 4 to 6 months</td>
<td>0 (0.0)</td>
<td>0%</td>
</tr>
<tr>
<td>During 7 to 9 months</td>
<td>0 (0.0)</td>
<td>0%</td>
</tr>
<tr>
<td>During 10 to 12 months</td>
<td>0 (0.0)</td>
<td>0%</td>
</tr>
<tr>
<td>Total</td>
<td>55 (53.4)</td>
<td>-----</td>
</tr>
</tbody>
</table>

All CRs occurred within 3 months

Secondary Endpoint: Durability of Response
High-Grade Recurrence-Free Survival in Patients who Achieved CR

CIS cohort

High grade Ta/T1 cohort

Overall at 12 months: high grade DFS

24.3% of the CIS ± Ta/T1 cohort

43.8% of the Ta/T1 cohort

74% of patients were free of cystectomy
Intravesical therapy: What’s Next?

Vista Trial

Phase 3 Registration Study of Vicineum for BCG-unresponsive NMIBC
Vicineum

*Oportuzumab Monatox—Anti-EpCAM + Pseudomonas Exotoxin*

- EpCAM overexpressed in >98% of HG NMIBC
- Phase I and II studies established safety; 15.6% CR rate at 12 months

**Vista Trial**

*Phase 3 Registration Study of Vicineum for BCG-unresponsive NMIBC*

**Duration of response:** 52% of CIS patients who had a CR at 3 months remained disease-free for a total of 12 months after starting treatment.

- 3 month 40% CR with CIS
  - Durability of response
  - 52% retain a CR at 9 months
  - 39% retain a CR at 15 months

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Vanderbilt University Medical Center

**Median duration of response is 287 days (95% CI, 154–NE* days) (9.4 months)**

*Not estimable, the upper bound for the 95% confidence interval has not reached the median.*

**Note:** data reflect an ad hoc analysis of pooled results of patients in cohorts 1 and 2. Median duration of response for the primary endpoint, Cohort 1 (n=86) is 273 days (95% CI=122–NE), and duration of response for Cohort 2 (n=7) is 290 days (95% CI = 167–NE), based on the Kaplan-Meier method.

Current Clinical trials

• KEYNOTE-676
• ALBAN Trial
• CREST Trial

• Only a partial list as new agents and new delivery systems are being formulated and studied
KEYNOTE-676 Study Design Schema

Eligibility
- Has histologically-confirmed diagnosis of non–muscle invasive (T1, high-grade Ta and/or CIS) transitional cell carcinoma (TCC) of the bladder
- Has been treated with one adequate course of BCG induction therapy for the treatment of HR NMIBC

Estimated enrollment: 550

Primary Endpoint
- CR rate by BICR

Key Secondary Endpoints
- EFS
- RFS
- OS
- DOR
- Time to Cystectomy
- Safety
- Time to True Deterioration
- QLQ-C30, QLQ-NMIBC24, etc.

BICR, blinded independent central review; EFS, event-free survival; RFS, recurrence-free survival; DOR, duration of response. ClinicalTrials.gov
Objective: to investigate whether atezolizumab improves the outcome of patients treated with BCG for high-risk NMIBC

Inclusion criteria
High-risk NMIBC defined as
- High-grade OR
- T1 OR
- In situ carcinoma

Primary endpoint
- RFS

Secondary endpoints
- PFS, OS
- Cancer specific survival
- Disease worsening
- QOL, safety

TURBT Randomization
N=614 patients

Control
BCG : 6 (induction) + 3 (maintenance, 1 year)

Experimental
BCG : 6 + 3 (1 year) + atezolizumab IV (1 year)

CREST Trial

STUDY OF SASANLIMAB (PF-06801591) IN COMBINATION WITH BACILLUS CALMETTE-GUERIN (BCG) IN PARTICIPANTS WITH HIGH-RISK NON-MUSCLE INVASIVE BLADDER CANCER

A subcutaneous monoclonal antibody (mAb) that blocks the interaction between PD-1 and PD-L1/PD-L2

Three arm trial:
A: SASANLIMAB (PF-06801591) + BCG (Induction and maintenance)
B: SASANLIMAB (PF-06801591) + BCG (Induction alone)
C: BCG alone (induction and maintenance)

Primary Endpoint: Event Free Survival
Conclusions

• BCG shortage may continue to influence our treatment choices for the coming decade
• FDA-approved systemic therapy currently available: pembrolizumab
• Exciting options are being evaluated by the FDA and are currently in trials with intravesical therapies combined with systemic therapies