Non-muscle Invasive Bladder Cancer
Bladder Cancer: Facts

- 80% present with NMIBC:
  - 70% Ta (papillary)
  - 20% T1 (lamina propria)
  - 10% CIS (high grade, flat)
Natural History

- Difficult to predict (tumor heterogeneity)
- Two characteristic features:
  1. Recurrence:
     - 70% recurrence with TUR alone
  2. Tumor progression:
     - 30% tumor progression w/TUR alone
Treated Natural History of NMIBC
15 Year Follow-up

• 86 high-risk patient with NMIBC
• Treated with TUR alone or TUR+BCG
• Progression in 53%, 18% UTT
• 36% underwent cystectomy
• 15-yr DSS was 63%, 34% dead of disease
• Life-long bladder and UTT surveillance

## APPROXIMATE PROBABILITY OF RECURRENCE AND PROGRESSION

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Approximate Probability of Recurrence in 5 years</th>
<th>Approximate Probability of Progression to Muscle Invasion</th>
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</thead>
<tbody>
<tr>
<td>Ta, low grade</td>
<td>50%</td>
<td>Minimal</td>
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<tr>
<td>Ta, high grade</td>
<td>60%</td>
<td>Moderate</td>
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<tr>
<td>T1, low grade (rare)</td>
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<td>T1, high grade</td>
<td>50% - 70%</td>
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<td>Tis</td>
<td>50% - 90%</td>
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</table>
BCG Is Standard of Care

- Most intermediate and all high risk NMIBC
- Superior to intravesical chemotherapy
- Supported by meta-analysis (9 RCTs)
  - 68% initial CR
  - 47% durable CR (3.6 yr median f/u)
- Endorsed by AUA, EAU NCCN Guidelines
- Best results with maintenance

Has Become U.S. Standard of Care
SWOG 8507 - BCG Maintenance

2-year RFS 82% vs. 62% with/without maintenance

5-year RFS 60% vs. 41% with/without maintenance

Lamm, DL et al, J Urol 163:1124, 2000
The Problem: Some Will Fail BCG

• Despite the benefits of BCG, long-term disease-free and progression-free survival may be difficult to achieve
• 50% will recur after induction BCG, and ≅30% salvaged with additional BCG
• But, BCG failure may be lethal if untreated
• Key: identify early those failures

Logan C et al. BJU Int. 2012;110:12-21
Potential Causes of BCG Failure

- Host immune incompetence
- Inadequately resected or occult invasive
- Resistant or non-antigenic tumor
- Inadequate treatment schedule
- Inadequate dose: too few CFU
- Inadequate contact of BCG and UCC
- Excess BCG inducing immunosuppression
Definitions of BCG Failure

- **Intolerant:** recurrent disease in setting of inadequate BCG treatment due to side effects
- **Resistant:** recurrence of lesser or improving disease that resolves with further BCG
- **Relapsing:** recurrence after achieving 6 month CR, i.e. disease resolves after BCG then returns
- **Refractory:** No CR by 6 months after BCG... not improving or worsening disease despite two courses of BCG or maintenance

Determining BCG Resistance: BCG Response over Time

- 6 months is the treatment period to identify high-risk tumors as truly refractory
BCG Refractory

- Failure to achieve a disease free state 6 months after initial BCG therapy with either maintenance or retreatment at 3 months due to either rapidly recurrent or persistent high grade disease.

Time 0
BCG Induction

Time: 3 months
Tumor +

Re-induction or Maintenance

Time: 6 months
Tumor +

Ultimately, determining when a patient has “failed” BCG is a shared decision between urologist and patient.
Novel Definition: Molecular Failure

- Goal: Incorporate FISH testing to predict BCG failure before it becomes clinically apparent
- 143 patients treated with BCG Ivi therapy followed prospectively for 2 years
- FISH assays collected at 6 weeks and 3 months
- Results of the FISH assays were correlated with clinical outcomes

Recurrence and Progression-Free Survival based on FISH

Novel Definition:
Molecular Failure

- Result: FISH results correlated with recurrence
- Conclusion: Patients with an early positive FISH and a negative cystoscopy at 3 months should be considered “molecular BCG failures” and could enroll in prospective RCT’s

Treatment Dilemma

- Cystectomy recommended as a standard of care after BCG failure
- Cystectomy has high rate of cure if before progression to muscle invasion
- Unfortunately, morbidity remains high
- And, many with high risk NMIBC who fail BCG are not candidates for cystectomy
Strategies to Reduce Persistence and Recurrence of BCG Refractory CIS

• Better Surgery ➔ Enhanced detection and more complete fulguration
• Better Agents ➔ Enhanced IVe chemotherapy and immunotherapy
• Better Delivery System ➔ Enhanced Bladder Penetration
• Better Diagnostics ➔ Enhanced Predictive and Prognostic Tools
PDD exploits the photoactive properties of compounds such as hexamino levulinate (HAL) (Hexvix\textsuperscript{TM}, Cysview\textsuperscript{TM}). Following instillation, HAL accumulates in neoplastic tissue. Illumination with blue-violet light produces a clearly demarcated red fluorescence from malignant tissue.

Photodynamic Diagnosis of Non–muscle-invasive Bladder Cancer with Hexaminolevulinate Cystoscopy: A Meta-analysis of Detection and Recurrence Based on Raw Data

Maximilian Burger\textsuperscript{a,*}, H. Barton Grossman\textsuperscript{b}, Michael Droller\textsuperscript{c}, Joerg Schmidbauer\textsuperscript{d}, Gregers Hermann\textsuperscript{e}, Octavian Drăgoescu\textsuperscript{f}, Eleanor Ray\textsuperscript{g}, Yves Fradet\textsuperscript{h}, Alexander Karl\textsuperscript{i}, Juan Pablo Burgués\textsuperscript{j}, J. Alfred Witjes\textsuperscript{k}, Arnulf Stenzl\textsuperscript{l}, Patrice Jichlinski\textsuperscript{m}, Dieter Jocham\textsuperscript{n}

- Prospective studies: 1345 patients
- FC cystoscopy used as an adjunct to white light (WL) cystoscopy
- Outcome: Detection of NMIBC up to 1 year
- FC cystoscopy detected significantly more tumors than WL
  - Ta tumors (14.7%; \( p < 0.001 \))
  - CIS lesions (40.8%; \( p < 0.001 \))
- In 26.7%, CIS was detected only by FC (\( p < 0.001 \))
- Recurrences were significantly lower with FC
  - 34.5% vs. 45.4% (\( p = 0.006 \))
Narrow Band Imaging™ (NBI)

- Olympus Optical imaging technology enhances visibility of vessels on mucosal surfaces
- Filters WL into specific light wavelengths that penetrate only surface of human tissue and are absorbed by HgB
- Bluish light enhances superficial capillary network (brown)
- Greenish light enhances deeper vessel visibility: vessels are greenish-blue (cyan)

Cauberg EC et al. Urol 76: 658, 2010
Collectively, these studies show superior sensitivity and negative predictive value >90% for NBI over WL.

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<tr>
<th>Series</th>
<th>No.</th>
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<td>Herr &amp; Donat</td>
<td>67</td>
<td>WL/NBI</td>
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<td>Shen</td>
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<td>WL/NBI</td>
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Herr HW. Curr Urol Rep 2014
Strategies to Reduce Persistence and Recurrence of BCG Refractory CIS

- Better Agents ➔ Enhanced IVe chemotherapy and immunotherapy
Valrubicin: Pivotal Study

- Open-label, phase III trial
- 90 patients with CIS after prior IVe therapy
- 21% CR at 6 months
- 32% CR at 6 months if you consider that with low grade recurrences (10 pts)
- Overall progression was low
- But, only 8% remained NED at 30 months

• FDA-approved for patients with CIS who fail BCG and are unfit or unwilling to undergo a radical cystectomy
• Despite FDA approval, long-term DFS remains poor and highlights the need for additional bladder-conserving therapies
Gemcitabine Trials

- Inhibits DNA synthesis
- Introduced by Dalbagni (2002) as safe
- Efficacy demonstrated in multiple Phase II trials with

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<th>Recurrence</th>
<th>Median time to recurrence</th>
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<td>Dalbagni 2002</td>
<td>39% at 8-week follow-up</td>
<td>NA</td>
<td>NA</td>
<td>Phase I trial, no serious adverse events</td>
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<td>Dalbagni 2006</td>
<td>50% at 8-week follow-up</td>
<td>90% of patients at 2 years</td>
<td>3.6 months</td>
<td>All patients had failed BCG</td>
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<td>Sternberg 2013</td>
<td>39.1% at 8-week follow-up</td>
<td>62% DFS at 12 months</td>
<td>NA</td>
<td>Cumulative 5-year incidence of progression was 20%</td>
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<td>Bartoletti 2005</td>
<td>Not reported</td>
<td>74.6% DFS at 12 months</td>
<td>7 months</td>
<td>Progression in 7/116 patients; 70 of 116 patients in this trial were naïve to BCG</td>
<td>116</td>
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<td>Skinner 2013</td>
<td>47% at 12 weeks</td>
<td>27.6% DFS at 12 months</td>
<td>6.1 months</td>
<td>Induction with 10-month maintenance</td>
<td>47</td>
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<td>Perdona 2010</td>
<td>NA</td>
<td>45% DFS at median 15.2 months</td>
<td>3.5 months</td>
<td>Induction and maintenance therapy</td>
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</table>

CR=Complete response, NA=Not assessed, DFS=Disease-free survival, BCG=Bacillus Calmette-Guérin

Gemcitabine: SWOG S0353

• U.S. Phase 2 Trial
• 47 patients with HG Ta, T1 and/or CIS who has received at least 2 prior courses of BCG
• Received 2 grams in 100cc NS q week x 6 weeks and the q month x 10 months
• Results: Recurrence-free
  – 3 months: 47% CR
  – 12 months: 28% CR
  – 24 months: 21% CR

Skinner EC et al, JU 2013
Taxane Trials

• Inhibits microtubule depolymerization
• Introduced in BCG failures by McKiernan (2006) with no dose-limiting toxicity at 75 mg
• Efficacy demonstrated in several Phase I / II studies, most with some form of maintenance

| Author       | CR     | Recurrence       | Median time to recurrence | Comments                                                                 | n   
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<tr>
<td>McKiernan 2006[23]</td>
<td>55% at 4 weeks</td>
<td>22.2% DFS at 28 months</td>
<td>Not reported</td>
<td>Phase I trial, no dose-limiting toxicities, follow-up demonstrated progression in 11.1% of patients</td>
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<td>Laudano 2010*[14]</td>
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<tr>
<td>Barlow 2009[23]</td>
<td>61%</td>
<td>1 year DFS: 45%</td>
<td>Not reported</td>
<td>Induction with 9-month maintenance therapy in select patients</td>
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<td>2 year DFS: 32%</td>
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<tr>
<td>Barlow 2009[24]</td>
<td>76.9%</td>
<td>46.2% DFS at 13 months</td>
<td>Not reported</td>
<td>Received induction and 9 months of maintenance</td>
<td>13</td>
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<td>Barlow 2013[27]</td>
<td>59%</td>
<td>1 year DFS: 40%</td>
<td>With docetaxel maintenance 39.3 vs 19.0 months in those without maintenance</td>
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<td>54</td>
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<td>3 year DFS: 25%</td>
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</table>

*Long-term follow-up of phase I study cohort. CR=Complete response, DFS=Disease-free survival, BCG=Bacillus Calmette-Guérin
Docetaxel

- 54 patients
- All failed prior BCG – 22 had only one prior course
- 83% high grade, 53% with CIS

Recurrence-free Survival
DFS at 12 months = 40%
DFS at 36 months = 25%

Barlow et al, J Urol 189:834, 2013
Phase II study of 28 patients recurrent Tis, T1 and Ta who failed at least 1 cycle of BCG
6 weekly nab-paclitaxel 500 mg/100 ml, and monthly maintenance for 6 months

CR 35% and 8 of 10 completed 6 months, 7 of 8 CR at 21 months

McKiernan et al, J Urol. 2014; 192:1633-8,
BCG + IFN in BCG Failures

- Luciani, Urol. 2001:
  - 9/15 (60%) CR (NED) with median F/U 18 months
- Lam, Urol Oncol, 2003:
  - 12/20 (60%) NED with median F/U 22 months
- Punnen, Can J Urol, 2003:
  - 6/12 (50%) NED at 12 months
- O’Donnell, 2004:
  - 231 pts: 42% remaining disease-free at 24 months
BCG + IFN

- Multicenter Phase II: 1,007 pts BCG naïve and failure
- At 24 months, 45% of BCG failure were disease-free
- Those with >/=2 prior courses of BCG or BCG-refractory had worse outcomes

Rosevear, J Urol 2011; 186:817
For Certain High Risk, NMIBC: The Most Definitive Therapy
Strategies to Reduce Persistence and Recurrence of BCG Refractory CIS

- Better Delivery System ➔ Enhanced Bladder Penetration
Hyperthermia Synergy

- Delivery of hyperthermic chemotherapy with temp 41° - 44° C
- Mechanism:
  - Direct cytotoxic effects
  - Enhanced penetration of chemo agent
MMC and Hyperthermia

- 160 patients: 129 (80.6%) BCG failures from a combined “10-year single center experience”
- MMC induction plus maintenance
- Median F/U 75 months
- RFS: 60% (1 year)
- RFS: 47% (2 years)
- Progression to MIBC: 4.3%
- 6.3% discontinued due to side-effects

Arends TJH et al. J Urol 2014
Hyperthermia Systems

- **Synergo**
  - Intravesical microwave applicator
  - 5 thermocouplers deliver hyperthermia to the bladder via direct contact

- **Combat BRS**
  - Bladder Recirculation System
  - External warmer

van der Heijden AG et al. Eur Urol 2004
Souas A et al. Int J Hyperthermia 2014
Photodynamic Therapy (PDT)

- Photosensitizing agent with activation by light
- Initial report w/BCG failures with 5-ALA by Waidelich (2001) with 60% CR in CIS and 21% papillary tumors
- ALA may cause hypotension requiring intervention
- Pilot studies with HAL and Radachlorin show promise

<table>
<thead>
<tr>
<th>Agent</th>
<th>CR</th>
<th>Recurrence</th>
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</thead>
</table>
| 5 ALA\(^{[35]}\) | 19/24 patients | DFS of 60% of patients with CIS at publication  
DFS of 21% without CIS at publication | Good response seen in CIS                  | 24 |
| 5 ALA\(^{[37]}\) | 7/11 patients at 3 months | DFS in 5/11 patients at median of 18 month follow-up | Systemic toxicity with hypotension and skin sensitization | 11 |
| HAL\(^{[38]}\)   | 52.9%    | DFS at 21 months was 11.8%                           | No dose-limiting toxicity in phase 1 study  | 17 |
| Radachlorin\(^{[39]}\) | 100% at 12-week follow-up | DFS at 30 months of follow-up was 60.1%             | Prospective trial, safe with no dose-limiting toxicity  
All patients had high-grade disease | 34 |

PDT=Photodynamic therapy, CR=Complete response, DFS=Disease-free survival, BCG=Bacillus Calmette-Guérin, CIS=Carcinoma in situ, ALA=Aminolevulinic acid, HAL=Hexamethylenelinate

Lots of Medications In Trials

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<tr>
<th>Drug</th>
<th>Trial Number</th>
<th>Phase</th>
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<td>rAd-IFN/Syn3 (Instiladrin)</td>
<td>NCT01687244</td>
<td>II</td>
<td>Interferon-α2b transfected into urothelial cells via adenovirus vector</td>
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<td>RAD001 (Everolimus)</td>
<td>NCT01259063</td>
<td>I/II</td>
<td>Intravesical gemcitabine + oral everolimus (mTOR inhibitor)</td>
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<td>Dovitinib</td>
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<td>Oral dovitinib (tyrosine kinase inhibitor) for patients with FGFR3 over-expression/mutation</td>
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<td>Sunitinib</td>
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<td>EN3348</td>
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<td>Mycobacterial cell wall-DNA complex Vs. Mitomycin C</td>
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<td>ALT-801</td>
<td>NCT01625260</td>
<td>I/II</td>
<td>Recombinant protein – IL-2 + anti-p53-receptor</td>
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<tr>
<td>DTA-H19/PEI</td>
<td>NCT00595088</td>
<td>II</td>
<td>dsDNA plasmid – diphtheria toxin gene under H19 regulation (upregulated in tumor cells)</td>
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<td>CG0070</td>
<td>Pending</td>
<td>II</td>
<td>GM-CSF transfected into urothelial cells via adenovirus vector</td>
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<tr>
<td>nab-rapamycin</td>
<td>Pending</td>
<td>I/II</td>
<td>Intravesical nanoparticle albumin-bound rapamycin (mTOR inhibitor)</td>
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</tbody>
</table>
BCG Unresponsive Trials

- Ad-IFN gene therapy (FKD) – SUO-CTC
- Viccinium (Viventia)
- Atezolizumab (SWOG S1605 - Roche/GNE)
- Pembrolizumab (Merck)
- ABI-009 Phase I/II (AADi LLC)
- Cabazitaxel, gemcitabine, and cisplatin Phase I (Columbia)
- BGJ 398 FGFR targeted therapy (MSKCC)
- ChemoXRT for T1 (RTOG 0926)
Strategies to Reduce Persistence and Recurrence of BCG Refractory CIS

- Better Diagnostics ➔ Enhanced Predictive and Prognostic Tools
Optimizing BCG Therapy

- BCG reduces recurrence and progression
- ~30% patients fail BCG therapy
  - In non-responders, disease often progresses before curative cystectomy
  - Decreased survival
- If we can identify non-responders early, offer alternate therapy at earlier time point
Cytokines and BCG Response

- **Cytokine** response to BCG does differentiate responders from non-responders
- Responders have higher levels of BCG induced cytokines at BCG – 6
- Magnitude of induction of cytokines correlates with recurrence rate and time to recurrence
- Complex interplay of cytokines
ΔIL-8 with 6th BCG

p = 0.041

Courtesy of Dr. Ashish Kamat, MDACC
Cytokine Nomogram

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Courtesy of Dr. Ashish Kamat, MDACC
Recommendations

- Repeat TURBT with PPD or NBI technology
- Fulgurate all abnormal appearing areas
- If > 1 year from BCG, attempt BCG again
- If it has been < 1 year since BCG: Consider RC
- If unwilling or unfit for cystectomy
  - Clinical trial preferred
  - If HG Ta, IVe chemo gemcitabine, taxotere
  - For CIS, IVe valrubicin
Conclusions: BCG Failure

- BCG failure group remains poorly defined
- Best salvage therapy to be determined, modest durable response rates modest
- Risk of progression is significant, increasing with each round of failed therapy
- Cystectomy remains the most durable option for appropriate surgical candidates
Forecast for the Future:
We need to develop…

• Markers that predict response or failure
• Better surgical strategies to eradicate CIS
• More effective, less toxic salvage regimens
• Enhanced delivery for salvage therapy
• Personalized therapy tailored to individual patient and tumor risk profiles
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