Management options for high-risk, BCG-refractory NMIBC

Alan M. Nieder, M.D.
Columbia University Division of Urology
Mount Sinai Medical Center
Bladder Cancer in U.S.

- 4\textsuperscript{th} most common cancer in men
- 9\textsuperscript{th} most common cancer in women
- 60,000 cases/year newly diagnosed
- 12,000 deaths/year

- \textit{Florida 4\textsuperscript{th} most populous state (>17 million)}
• Only a slight decline in the overall incidence of BC in Florida over the last 25 years
• Only a slight decline in the % of advanced BC
  – Lowest rates of reduction in white & black females
• Rates of advanced BC are similar in blacks & whites despite substantially lower over all rates in blacks
• Only a minimal decline in the BC mortality rates for Black and Whites, but not Hispanics

Results: BC mortality

How to improve BC outcomes

1. Prevention
2. Increasing awareness/education
3. Early identification of BC
4. Improved stratification
5. Aggressive treatment of high-risk BC
6. Improved surgical treatment
Earlier Cystectomy

- Significant survival benefit for pT1 vs. pT2 BC:
  - pT1: 90% 5-year survival
  - pT2: 50% survival
- RC for pT1: 30% upstaged, 10-15% N+

Chalasani et al. RC for T1 BC. CUAJ 2011.
Cystectomy even for elderly

- Retrospective study of > 1000 pts
- Stratified by < 60, 60s, 70s, > 80yo
- No mortality difference (1%, 3%, 4%, 0%)
- No sig difference for those > 70 for IC vs. NB

Conclusion:
- Chronological age not a contraindication for RC
- Carefully selected older pts can have NB

Variability in the Recurrence Rate at First Follow-up Cystoscopy after TUR in Stage Ta T1 Transitional Cell Carcinoma of the Bladder: A Combined Analysis of Seven EORTC Studies

Maurizio Brausi\textsuperscript{a}, Laurence Collette\textsuperscript{b}, Karlheinz Kurth\textsuperscript{c}, Adrian P. van der Meijden\textsuperscript{d}, Wim Oosterlinck\textsuperscript{e}, J.A. Witjes\textsuperscript{f}, Donald Newling\textsuperscript{g}, Christian Bouffio\textsuperscript{x}, Richard J. Sylvester\textsuperscript{b,*}

EORTC Genito-Urinary Tract Cancer Collaborative Group.

- Retrospective review of previous multicenter trials including 2400 pts
- Evaluated risk of recurrence at 3 months
- Also stratified by intravesical therapy use

Need to improve TURBTs

- Recurrence varied from 3% - 20% (for single BT) to 7% - 46% (for multiple BTs)

Conclusion:
- Risk of recurrence at 3 months: huge variation depending upon center/surgeon
- TURBTs are not being performed appropriately

Intravesical BCG

• First line treatment for CIS and to prevent recurrence after T1 or HG Ta BTs
  – AUA & EUA guidelines
• Sylvester et al meta-analysis (2005):
  – 68% complete response compared to 50% for chemo
  – At 3.5 years: 50% vs 25% remained disease free (BCG vs chemo)
• Minimal efficacy after 2 cycles

Maintenance BCG

• 3 weekly doses at 3, 6, 12, 18, 24, 30, 36 months
• Clearly reduces recurrence
• Lamm: 75% vs 47% RFS (maint vs induc)
• Hinostu: 93% vs 65% RFS (maint vs induc)

BCG Failures

- **Refractory**: persistence of disease
- **Relapse**: after >3 or 6 months of disease-free
  - Early: < 1 year (worse prognosis)
  - Intermediate: 1-2 years
  - Late: > 2 years
- **Intolerant**: unable to receive full dose
Management Options for those who refuse RC (or are unfit)

- **CYSTECTOMY**

- Why are they refusing?
  - Have patients discuss with other patients potential lifestyle changes
  - Demonstrate photos of ileal conduits

- Suggest second-opinion
Management Options for those who refuse RC (or are unfit)

• More BCG
• BCG/IFN
• Valstar
• MMC
• Docetaxel
• Gemcitabine
More BCG?

- Failure to achieve complete response to induction: sig risk of progression/death
- < 10-20% efficacy after 2nd dose

Lerner et al. Failure to achieve complete response... *Urologic Oncology*, 2009.
Prospective, multi-center, randomized study 670 patients

4 arms: BCG naïve pts: BCG vs BCG/IFN & megadose vs RDA vitamins

Received Maint

End point: + Biopsy or + cytology
BCG/IFN with vitamins

- No difference in RFS at 24 months
- IFN cohort: increased fevers and constitutional symptoms

Conclusion: no benefit to addition of IFN or oncovite

Prospective randomized study MMC vs BCG (followed by maintenance) of 261 pts

- BCG: sig improved RFS vs MMC
  - No difference in progression
  - Crossover treatment: BCG >> MMC

Conclusion: BCG superior to MMC for recurrence but not progression or survival

Combined Thermo-Chemotherapy for Recurrent Bladder Cancer After Bacillus Calmette-Guerin

Ofer Nativ, * J. Alfred Witjes, Kees Hendricksen, Michael Cohen, Daniel Kedar, Ami Sidi, Renzo Colombo and Ilan Leibovitch

- Retrospective review of 111 pts who failed BCG
- Synergo: thermo-chemo with MMC weekly x 6 weeks
- DFS: 56% at 2 years
- Improved efficacy in maint cohort (61% vs 39%)
- Progression: 3%

Conclusion: Thermo-chemo may be effective (but needs maint)

Not Approved in U.S.

EMDA
(Electromotive Drug Administration)

- Uses an electric field to increase cell permeability
- Physion (Italy)
- Studied in MMC and BCG (with improvements over non-EMDA treated pts)
- Role in BCG Refractory patients?

Intravesical Valrubicin

- Only FDA-approved therapy for BCG-refractory CIS
- <10% efficacy at 2 years (and not for T1)

Intravesical valrubicin in patients with bladder carcinoma in situ and contraindication to or failure after bacillus Calmette-Guérin☆

Colin P. N. Dinney, M.D.ᵃ,⁎, Richard E. Greenberg, M.D.ᵇ, Gary D. Steinberg, M.D.ᶜ

• Retrospective review of two updated Phase III trials
• 80 BCG-refractory CIS pts received Valrubicin 800mg/weekly
• 40% had received > 2 BCG courses

Intravesical Valrubicin

- Complete Responders: 18%

Conclusion: those who are NR should undergo RC

Long-Term Survival Outcomes with Intravesical Docetaxel for Recurrent Nonmuscle Invasive Bladder Cancer After Previous Bacillus Calmette-Guérin Therapy

LaMont J. Barlow,* James M. McKiernan and Mitchell C. Benson

- Retrospective review, 54 patients for salvage docetaxel therapy (2003-2012)
- Induction: 6 weekly installations (75mg/100ml)
- Maintenance: monthly x 9 months

Intravesical Docetaxel

Results:
- 60% had complete response after induction
  - 18 continued on maintenance
- Median time to recurrence: 39 vs. 19 months (maint vs induction only)
- 1 & 3 year recurrence-free survival: 40% & 25%
- 30% underwent RC
- 5-Year DSS/OS: 85% and 70%

Conclusions:
- Consider Intravesical docetaxel for BCG failures
- Induction + Maint appears to be most appropriate

• Retrospective review 1999-2011: 69 patients (37 BCG refractory, 30% recurrent)

• Instillations: BIW x 6 weeks (2000mg/100ml)

Results:
• 5-yr OS: 58% vs 71% (BCG refrac vs others)
• 40% achieved complete response
• 30% underwent RC

Conclusion: Consider for those who refuse RC or are unfit

Conclusions

• High-risk NMIBC is deadly
• Must confirm not actually muscle-invasive
  – ReTURBT
• Early Cystectomy is always first choice
• Options limited for those who refuse or are unfit
  – Mixed short-term results with other agents
• **Recommend second opinions**