Recurrent Non-Muscle-Invasive Bladder Cancer: Treatment Options When BCG Doesn’t Work

Scott M Gilbert, MD, MS, FACS
Department of Genitourinary Oncology
Department of Health Outcomes and Behavior
H. Lee Moffitt Cancer Center & Research Institute
Tampa, FL
No Relevant Disclosures

NCI R01 CA164128 (PI McMullen)
Florida Bankhead Coley Research Program 3BN03 (PI Gilbert)
## NMIBC Risk Groups

| Low-Risk                                                                 | Primary solitary, Ta, low-grade, <3 cm, no concurrent carcinoma in situ (CIS) detected  
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Small volume (&lt;3 cm) low-grade Ta</td>
</tr>
</tbody>
</table>
| Intermediate-Risk                                                      | Primary, solitary low-grade tumors >3 cm  
|                                                                        | Multiple primary low-grade Ta tumors  
|                                                                        | Solitary recurrent low-grade Ta tumor  
|                                                                         | Multifocal and/or large volume low-grade Ta  
|                                                                         | Low-grade Ta tumor recurrent within 1 year  
|                                                                         | High-grade Ta, <3 cm  
|                                                                         | Low-grade T1                                                                             |
| High-Risk                                                              | High-grade tumors, any lamina propria invasion (T1), carcinoma in situ  
|                                                                        | Multiple, recurrent low-grade Ta tumors >3 cm  
|                                                                        | High-grade Ta > 3cm or any recurrent high-grade Ta  
|                                                                        | Any CIS; High-grade T1  
|                                                                        | Any variant histology, any LVI, any BCG failure, any PU  

Chang et al. AUA guidelines for NMIBC, [www.auanet.org/guidelines](www.auanet.org/guidelines)
Immune Response to BCG

**Mechanism**

Attenuated mycobacterium binds to fibronectin

Direct stimulation of cell-mediated immune response

Cytokine (TNF-α, INF-γ, IL-2, IL-12, IL-18) induction of intense Th-1 response

Response/Effectiveness of Initial BCG Course

Initial response rates of approximately 70%...
Recurrence observed in approximately 40% of patients after 4-5 years
  • Large meta-analysis reported 68.1% complete response rate and a long-term disease-free rate of 46.7% at 3.6 years among patients with CIS

Latent effect of 3-6 months reported on follow-up biopsies

BCG therapy may reduce risk of tumor progression
  • EORTC-GUCG meta-analysis including 4,863 patients reported 9.8% progression in BCG treated patients compared to 13.8% in control groups (median follow-up 2.5 years)
  • Up to 30% of BGC non-responders may progress by 5 years

## Results with Second BCG Induction

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>N</th>
<th>Recurrence</th>
<th>2-Year recurrence free</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merz</td>
<td>pTCC/CIS</td>
<td>15</td>
<td>4/15</td>
<td>27%</td>
</tr>
<tr>
<td>Berdon</td>
<td>pTCC</td>
<td>28</td>
<td>10/28</td>
<td>36%</td>
</tr>
<tr>
<td>Nadler</td>
<td>pTCC</td>
<td>66</td>
<td>22/66</td>
<td>41%</td>
</tr>
<tr>
<td>Yamada</td>
<td>pTCC</td>
<td>31</td>
<td>11/31</td>
<td>35%</td>
</tr>
<tr>
<td>Oversea</td>
<td>CIS</td>
<td>17</td>
<td>4/17</td>
<td>24%</td>
</tr>
<tr>
<td>Drake</td>
<td>HGT1</td>
<td>37</td>
<td>19/37</td>
<td>51%</td>
</tr>
<tr>
<td>Pamadora</td>
<td>GHT1</td>
<td>22</td>
<td>6/22</td>
<td>27%</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>216</td>
<td>76/216</td>
<td>35%</td>
</tr>
</tbody>
</table>
U.S. Drug Shortages Frustrate Doctors, Patients

Drugs in short supply include cancer treatments and antibiotics; manufacturing snafus

Robin Miller, a 62-year-old oncologist in Atlanta with bladder cancer, was scheduled to receive a potentially lifesaving drug in December. But her doctor’s office called shortly before the appointment to say: “Sorry, we don’t have any. We can’t give it to you,” according to Dr. Miller.

The disruption was due to a global shortage of the drug, BCG, which arose after manufacturing problems at two of the few global suppliers. Without the drug, Dr. Miller feared her cancer would come back and she would have to have her bladder removed, a step she called “barbaric.”
BCG Strains May Not Be Equal

<table>
<thead>
<tr>
<th>BCG Strain</th>
<th>5-year survival estimate</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recurrence-free survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connaught</td>
<td>74.0</td>
<td>62.8-87.2</td>
<td>0.011</td>
</tr>
<tr>
<td>Tice</td>
<td>48.0</td>
<td>35.5-65.1</td>
<td></td>
</tr>
<tr>
<td><strong>Progression-free survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connaught</td>
<td>94.1</td>
<td>87.8-100</td>
<td>0.344</td>
</tr>
<tr>
<td>Tice</td>
<td>87.9</td>
<td>76.5-100</td>
<td></td>
</tr>
</tbody>
</table>

n=142, no maintenance therapy
*no significant difference in disease-specific/overall survival

EORTC meta-analysis did not show significant differences in efficacy between different BCG strains, but a few individual studies

Reasons for BCG Failure

Inadequate/insufficient immune response
- Immune suppression (age > 80 yrs, immunosuppressive medications)
- BCG anergy
- Incomplete dose/suboptimal administration
- Polarized Th2/Th1 response (reported with higher BCG doses)
- Tumor induced immune suppression (e.g. PD1/PDL1 axis)

Intrinsic tumor resistance to immune surveillance
- Cell death receptor/signal loss
- Failed immune recognition
- Immune response modification (e.g. NRAMP1 gene polymorphisms)
**BCG Failure Definitions**

**BCG failure**: Presence of high-grade NMIBC at 6 months from initial diagnosis/treatment, or progression or worsening disease at 3 months

**BCG-refractory**: failure to achieve disease-free state at 6 months following initial BCG therapy with either maintenance or re-treatment

**BCG resistance**: recurrence or disease persistence at 3 months following BCG induction

**BCG relapse**: disease recurrence after disease-free interval achieved at 6-months following initial successful BCG induction

**BCG intolerance**: disease recurrence/persistence secondary to inability of patient to receive/tolerate adequate BCG treatment course

Nieder et al. Urology 2006;67:737-41
Clarified Definition of **Unresponsive** Disease

**Refractory**: Persistent high-grade disease at 6 months despite adequate BCG treatment, or any stage or grade progression by 3 months after the first cycle of BCG.

**Recurrent**: Recurrence of high-grade disease after achieving a disease-free state at 6 months after adequate BCG.

**Intolerant**: Disease persistence as a result of inability to receive adequate BCG secondary to treatment toxicity.

**Unresponsive**: BCG refractory or relapsing disease within 6 months of last BCG exposure (subgroup of highest risk recurrence/progression) **Additional BCG not indicated**
Validation of BCG Unresponsive Definition

Patients with Any CIS
Prior BCG Interval/Number of BCG Course

Second-Line/Salvage/Rescue Therapy Options

Conventional chemotherapy (e.g. mitomycin, valrubicin)

Single agent immunotherapy (BCG or INF)

Combination immunotherapy (BCG + INF/IL2/GMCSF)

Alternative single agent chemotherapy (e.g. gemcitabine, docetaxel)

Combination chemotherapy (e.g. gemcitabine + mitomycin)

Novel/investigational agents
## Outcomes with Conventional Agents

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Agent</th>
<th>Histology</th>
<th>N</th>
<th>2/3 year DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalona (1987)</td>
<td>3rd cycle BCG</td>
<td>Mixed</td>
<td>11</td>
<td>20%</td>
</tr>
<tr>
<td>Williams (1996)</td>
<td>Interferon</td>
<td>CIS</td>
<td>34</td>
<td>12%</td>
</tr>
<tr>
<td>Malstrom (1999)</td>
<td>Mitomycin</td>
<td>Mixed</td>
<td>21</td>
<td>19%</td>
</tr>
<tr>
<td>Steinberg (2000)</td>
<td>Valrubicin</td>
<td>CIS</td>
<td>90</td>
<td>8%</td>
</tr>
<tr>
<td>First author</td>
<td>Treatment modality (study phase)</td>
<td>n</td>
<td>Failures</td>
<td>Follow-up</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Dalbagni [37]</td>
<td>IV gemcitabine</td>
<td>30</td>
<td>26</td>
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<tr>
<td>Bartoletti [39]</td>
<td>IV gemcitabine</td>
<td>116</td>
<td>40</td>
<td>13.6 mo</td>
</tr>
<tr>
<td>Mohanty [40]</td>
<td>IV gemcitabine</td>
<td>35</td>
<td>35</td>
<td>18 mo</td>
</tr>
<tr>
<td>Di Lorenzo [41]</td>
<td>IV gemcitabine</td>
<td>80</td>
<td>80</td>
<td>15.5 mo</td>
</tr>
<tr>
<td>Addeo [42]</td>
<td>IV gemcitabine</td>
<td>54</td>
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<tr>
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<td>18</td>
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<td>48.3 mo</td>
</tr>
<tr>
<td>Barlow [51]</td>
<td>IV docetaxel</td>
<td>33</td>
<td>33</td>
<td>29 mo</td>
</tr>
<tr>
<td>Bassi [54]</td>
<td>IV paclitaxel</td>
<td>16</td>
<td>16</td>
<td>1 wk</td>
</tr>
<tr>
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<td>6 wk</td>
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<td>Joudi [36]</td>
<td>BCG plus interferon-α</td>
<td>1007</td>
<td>467</td>
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<tr>
<td>Witjes [45]</td>
<td>Thermochemotherapy</td>
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<td>10</td>
<td>23.7 mo</td>
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<tr>
<td>Breyer [56]</td>
<td>MMC plus gemcitabine</td>
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Final Results of BCG+INF Phase II Trial

Phase II (single-arm) study of BCG+INF

1106 BCG naive and failure patients (467 BCGx1 or more failures) recruited b/w 1999-2001

Induction with 1/3 BCG dose + 50 million units of interferon-α2B with maintenance (re-induction in 50% of cases)

13% BCG refractory, 34% failed within 6m, 28% failed b/w 6-12m, 15% within 12-24m, and 10% after 24m

T1 stage (HR 1.42), tumor size >5cm (HR 1.59), prior BCG >=2 courses (1.56) and multifocality (HR 1.34) significantly associated with recurrence

*sponsored by Schering-Plough, Inc.
Valrubicin

Study A9303 (open-label phase II/III, single arm)

Enrolled 80 patients with CIS alone or in combination w/ Ta/T1 treated with 6-9 week induction of IV valrubicin (800mg)

39% of patients had received >= 2 BCG courses

24/80 patients disease free at 3 months and 14/80 defined as complete response (disease free at 3 and 6 months)

Disease-free status probability 22% at 6 months, 10% at 12 months and 4% at 24 months
Valrubicin

Open label noncomparative study
90 patients with recurrent CIS +/- completely resected papillary tumor previously treated with at least 2 IV agents (one of which was BCG)

6 week induction of IV valrubicin

19/90 (21%) patients deemed complete responders (no disease at 3 or 6 month evaluation)

Treatment failed in 10 non-responders with low-grade papillary tumors only (therefore potential benefit in 32% of study subjects)

Steinberg et al. J Urol 2000;163:761-767
Intravesical Gemcitabine

**Phase III RCT Gemcitabine vs. Mitomycin**
- 120 patients w/ recurrent NMIBC after BCG failure (85%) or BCG ineligible treated w/ epirubicin (15%)
- 10 pts. recurred w/ progression
- 1 pt died of metastatic disease

**Phase II RCT Gemcitabine vs. BCG**
- 80 patients w/ recurrent NMIBC after 1 BCG course (*gemcitabine given twice weekly x6 weeks, 1/3 patients w/ low-grade disease*)
- 35/40 (87.5%) recurrent disease
- 13/35 (37.5%) w/ progression to cx
- 21/40 (52.5%) recurrent disease
- 7/21 (33%) w/ progression to cx
Intravesical Gemcitabine

Phase II (single-arm) S0353

58 intermediate or high risk who failed prior BCG instillations recruited b/w 2007-2009

Induction with 2 gm gemcitabine in 100 mL saline for 1 hour x 6 weeks with 10 monthly maintenance if recurrence free

96% pts. completed all treatments

3-month complete response in 40%

Median RFS 6.1 months

24-month estimated DFS 21%

Disease progression/cystectomy in 36%

62% grade 1-2 toxicity (dysuria/frequency)

2 pts. w/ grade 3 toxicity (dysuria/frequency/neutropenia)

Recurrence-Free survival

Overall survival

Single Agent Docetaxel

**Long-term follow-up results from Phase I**

Dose escalation phase I trial with initial (4-week post IV tx) complete response in 10/18 (56%) patients

Durable complete response in 4/18 (22%) at median follow-up of 48 months

**Extension study with maintenance**

54 patients (including 18 phase I subjects) with addition of monthly maintenance for 12 months (75mg/100mL)

1- and 3-year recurrence-free survival 40% and 25%, respectively

69% of patients retained their bladder at a median 24 months

Laudano et al. Urology 2010;75:134-137
Barlow et al. J Urol 2013;189:834-839
Sequential Gemcitabine/Mitomycin

3-site non-comparative study using gemcitabine 1 gram/50 mL + mitomycin 40 mg x 6 weeks with monthly maintenance x 12 months

47 BCG failure/intolerant patients treated b/w 2000 and 2010 (*10 patients BCG naive but immunosuppressed)

14/47 (30%) of patients remained recurrence free at median of 26 months

Complete response, 1-year RFS and 2-year RFS 68%, 48% and 38%, respectively

No difference b/w BCG naive and failure groups

10 patients treated with cystectomy for recurrence, 2 patients died of metastatic disease
Sequential Gemcitabine/Mitomycin

**Administration/Follow-up**
Gemcitabine 1 gram in 50 mL sterile water instilled for 90 minutes
Mitomycin 40 mg in 20 mL in sterile water instilled for 90 minutes
Gemcitabine administered first (thought to be better tolerated and could be made less effective by DNA cross-linking action of mitomycin)
Patients evaluated with cystoscopy, bladder washings, bladder biopsies/resection 6 weeks following completion of the intravesical therapy course and then with 3 month cystoscopies

**Tolerance**
10 patients reported frequency, urgency and/or dysuria (grade 1-2)
3 patients reported significant rash
1 patient developed pericarditis attributed to MMC exposure

Lightfoot et al. Urol Oncol 2014;32:35.e15-35.e19
Sequential Gemcitabine/Docetaxel

University of Iowa Pilot Study
45 patients treated with sequential combination gemcitabine/docetaxel b/w 2009-2014 for intravesical salvage (compassionate indication)

Docetaxel replaced mitomycin in 2009 due to mitomycin shortage

41/45 (91%) patients previously treated with BCG (37 recurrent, 4 intolerant)

Gemcitabine instilled first b/c requires DNA synthesis to be effective and docetaxel inhibits mitosis by blocking tubulin disassembly

Alkalinization with 1300 mg sodium bicarbonate evening prior and morning of instillation to buffer acidity of gemcitabine (pH 2.5)
Gemcitabine/Docetaxal Instillation Protocol

Alkalinization with 1300 mg sodium bicarbonate evening prior and morning of instillation to buffer acidity of gemcitabine (pH 2.5)

1 gram gemcitabine in 50 mL sterile water instilled for 90 minutes, followed by 37.5 mg docetaxel dissolved in 50 mL in saline for 120 minutes

6-week induction course with re-revaluation (cystoscopy vs. biopsy) 6-8 weeks after intravesical treatments are completed

Monthly maintenance administered for 24 months if recurrence free
Initial Results with Intravesical Gem/Doce

**Tolerance**
5 (11%) patients unable to tolerate full 6 treatment course
28 (62%) patients reported symptoms, 7 (16%) delayed treatment schedule
Most common symptoms were: mild dysuria (33%), mild urinary frequency/urgency (33%), hematuria (11%), nausea (7%)

**Effectiveness**
66% response rate at 3 month surveillance, 54% at 1 year, and 34% at 2 years
Median time to failure 3.1 months, 67% of failures occurred within first 6 months
Stage, +/- CIS, number or type of BCG failure not associated w/ success

Steinberg et al. Bl Cancer 2015;1:65-72
Natural History of Unresponsive NMIBC

(Safety Margin)

Median time to progression in 14 T1G3 BCG series is 24 months (rare progression at 6 months)

Untreated CIS has annual progression rate of 5%, likely higher given that 30-40% of initial responders fail

Reported progression 3.3% at 6 months and 8% at 1 year, with mortality 0.4% at 6 months and 1% at 1 year

Timing of cystectomy:

90 patients at MSK, 35 recurrences, 55 progressions

Surgery < 2 years: 92% DFS, 18% progression

Surgery > 2 years: 56% DFS, 41% progression (Herr, J Urol 2001)

Although substantial risk under staging with early cystectomy (27-50%), most recent BCG failure series report a high rate of pT0/<pT2

Valrubin study: cx in 44/79 pts. at median of 24m, 80% T0-T2, 2 pts. w/ +LN

Gem/Mito study: cx in 10/52 pts., 2 pts. died of metastatic disease

Gem/Doce study: cx 10/45 pts. at median of 5.6m, 3 T0, 5 CIS, 1 T1, 1 T4

S0335: cx in 15/58 pts. 12 < T2, 3 w/ T2+
<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial #</th>
<th>Institution/Sponsor</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPM1002BC</td>
<td>NCT02371447</td>
<td>Swiss Group for Clinical Cancer Research</td>
<td>I</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>NCT02625961</td>
<td>Merck Sharp &amp; Dohme Corp</td>
<td>II</td>
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<tr>
<td>PANVAC</td>
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<tr>
<td>Atezolizumab +/- BCG</td>
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<td>Recruiting</td>
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<td>Hypothermia+MCC vs. 2nd BCG</td>
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<td>Cancer Research Campaign Clinical Trials Center</td>
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<tr>
<td>Instiladrin (rAd-INF/Syn3)</td>
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<td>FKD Therapies</td>
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<td>CG0070 Oncolytic Virus</td>
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<td>Cold Genesys, Inc</td>
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<td>12-week course of 2nd BCG</td>
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<td>Memorial Sloan Kettering</td>
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2016 AUA Guideline Recommendations

**BCG Relapse and Salvage Regimens**

22. In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, a clinician should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)

23. In an intermediate- or high-risk patient with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, a clinician should offer a second course of BCG. (Moderate Recommendation; Evidence Strength: Grade C)

24. 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. (Moderate Recommendation; Evidence Strength: Grade C)

25. A clinician should not prescribe additional BCG to a patient who is intolerant of BCG or has documented recurrence on TURBT of high-grade, non-muscle-invasive disease and/or CIS within six months of two induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)

26. In a patient with persistent or recurrent intermediate- or high-risk NMIBC who is unwilling or unfit for cystectomy following two courses of BCG, a clinician may recommend clinical trial enrollment. A clinician may offer this patient intravesical chemotherapy when clinical trials are unavailable. (Expert Opinion)
Summary

Careful patient selection, discussion of risks and unwillingness to accept or undergo cystectomy

Complete restaging evaluation (including upper tract) necessary

BCG combination immunotherapy reasonable for late relapse (>12m) in previously BCG treated patients

Single agent gemcitabine and docetaxel reasonable for moderate risk BCG failures, but may not have durable effect

High-risk cases, non-surgical candidates and patient refusing cystectomy may best be treated with combination/sequential second-line agent intravesical therapy, but we really need better studies

Clinic trial best options if available at your practice

Maintain awareness of 1-2 year timeframe of BCG failure where disease typically stays localized within the bladder