BCG Shortage: The Practice Environment

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Disclosures

• Clinical trials
  • Endo, FKD, JBL (SWOG), Genentech (SWOG), QED, UroGen, Vaxiion, Viventia

• Consultant/Advisory Board
  • Aura Bioscience, C2i Genomics, FerGene, Genentech, Merck, Pfizer/EMD Serono, Stimit, UroGen, Vaxiion, Verity

• Patent – TCGA classifier

• Honoraria – Annenberg, Clinical Care Options, Grand Rounds Urology, Ology, UroToday
Outline

- BCG shortage update
- AUA and stakeholder guidelines
- Treatment options based on risk stratification with no or limited supply of BCG
- Survey - Impact of BCG shortage on academic and community settings
BCG Indications

• **Any patient with high risk NMIBC**
  – TaHG, T1, Tis; multifocal and recurrent and >3cm
  – Induction + 3 years maintenance is SOC
  – TaLG – (Use intravesical chemo due to BCG shortage)

• **Recurrent**
  – BCG failure (induction only) if no indication for cystectomy or medically unfit

• **US FDA approved for CIS and high-risk Ta,T1**
• Connaught strain (Sanofi Pasteur) off line since 2012 then closed permanently in 2017

• Merck manufactures Tice in a single plant in US for global distribution in 70 countries
  – US market was 28 percent of the total product at time SP went off line
  – Increased production by more than 100 percent
  – In late 2016, at full capacity enabling approximately 600,000 to 870,000 vials annually
BCG Supply

• In January, 2019 Merck began allocation distribution through their authorized vaccine distributors
  – https://www.merck.com/research-and-products/distributors
• Demand in the US decreased during pandemic but still > supply
• Demand is increasing now
• Revised US % of market not provided
• BCG should **not** be used for low-risk disease.
• Intravesical chemotherapy first-line option for patients with intermediate-risk NMIBC.
  – An alternative intravesical chemotherapy should be used for second line intermediate risk disease
• Patients with high-risk NMIBC prioritized for full-strength BCG. If not available, dose reduce to 1/2 to 1/3
• If supply exists for maintenance therapy for patients with NMIBC, every attempt should be made to use 1/3 dose BCG and limit dose to one year.
• BCG supply shortage: maintenance therapy should not be given and prioritize induction for BCG-naïve patients with high-risk disease.

• If BCG is not available: alternative chemotherapy options include mitomycin gemcitabine, epirubicin, docetaxel, valrubicin or sequential gemcitabine/docetaxel or gemcitabine/mitomycin

• Consider RC T1HG + CIS, LVI, P urethra, variant histology.

• Merck to build new plant that will triple production (Jan 2021)
  – Project has begun and 4-5 years before on line (personal communication, Merck 09/23/21)
BCG Dose Reduction

- Sometimes less is better
- An appropriate cytokine response can be achieved with as little as 1/100 of a standard dose\(^1\)
- Dose reduce in face of toxicity rather than abandon potentially effective therapy
  - 1/2, 1/3, 1/10, 1/30, 1/100

<table>
<thead>
<tr>
<th>Dose Levels</th>
<th>Full Dose</th>
<th>-1 Level</th>
<th>-2 Level</th>
<th>-3 Level</th>
<th>-4 Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>16.67 mg</td>
<td>12.5 mg</td>
<td>5 mg</td>
<td>0.5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1/3 dose)</td>
<td>(1/4 dose)</td>
<td>(1/10 dose)</td>
<td>(1/100 dose)</td>
<td></td>
</tr>
</tbody>
</table>
AUA Split Dosing Policy

• Split dosing is now supported by new HCPCS code J9030 allowing billing for 1/mg BCG and replaces J9031 (1 vial/BCG) & became effective 7/01/2019.

• But billing for 2+ patients for split vial use may vary by state/region – should verify with carrier
50mg powder (1-8 x 10^8 CFU)

Full dose = 1 vial in 50ml NS

1/3 dose = Split 50ml BCG solution into 3 syringes and reconstitute up to 50ml

Administer to 3 patients within 2 hrs (keep refrigerated 2-8°C)
Optimized Mitomycin C (1B)

- 40mg/20cc
- Dehydrate patient – NPO after midnight
- Sodium bicarbonate (1.3g po night before, and in am of tx)
- Use bladder scanner to ensure bladder is empty prior to instillation (PVR<10cc)

Au et al, JNCI 93:597, 2001
Gemcitabine/Docetaxel

- One and 2-year RFS rates 60% and 46%
- 3.6% progression and cystectomy free survival 84%
- No patient, disease, or prior treatment factors predict relapse
- Maintenance matters
## BCG Naïve Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>SPONSOR</th>
<th>AGENT</th>
<th>PHASE</th>
<th>NUMBER PTS</th>
<th>START DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>POTOMAC</td>
<td>ImmunityBio</td>
<td>Alt 803 + BCG vs. BCG</td>
<td>IIb</td>
<td>596</td>
<td>Jul-14</td>
</tr>
<tr>
<td>POTOMAC</td>
<td>Astra Zeneca</td>
<td>Durvalumab + BCG vs. BCG</td>
<td>III</td>
<td>1019</td>
<td>May-18</td>
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<tr>
<td>POTOMAC</td>
<td>Hamlet</td>
<td>Alpha 1 H (α-lactalbumin+oleic acid)</td>
<td>I/II</td>
<td>57</td>
<td>May-18</td>
</tr>
<tr>
<td>Alban</td>
<td>Unicancer (FR)</td>
<td>Atezo + BCG vs. BCG</td>
<td>III</td>
<td>516</td>
<td>Jan-19</td>
</tr>
<tr>
<td></td>
<td>NanOlogy</td>
<td>NanoDoce</td>
<td>I/II</td>
<td>75</td>
<td>Apr-19</td>
</tr>
</tbody>
</table>

Source: www.clinicaltrials.gov September 2021
### BCG Naïve Clinical Trials

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<th>NUMBER PTS</th>
<th>START DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>BladderGate</td>
<td>Fundacion Oncosur(SP)</td>
<td>Atezo + BCG</td>
<td>1b</td>
<td>40</td>
<td>Feb-20</td>
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<tr>
<td></td>
<td>Hopkins</td>
<td>Gem/Doce</td>
<td>II</td>
<td>26</td>
<td>Jul-20</td>
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<td>Keynote-676</td>
<td>Merck</td>
<td>Pembro + BCG vs. BCG (Cohort B)</td>
<td>III</td>
<td>1525</td>
<td>18-Dec</td>
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<tr>
<td>CREST</td>
<td>Pfizer</td>
<td>Sasanlimab (PF-06801591) + BCG vs. BCG</td>
<td>III</td>
<td>999</td>
<td>19-Dec</td>
</tr>
<tr>
<td>EVER</td>
<td>Verity</td>
<td>Verity (Russian strain) BCG vs Tice BCG</td>
<td>III</td>
<td>540</td>
<td>Not started</td>
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</table>

Source: www.clinicaltrials.gov September 2021
Summary – BCG Shortage

- BCG shortage continues to plague access to standard of care and creates challenges in clinical trial enrollment
- Driving innovation and alternative risk adapted therapies
- S1602 – CR and durability results in CIS patients will be reviewed
- Optimized intravesical MMC and doublet chemotherapy regimens are active in both intermediate and high-risk disease
- Robust clinical trials portfolio for high-risk BCG naïve
BCG Shortage Survey

- BCAN (94), SUO(1010), LUGPA(2200)
- Completed surveys n = 255
- Preliminary data

- New England
- Mid Atlantic (22%)
- South Atlantic
- East North Central
- West North Central
- East South Central
- West South Central
- Mountain
- Pacific

Academic 84 (32%)
Community 150 (58%)
Hybrid 19
Other 6
• For what proportion of high-risk NMIBC treated in the last 12 months did you avoid giving any maintenance BCG due to the BCG shortage
  – 0-25% (58%)

• For what proportion of high-risk NMIBC did you treat with maintenance for less that 3 years due to the BCG shortage?
  – 50-100% (58%)
BCG Shortage Survey

Preference for BCG vs Ctx for intermediate risk (%)

- BCG (56%)
- Ctx (33%)
- No tx (5%)
- Other

BCG
Academic 33%
Non-academic 66%

Have you had to borrow BCG

Other: never, no one to borrow from, not allowed
BCG Shortage Survey

- Do you consider the development of non-BCG based alternative therapies as a high priority for BCG-naïve high-risk patients?
  - Yes (92%)
- Is the BCG shortage affecting your ability to enroll patients in clinical trials in the BCG-naïve, refractory or unresponsive?
  - Yes (24%)
BCG Shortage Survey Summary

- One-third respondents academic sites
- Majority have been able to maintain full dose induction
- Majority have been able to give maintenance but majority have also given < 3 years maintenance
- One-third of academic sites and 2/3 community sites continue to use BCG for patients with intermediate risk disease
- 39% report adverse outcomes related to BCG shortage
- Overwhelming majority favor developing alternatives to BCG for patients with BCG naïve high risk disease
- One-quarter report negative impact on clinical trial accrual