Risk Adapted Treatment of Non-muscle Invasive Bladder Cancer

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Goals

- Minimize treatment for patients at lowest risk
- Focus on patients at high risk for recurrence and treat to reduce or delay need for treatment
- Identify patients at high risk of progression:
  - Select patients for early radical cystectomy
  - Treat the rest with aggressive intravesical therapy and meticulous follow-up
Case: J.V.

- 60-year-old woman
- Gross painless hematuria x 6 months
- Multiple courses of antibiotics

Solitary LG Ta tumor
Low risk disease
LOW RISK
Initial, solitary LG Ta
Infrequently recurrent LGTa

INTERMEDIATE RISK
Multifocal LG Ta
LG Ta (T1) w/ freq rec
Any LG T1

HIGH RISK
Any HG, Ta or T1
CIS

Risk of Recurrence ~ 50% at 3 years
Risk of progression negligible

**Goals:** Reduce recurrences, minimize burden of treatment

- Consider post-TUR chemo
- Don’t use BCG
- Consider less frequent cystoscopy
  - *EAU guidelines: if 3 month cysto is negative can go 9 months and then yearly*
- Office fulguration for small tumors
Controversies about post-TUR chemo

- Recommended by EAU guidelines, an option in AUA, NCCN guidelines

*BUT:*

- May mainly benefit lowest-risk patients
  benefit for high grade or with BCG less clear
  

- Rare *severe* side effects with treatment can occur
  

- Recent placebo-controlled studies with gemcitabine and apaziquone showed no benefit
Recent Meta-analysis

13 RCTs, 2548 total patients, overall benefit 38% reduction in rec

- Only 1 was double blind and placebo-controlled (gemcitabine)
- Only 4 were placebo-controlled
- Only 3 controlled the duration of CBI in either arm

➢ Conclusion – overall quality of data is poor!

Perlis EU 64:421, 2013
Post-TUR Epirubicin

- 214 patients epirubicin vs no instillation
- Most helpful for lowest risk tumors:

Did not change outcome for higher risk tumors:

- Recurrent

- Multifocal

- Risk score 3+
Gemcitabine trial showed no benefit

- 355 patients
- Ta-T1, G1-3, no CIS
- 22% recurrent
- Gem 2g in 100cc vs saline x 40 min
- Blinded, placebo-controlled
- All pts had CBI for > 20 hours

SWOG phase III trial awaiting analysis

Bohle et al, EU 56:495, 2009
Severe complications from post-TUR MMC

• Early randomized trials reported no increase in side effects

BUT

• MMC blocks healing – often see ulcer at TUR site for up to 6 months
• If it extravasates may cause very severe symptoms:
  Pain
  Acute peritonitis
  Rare ‘bladder cripple’ from single dose
Conclusions – Low Risk

- Minimize burden and toxicity of treatment
- Post-TUR may help but be careful
- Watch grade to pick up the few patients who may progress
What is the role of intravesical chemotherapy today beyond post-TUR treatment?

- Intermediate risk patients – reasonable alternative to BCG
- Patients in whom BCG is contraindicated (or not available)
- BCG failure
Case: A.R

- 54 year-old man
- LG,Ta tumor resected 2 yrs ago
- 1 previous recurrence MMC x1 post-TUR

Multifocal, recurrent LGTa = intermediate risk
• Immuno-compromized patients
  – AIDs, transplant patients
  – High-dose steroids
  – *Drugs for rheumatoid arthritis (ie TNF blockers)*

• Previous serious complications from BCG
  (ie: sepsis, hydronephrosis, arthritis, hepatitis)
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Thiotepa</td>
<td>Alkylating agent</td>
<td>Systemic absorption</td>
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<tr>
<td>Mitomycin C</td>
<td>Bioreductive alkylating agent</td>
<td>Severe desiccant</td>
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<tr>
<td>Doxorubicin</td>
<td>Topoisomerase inhibitor</td>
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<tr>
<td>Valrubicin</td>
<td>Topoisomerase inhibitor</td>
<td>FDA approved for CIS after BCG</td>
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<tr>
<td>Epirubicin</td>
<td>Topoisomerase inhibitor</td>
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<tr>
<td>Gemcitabine</td>
<td>Pyrimidine analog</td>
<td>Non-desiccant</td>
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<tr>
<td>Docetaxel, paclitaxel, nanoparticles</td>
<td>Microtubule inhibitor</td>
<td></td>
</tr>
<tr>
<td>Apaziquone</td>
<td>Bioreductive alkylating agent</td>
<td>Metabolized to MMC – stronger</td>
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</table>
• Treatments are topical
  – little penetration
  – little or no absorption into circulation

• Affected by bladder milieu  (pH, dilution, metabolism)

• Pharmacology not always well worked out

• Few comparative studies
Intravesical Chemotherapy

Side Effects from 6-week course:

• Chemical cystitis 15-30% (doxorubicin worst)

• Bladder contracture - 2-3%

• Systemic side effects are relatively rare – less than with BCG
- Increase concentration/dose
- Find better drugs
- Increase permeability of mucosa
- Increase dwell time of drug
1. **Increase concentration**
   40 mg in 20 cc

2. **Alkalinate urine**
   1.3 g sodium bicarb
   night before and in am

3. **Dehydrate patient**

4. **Use bladder scanner**
   to empty bladder

> Should do whenever you use MMC in the office
• 495 patients
• Intermediate risk
• Randomized:
  1) 6 wks BCG
  2) 6 wks MMC
  3) 6 wks MMC + monthly maintenance x 3 years

➢ Suggested for higher risk patients

Friedrich EU 52:1123, 2007
Intravesical Gemcitabine

- Dose 2gm/100cc, not absorbed
- Well tolerated

Dalbagni JCO:24:2729, 2006

May be useful as 2\textsuperscript{nd} line after 1\textsuperscript{st} course of BCG:

- 80 patients with intermediate to high risk who recurred after 1\textsuperscript{st} course BCG x 6
- BCG vs twice-weekly gem
- Maintenance 3 weeks at 3, 6, 12 mo.

New Intravesical Therapies

- Taxanes
  - Docetaxel
  - Abraxane (nanoparticle encapsulated paclitaxel)
- Apaziquone – more potent relative of mitomycin C
- Device – assisted mitomycin C
  - Heat (microwave)
  - Electromotive
- Gene therapy
- New Immunotherapies
Hyperthermia + MMC

- Microwave unit (Synergo™) - delivers heat directly to bladder wall via transurethral wires through 20F catheter
- Heat increases cell permeability to mitomycin C
- Sessions last 60 minutes
- Side effects mainly bladder irritation

Randomized trial compared to 20mg in 50cc MMC x 2

Colombo BJUI 107(6):912, 2011
MMC with hyperthermia

- 56 pts with HG T1, half failed prior BCG

Halachmi et al, Urol Onc 29:259, 2011
Electromotive MMC

- Delivers electricity from catheter to abdominal wall electrodes
- Increases MMC absorption
- Toxicity similar to MMC
- Not yet approved in US – trials starting

Randomized trial vs BCG or passive MMC
CIS +/- papillary lesions

<table>
<thead>
<tr>
<th></th>
<th>BCG</th>
<th>MMC</th>
<th>E-MMC</th>
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<tr>
<td>n</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>6mo CR %</td>
<td>64</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>Rec %</td>
<td>53</td>
<td>75</td>
<td>53</td>
</tr>
<tr>
<td>Progression %</td>
<td>16</td>
<td>22</td>
<td>16</td>
</tr>
</tbody>
</table>

BCG alternating with EMDA-MMC vs BCG alone – all T1 (40% G3T1)

Di Stasi Lancet Oncol 7:43, 2006
Increasing drug dwell time

- Nanoparticle-encapsulated docetaxel may improved drug dwell time on mucosa
  Lu et al, J Urol 185:1478, 2011

- Intravesical gene therapy induced production of urinary IFNα for 4-6 days after instillation
  Fisher J Urol (Supp)1907A, 2009
Conclusions

• Intravesical chemotherapy can reduce recurrence
  – Less effective than BCG in high-risk patients
  – Less side effects compared to BCG
  – Multiple instillations better than single post-TUR for intermediate risk patients
  – Maintenance may help

• New drugs/techniques may improve effectiveness
  – Almost no comparison studies between drugs

• No impact on progression

➢ Reasonable alternative to BCG in intermediate risk
Case R.C.

- 79-year-old woman
- CIS x 2 years
- BCG x 2 cycles, 6 weeks each
- Persistent positive cytology – bx CIS
• Six randomized trials > 2400 patients

• Meta-analysis showed 30% relative reduction in recurrence for BCG compared with MMC

• Only BCG plus maintenance (SWOG protocol) has been shown to decrease progression

• Few comparisons with newer regimens of intravesical chemotherapy

Shelley BJU Int, 93:485, 2004
• For low risk – DON’T USE IT!
• For intermediate risk – try mitomycin C
• Consider 1/3 dose – treat 3 patients at a time
• For high risk, consider optimized MMC, combination chemotherapies
• Clinical trial with device-assisted MMC
• For highest risk patients, consider cystectomy (especially recurrent CIS or HGT1)
4-arm Randomization – 1800 pts
Full dose, 1 vs 3 yrs maintenance
1/3 dose, 1 vs 3 yrs maintenance

**Conclusions**
- No difference in toxicity or progression
- High risk – FD + 3 yrs best
- Intermediate risk – FD + 1 yr

**Graphs:**
- Full dose vs 1/3 dose
- 1 yr vs 3 yr maintenance
Definitions of BCG failure

Intolerant: unable to tolerate side effects

Resistant: persistent disease at first evaluation (but responds with 2nd course)

Refractory: persistent disease after 2nd course

Relapsed: initial response, with early (< 1 yr) or late (>1 yr) recurrence
BCG plus Interferon Alpha

Multicenter phase II trial – 213 patients with CIS

- Patients with 2 or more prior courses of BCG or BCG-refractory have high failure rate
- Late relapse after 12 months can be re-treated (+/- Interferon)

Rosevear, JUrol 186:817, 2011
Multifocal/recurrent low-grade Ta:
- Consider switch to intravesical chemotherapy
- Liberal use of office fulguration, less frequent cystoscopy

Carcinoma-in-situ or high-grade Ta:
- Wait at least 6-8 weeks after BCG to re-evaluate patient
- Try a second 3-6 week course – 20-30% will respond
- Don’t call it “failure” until 6 month cystoscopy

High-grade T1
- Risk of progression is high with repeated course
- Consider cystectomy at first sign of failure

➢ Upper tracts and urethra must be cleared
Options for salvage therapy for high-risk patients

**Not effective:**
“Standard” intravesical chemotherapy
Additional BCG after second course
(unless > 1 year later)

**Currently available:**
BCG + Interferon
“Optimized” mitomycin C
Valrubicin (Valstar)
Gemcitabine, docetaxel
Doublet chemotherapies

**Not yet approved:**
Electromotive MMC (EMDA)
Synergo microwave MMC
New delivery systems
(gene therapy, docetaxel nanoparticle)
Post-market open-label study - 80 patients with CIS
39% had at least 2 prior courses of BCG
Received 6 or 9 weeks of Valstar

- 35% NED at 1st 3 mo eval (positive cytology allowed)
- CR at 6 months 18%
- Local side effects mostly mild-moderate

Recurrence-free survival
Gemcitabine

SWOG S0353

- 47 patients, all failed 2 prior courses of BCG
- 89% high risk, 60% CIS
- 6 weekly treatments 2g in 100cc, then monthly x 12

Results:
- 47% NED at 3 months
- 28% continuously disease-free at 12 mos

Skinner J Urol 190:1200, 2013
Docetaxel for BCG failure

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

Recurrence-free Survival

Barlow et al, J Urol 189:834, 2013
• Combinations clearly beneficial in systemic chemotherapy – block resistance

• Intravesical combinations tested:
  Gemcitabine followed by MMC
  Docetaxel followed by gemcitabine
  Others?
1g gemcitabine, then 40 mg MMC  
(sequential, 90 min each)

47 patients
- 76% intermed/high risk, 55% CIS
- 17 no prior BCG (10 immunocompromised)
- 55% ≥2 prior courses BCG

68% CR at 3 months
48 % NED at 1 year
38% NED at 2 years  (20-25% for HG/CIS)

Conclusions – BCG failures

• Best salvage intravesical therapy is not clear
  Most promising: doublet chemotherapies, device-assisted therapies (microwave/electromotive)

• For high-risk patients:
  – Durable responses < 30% with most salvage treatments
  – Cystectomy is still safest option if patient is surgical candidate
When is cystectomy indicated as primary therapy for NMIBC?
Case: DS

- 68-year-old smoker
- Two previous tumors, HGTa
  6 weeks of BCG after last tumor 2 years ago
- Upper tracts normal on CT

- Now has a 2 cm tumor, completely resected HGT1
High Grade T1

- Highly aggressive behavior – similar to T2
- Should not be considered ‘superficial’

Risk factors for progression:
- Multifocal, large tumor
- Deep LP invasion
- Associated CIS
- Lymphovascular invasion
- Failed prior BCG

Cystectomy
129 patients with T1 (80% HG)
- all treated with initial BCG
- Pathology re-reviewed

T1m = microinvasion
  single focus <0.5mm
T1e = extensive
  (more than that)
Predictors of Progression

- T1m vs T1e along with CIS, gender, predicted progression
- Better than EORTC risk group or T1a/b

Van Rijn BJUI 110:1169, 2012
## Outcome for HGT1 treated with BCG

<table>
<thead>
<tr>
<th>Study</th>
<th># pts</th>
<th>Med f/u (mos)</th>
<th>Progression</th>
<th>Delayed Cystectomy</th>
<th>DOD</th>
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<tbody>
<tr>
<td>Cookson</td>
<td>86</td>
<td>184</td>
<td>53%</td>
<td>36%</td>
<td>24%</td>
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<tr>
<td>Thalmann</td>
<td>92</td>
<td>64</td>
<td>30%</td>
<td>29%</td>
<td>23%</td>
</tr>
<tr>
<td>Kakiashvili</td>
<td>72</td>
<td>72</td>
<td>30%</td>
<td>18%</td>
<td>17%</td>
</tr>
</tbody>
</table>

### PROBLEMS WITH THESE DATA:

- Huge selection bias
- Many patients did not undergo repeat TURBT or maintenance BCG
- Treatment after recurrence varied

- No randomized prospective studies compared to early cystectomy

Cookson, J Urol 158:62, 1997
Thalmann, J Urol 172:70, 2004
Kakiashvili BJU Int 107:540, 2011
Repeat TUR for HGT1 disease

352 patients treated with repeat-TUR and BCG at MSKCC

Progression-free survival by 2nd TUR path

RECOMMEND:

T0, Ta or Tis → BCG

Persistent T1 or T2

Cystectomy

Herr et al, J Urol 177:75, 2007
Radiation for cT1 disease

- 141 patients
- Initial cT1 G3 (84) or G1-2 with CIS or large tumors
- treated with XRT +/- systemic chemo

Weiss JCO 24:2318, 2006

DSS with bladder preserved
- 210 patients with initial dx T1G3
- CIS allowed, no prior T2 or intravesical therapy
- Randomized to XRT vs intravesical BCG

➢ No difference in recurrence or progression

Harland J UROL 178:807, 2007
Patients upstaged to $\geq pT2$ do worse
Risk of cancer death continues > 15 years after BCG

BCG – MSKCC

Cystectomy – USC

- Be sure there is muscle in specimen
- Look at slides yourself
- **MUST** repeat TUR if considering intravesical therapy
- Have a ‘short fuse’ for considering cystectomy for BCG failures who can tolerate surgery
No difference in % upstaged or with CIS on final pathology

CIS strong predictor of cancer death

Ganzinger EU 53:146, 2008
CONCLUSIONS

• Patient selection is the key
• Repeat aggressive TUR can help with understaging and defining risk
• The longer you use ineffective intravesical therapies, the higher the chance of metastasis
• For healthy patients, early cystectomy may have some advantages
Thank you!
TURBT

Low risk
- Single post-TUR chemotherapy alone

Moderate risk (multifocal or recurrent)
- +/- Single post-TUR chemo
- 6-wks BCG or MMC

High risk (G3T1, CIS)
- +/- Single post-TUR chemo
- BCG + maintenance (MMC + maintenance if BCG contraindicated)
• 105 pts, G3T1 with at least 2 risk factors for progression (cis, large tumor, multifocality)

• 51 refused cx and treated with BCG. All ultimately had a delayed cystectomy (avg 11 months later)

• Cystectomy done at first sign of recurrence
  - T1 or TIS (66%)
  - T2 (34%)

➢ 5 yr CSS 83% vs 67%

Ganzinger EU 53:146, 2008