Current Experience with Intrapelvic/Intraureteral Irrigation/Ablative Therapy

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Disclosures

• Clinical trials
  – Endo, FKD, Roche/Genentech, Viventia

• Advisory Board
  – Ferring, Nucleix, OncoGeneX, Sitka, Taris

• Consultant
  – Biocancell, Telesta, UroGen, Vaxiion
UTT – Intracavitary Therapy

• First endoscopic treatment reported 1985\(^1\)

• Delivery via percutaneous nephrostomy or via ureteral catheter

• MMC, Epirubicin, Thiotepa, BCG, BCG/IFN\(^2\)

\(^1\) Huffman, et al Cancer 55:1422, 1985
EAU guidelines (2015)

• Antegrade instillation of BCG or MMC after complete tumour eradication is feasible as adjuvant tx or for conservative tx of CIS (LE: 3)
• Retrograde instillation via ureteral catheter can be dangerous due to possible ureteric obstruction and pyelovenous influx during instillation/perfusion.
• Reflux via double-J stent not advisable since it often does not reach the renal pelvis.
  – Japanese study (Tokyo strain) - 9/9 patients with high grade positive cytology converted to negative – mean duration 86 days (53-264)¹

¹ Irie, et al Urology 59:53, 2002
Upper Tract Irrigation

- Verify sterile urine
- Micro/mini drip chamber; 50cc volume; run in over hour
- Use manometer to keep intrapelvic pressure \( \leq 20\text{cm water} \)
Retrograde SP Catheter

- Place x-tra long guide wire to upper tract
- Fill bladder through cystoscope
- Percutaneous cystostomy w/ 18 ga needle
- Pass 2nd guide wire through sp site
- Grasp 2nd wire and deliver antegrade per urethra

Retrograde SP Catheter

- Dilate SP site to 10 Fr. w/ 8/10 coaxial dilator
- Leave 8 Fr. introducer externalized per urethra
- Pass x-tra long wire into 8 Fr. and pull into bladder

Retrograde SP Catheter

- J-wire 5 Fr. Pollack into upper tract
- Exchange x-tra long wire w/super stiff
- Pass single j stent over super stiff under fluoro into upper tract
- Remove guide wire, cap stent, suture stent in place

UTT – Intracavitary Therapy

- 55 patients treated with BCG via PCN
- 64 kidneys; 42 with CIS
- Less effective as adjuvant therapy

\[ p = 0.05 \]

\(^1\) Giannarini, et al Eur Urol: 60:955, 2011
Review of 12 series upper tract instillation

- Post resection Ta/T1 adjuvant therapy
  - N = 22 (renal units-ru) MMC recurrence 14-29% (9.5-31 mos)
  - N = 202 (ru); BCG recurrence 11-87% (9.5-59 mos)
  - Largest series (50 ru) BCG 36% recurrence at 61 mos

- Curative therapy for CIS using BCG
  - N = 176 (ru) RR 63-100%; Recurrence 0-55% (1-82 mos)
  - Largest series 42 (ru) 40% recurrence (42 mos)
Single Dose Peri-operative MMC

• Prospective n=19 patients (one bilateral)
• Exclusion: known HG cancer; tumor > 1.5 cm; incomplete laser ablation (majority LG)
• 5F open ended catheter
• MMC 40mg/40cc NS over 40 minutes; clamped + 20 minutes
• 13 cancer free long term (24 months)
  – 7 repeat ablation and MMC mean 4 months
• No systemic toxicity
• 3 ureter strictures

Aboumarzouk, et al Urol Annals 5:3, 184
UTT – Intracavitary Therapy

- Marker lesion trial standard of care for testing activity of new drugs for intravesical therapy
  - 23 studies with >1200 patients
  - CR in 30% to 50%; highest response rate
    Apaziquone (67%); CR ≈ higher RFS
  - No progression in intermediate risk patients
- Chemoablation of upper tract tumors?
MitoGel™ - Chemistry

- Poloxamer 407 based inverse thermosensitivity
  - Block co-polymer PEO-PPO-PEO
  - Also acts as surfactant
- MMC 4mg/1ml gel
- 20 cc gel = 80mg MMC
Pre-Clinical (swine model) studies results show:

- Dwell time of >6h were shown
- No occlusion / blockages
- No renal function impairment
- PK plasma within safety limits

The gel filled the renal cavity and ureter and dissolves slowly in few hours

Chamie et al AUA 2014
Syringe Housing

Syringe filled with Mitogel

Injector
MitoGel: Clinical Proof of Concept in UTUC: Chemoablation for Organ Sparing

Ongoing UTUC Compassionate Use Program
- 18 patients enrolled
- United States (MD Anderson, Baylor College), Netherlands, Switzerland; Israel
- Localized treatment of hard to resect tumors; extensive tumor burden
- 12 with confirmed low-grade disease
- 10 evaluated to date
- >90 instillations performed
- Feasibility and safety demonstrated.

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<th>Post</th>
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<td><img src="image1" alt="Pre-image" /></td>
<td><img src="image2" alt="Post-image" /></td>
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**Complete response**
- 7

**Partial response**
- 3

**Evaluated to date**
- 10

*Durability evaluations ongoing (as of June 2016)*

Images courtesy of Dr. Gregory Wirth, Geneva Hospital, Switzerland

**Reached primary evaluation time**
BCM – Patient 2

• 73 yo male
• Prior left nx for AML
• Long history of recurrent TaLG right renal pelvis dating to 2007
  – Bladder TaLG progressed to CIS Rx BCG
• Intracavitary MMC, BCG
• Most recent ureteroscopy minimal disease
• Completed 6/6 Mitogel 6mg/cc
• Follow up ureteroscopy necrotic tumor
  – No viable cancer
Treatment:

– Six (6) once weekly instillations of MitoGel™ Preparation.
– MMC dosage: 4mg per 1mL of TC-3 gel
  • Based on renal pelvis and calyx volume (5-15mL)
  • 20-60mg MMC total dose
  • 1.3gm NaHCO3 HS, AM and 30’ prior to tx

Target Patient Population:

– 74 patients with Pathologically confirmed LG non-invasive UTUC
– 90% power to demonstrate that the observed CR rate is superior to the rate of 15%.
## Study Design:
- A prospective Phase 3, open label, single arm trial, in patients with LG UTUC

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<th>Treatment</th>
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<td>1-3 Weeks</td>
<td>6 Weeks</td>
<td>3 ± 1 Weeks</td>
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**Product:**
- Mitogel™ kit (0.4% MMC; hydrogel)

**Study Objectives:**
- Efficacy and safety of Mitogel™ instillation in the treatment of UTUC
Summary

• Intracavitary (renal pelvis) treatment with BCG or MMC safe and minimal toxicity
• Deliverable via PCN, ureteral catheter, suprapubic ureteral catheter
  – Monitor intrepelvic pressures ≤ 20 cm water
• Reverse thermosensitive polymers facilitate 4-6 hours exposure with MMC
• Compassionate use in the upper urinary tract demonstrates feasibility and safety
• Phase III trial planned for 2016
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