Neoadjuvant Targeted Treatments for Advanced RCC

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Objectives

- At the conclusion of this symposium the participants should be able to:
  - Assess non-surgical and surgical treatment for the patient in collaboration with medical oncology to optimize patient outcomes
  - Integrated targeted therapy for downsizing of tumors prior to surgery into clinical practice
- Potential COI
  - Investigator: GSK
  - Speaker, investigator: Pfizer

Debulking Nephrectomy

- Overall survival favored nephrectomy group (13.6 months vs. 7.8 months; p=0.001)
Cytoreductive Nx Criteria
Fallick et al., J Urol, 1997; 158: 1691

• > 75% tumor debulking: Columbia data supports (McKiernan et al., 2006)
• No CNS or liver metastases
• Adequate pulmonary and cardiac function
• ECOG PS of 0 or 1
• Predominately clear cell histology ???

• Poor prognostic factors per MDACC: low albumin, high LDH, anemia, symptoms due to mets, liver mets, lymphadenopathy, multiple sites of disease.

Progression-Free Survival by Percentage of the Primary Removed

Phase 3 Randomized Study Comparing Nephrectomy Plus Sunitinib vs Sunitinib Without Nephrectomy in First-Line Metastatic RCC: CARMENA

• Primary Objective: Overall Survival
Neoadjuvant Rx and Consolidative Surgery in 2013

- Increasingly common scenario in era of targeted agents
- RR approaching 40%
- Tumor shrinkage or stabilization in 70-80%
- Responses in primary tumor now more common too
- Patients live longer
- More opportunities to integrate surgery, although must do selectively

Rini, Campbell, Urology, 2007

Neoadjuvant Targeted Therapy
Consolidative Surgery
Cleveland Clinic Experience

4) TKI (Pazopanib) to enable or facilitate P Nx, in progress

Choosing Therapy Based on Response Rate

<table>
<thead>
<tr>
<th>Agent</th>
<th>Objective response rate</th>
<th>Tumor stable or shrinkage rate</th>
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</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>40-45%</td>
<td>~70-75%</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>30%</td>
<td>~65-70%</td>
</tr>
<tr>
<td>Bevacizumab + IFN</td>
<td>25-30%</td>
<td>~70-75%</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>2-10%</td>
<td>~70-75%</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>9%, 1%</td>
<td>~60%</td>
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<tr>
<td>Everolimus</td>
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Response of the Primary Tumor

Does the Primary Tumor Respond?

- N = 19 patients, 21 tumors at Cleveland Clinic, 2006-2008
- Unsuitable for primary Nx, Rx'd Sunitinib
  - 13 with combinations of large tumor size, bulky regional LN's, high level IVC involvement, invasion of adjacent organs, proximity to vital structures, all but 3 with mets too
  - 6 patients with extensive burden metastatic disease, with some overlap with above category
  - 2 bilateral extensive RCC

J Urol, 181:518-23, 2009

Patient Population

- Mean age: 64
- Median tumor size: 10.4 cm
- N+ (12), M+ (16)
- Most had advanced RCC, locally and with metastases too

Primary Tumor Response

- CR: none
- PR: 3 (14%)
- PR or Tumor shrinkage: 8 (42%)
- Mean Tumor Downsizing: 24%
- Progression: 9 (43%)
Pre-surgical VEGF-Targeted Therapy in RCC

<table>
<thead>
<tr>
<th>Approach</th>
<th>Patient population</th>
<th>No. of pts with primary tumor shrinkage</th>
<th>Amount of primary tumor shrinkage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib (CCF/retrospective)</td>
<td>RCC (n=21)</td>
<td>42%</td>
<td>24% (range, 2-64%)</td>
</tr>
<tr>
<td>Sunitinib (Netherlands/retrospective)</td>
<td>M+ pts with primary in place (n=52)</td>
<td>73% (range, 2-33%)</td>
<td>12%</td>
</tr>
<tr>
<td>Sunitinib (CCF/prospective)</td>
<td>Unresectable RCC (n=30)</td>
<td>80%</td>
<td>22% (range, 1-44%)</td>
</tr>
<tr>
<td>Sorafenib (UNC/prospective)</td>
<td>≤T2 RCC: orals: 400 mg BID x 4-8 wks pre-resection (n=26)</td>
<td>77%</td>
<td>10% (range, 0-48%)</td>
</tr>
<tr>
<td>Bevacizumab (MDACC/prospective)</td>
<td>Metastatic RCC pts with at least erlotinib prior to nephrectomy; 10% reduction in size (n=50)</td>
<td>55%</td>
<td>15% with at least 10% reduction in size</td>
</tr>
<tr>
<td>Sorafenib, UCSD, retro. Loc.</td>
<td>NSS (12)</td>
<td>100%</td>
<td>21%</td>
</tr>
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</table>

Averages: 50-80% 10-25%

Largest Series to Date

- MDACC, N = 168 with mRCC, primary tumor in situ
- Multiple reasons for systemic Rx first: widespread mets, brain mets, non-clear cell or sarcomatoid, poor PS, clinical trial
- Multiple different agents used
- Median max change in size: -7.1%
- 6% PR, 90% tumor stable or some shrinkage
- Very modest gains
- 33% went on to cytoreductive Nx
- Cytoreductive Nx still standard of care


Targeted Therapy Prior to IVC Thrombectomy

- MDACC, N = 25
- 7 (28%) had ↓ in thrombus height
- 7 (28%) no change
- 11 (44%) had ↓ in thrombus height
- One (4%) had ↓ in thrombus level, 3 (12%) had ↓ in thrombus level
- Only one (4%) where surgical approach was affected by ↓ in thrombus level (IV → III)

Surgery in our Series

- Median follow-up of 6 mo (1-25 mo)
- 6 patients had surgery (29%)
  - 4 Radical Nx
  - One Rad Nx and contralateral P Nx
  - One bilateral P Nx
- All tumors with viable cancer
- No complications

Consolidative Surgery
Cleveland Clinic Experience
How Safe is Surgery in this Setting?

- June 2005 to August 2008, all of protocol
- N = 19 patients (median age 61)
- 21 operations
  - Locally advanced (8), most with mets too
  - Locally recurrent (6)
  - Metastasectomy (3)
  - Bilateral, extensive RCC (2)

J Urol, 182:881-6, 2009

Bevacizumab: Summary

- 1.5-2% bowel perforation in certain populations: mCRC pts predisposed
- 5% risk arterial thrombotic events when given with chemo
- Real risk bleeding, particularly in certain clinical settings – centrally located lung cancer
  - How much applies to mRCC?
  - How much will apply to TKI’s?
Management

• Prior Therapy: Sunitinib (12), Sorafenib (3), Bevacizumab and IL-2 (4), Targeted therapy held at least 1 week prior to surgery

• Surgery: Open (18), MIS (3)
  - Radical Nephrectomy with or without IVC Thx (9)
  - Metastasectomy (3)
  - Resection of local recurrence (6), 3 with en bloc resection adjacent organs
  - P Nx (3) for locally advanced RCC

• Pathology: Clear cell (16), Chromophobe 1, unclassified (3), pCR (1), only one we have seen thus far

Perioperative Outcomes

• Median blood loss 700 cc (50-4500 cc)

• Complications: one of each
  - DIC, MSOF: related to partial hepatectomy
  - Anastomotic bowel leak with abscess, with good recovery after repair
  - Wound seroma: minor
  - Ventral hernia: minor

• Overall, surgery after targeted therapy appears safe

Consolidative Surgery

Perioperative Morbidity: MDACC

44 targeted Rx then surgery vs. 58 with up front surgery

<table>
<thead>
<tr>
<th>Bevacizumab</th>
<th>Sorafenib</th>
<th>Sunitinib</th>
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<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Median months Rx</td>
<td>6.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Median days Rx to surgery</td>
<td>40</td>
<td>11</td>
</tr>
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Complications: MDACC

<table>
<thead>
<tr>
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<th>Targeted Rx then Surgery</th>
<th>Upfront Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a complication</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Mortality</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reoperation</td>
<td>4.5%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>4.5%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0</td>
<td>3.4%</td>
</tr>
<tr>
<td>Wound related</td>
<td>9.1%</td>
<td>6.9%</td>
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Update on MDACC Experience
Chapin et al, Eur Urol, 60:964-971, 2011

- 70 targeted Rx followed by CytoredNx vs. 103 primary Cytored Nx
- Neoadjuvant group associated with:
  - Complications after 90 days (p = 0.02)
  - Multiple complications (p = 0.013)
  - Wound complications (p < 0.001), 2 fascial dehiscences in neoadjuvant group vs. none other group
- On Multivariate analysis:
  - Not associated with overall complications
  - Not predictive for severe (Clavien 3 or greater) complications
- In series from Cleveland Clinic and UCSD: complications after PNx have been reasonably low and manageable

Safety of Surgery after Primary Targeted Rx

- 22 patients SP 3 cycles of Sunitinib Rx
- Cytored Nx performed 3 weeks later
- Multiple complications observed
  - Bowel injury leading to hemicolecctomy
  - Duodenal reconstruction
  - IVC injury
  - Splenectomy
  - Wound infection
  - Delayed healing
  - Lymphocele
- 15% Clavien IV or V complications, including one death
Effect of Sunitinib on Primary RCC Tumors and Facilitation of Subsequent Surgery

- Prospective, Phase 2
- N = 28 (35 renal units)
- Unresectable RCC, treated with Sunitinib (4/2 standard regimen changed to continuous 50 mg per day) to downsize and enable surgery
- Median number of cycles 3
- Median age = 61, 72% male


A Phase II Study of Sunitinib in Patients with Renal Cell Carcinoma and Unresectable Primary Tumors

Biopsy-proven RCC with unresectable primary tumor:
- Large tumor size (e.g. > 15 cm)
- Bulky lymphadenopathy (e.g. > 4 cm or encasement of renal vessels or great vessels)
- Venous thrombosis (e.g. high level/invasive disease requiring IVC reconstruction or hypothermic circulatory arrest)
- Proximity to vital structures (e.g. mesenteric vasculature)

Sunitinib 50 mg continuous dosing

Surgery performed (when primary tumor becomes resectable), and after surgery in patients with residual/metastatic disease.

Continued Sunitinib:
- In patients who do not become resectable, and
- After surgery in patients with residual/metastatic disease.

Tumor Parameters

- Clear cell 76%; median tumor size 7.2 cm (1.7-20.6)
- Distant metastases: 19 (66%)
- Primary reason unresectable (surgeon’s judgment)
  - Prox to vital structures: 12 (41%)
  - Bulky lymphadenopathy: 9 (31%)
  - High level venous thrombus: 6 (21%)
  - Very large tumor size: 2 (7%)
  - Most had multiple factors
Tumor Responses

- 28/35 (80%) of tumors demonstrated at least some shrinkage
- Median change in primary RCC tumors was 22%, or 1.6 cm on average for those that were downsized
- Overall 25% PR, all in clear cell
  - Clear cell
    - 26/27 tumors (96%) at least some shrinkage
    - 33% PR, compared to none for non-clear cell
    - Median reduction in size 28%, compared to 1.4% in non-clear cell RCC
  - Non-clear cell much less likely to respond

N = 28
Preliminary Biopsy

- Essential but limited in accuracy due to wide differential diagnosis and necrosis
- Similar experience per MDACC
  - Limited ability to identify non-clear cell histology, Fuhrman grade, or sarcomatoid features
  - Multiple cores needed, including ones targeting peripheral areas


Surgery

- Overall, 13/28 (46%) patients went on to surgery: primary goal of therapy
  - Clear cell: 59% went on to surgery, all had viable cancer in final specimen
  - Non-clear cell: none went on to surgery
- Morbidity of surgery: no wound healing or bleeding or thromboembolic complications
  - Median EBL 500 ml, 7 transfused
  - UTI (3), AFib (2), CHF (1), 2 with ARF, all resolved with conservative management

Conclusions

- Neoadjuvant Rx for unresectable tumors is a viable approach
- Overall responses are modest, but can facilitate surgical resection
- Clear cell tumors respond best to sunitinib, ideally would exclude non-clear cell, but biopsy in this setting has clear limitations
- Continuous dosing is often required due to tumor regrowth
- Most tumor responses seen early, after 2-3 courses of therapy
- Surgery in this setting appears to be safe
TKI Downsizing

- Better responses for smaller tumors
- Localized disease, to enable PNx, might be best use

Kroon et al. Probability of downsizing primary tumors of RCC by targeted Rx is related to size at presentation. UROLOGY, 81:51-5, 2013
Yuasa T et al. Tumor size is a potential predictor of response to TKIs in RCC. UROLOGY, 77:831-4, 2011

Case 1
Solitary Kidney, Hilar Mass

- 60-year-old man from Bangladesh
- Solitary kidney, hilar tumor
- PMH/PSH: healthy
- FH: no GU cancer or syndromes
- Hx L Nx for stone disease 25 years prior
- Labs: SCr 1.45 (eGFR >52)
- CT: lower and midpole R renal mass, into hilum: 8 cm, possibly into renal vein branch
- Met evaluation negative
RMB then TKI Trial

- Clear Cell RCC, G3
- RENAL = 11A
  - R: Radius: < 4 cm, 4-7 cm, > 7 cm
  - E: Exophytic vs. Endophytic
  - N: Nearness to the collecting system
  - A: Anterior or Posterior
  - L: Location: relative to center of the kidney
    - Max score is 12, 10-12 represents high complexity
- TKI trial with Pazopanib: 2 month course
- CT with necrotic tumor: down to 5.6 cm
  - RENAL down to 9a
  - Pulled away from hilum

A single arm phase II study of pazopanib in patients with localized RCC to enable partial nephrectomy

- Patients with localized RCC in whom partial nephrectomy is desired but not currently possible (n=30)
  - Tumor amenable to partial nephrectomy
  - Tumor not amenable to partial nephrectomy
    - Partial nephrectomy: performed after 1 week off pazopanib
    - Radical nephrectomy: performed after 1 week off pazopanib

Pazopanib 800 mg QD x 8 - 16 weeks (depending on tumor response)
Management Options:
Your choice?

A. Thermal ablation
B. Lap Partial Nx
C. Open Partial Nx
D. Lap Radical Nx
E. Continue TKI and then reassess
**Surgery**

- Open PNx
- Held Pazopanib for 7 days preop
  - Duodenum stuck to tumor, peeled off sharply, thin layer of serosa left on tumor, oversewed duodenum to bolster it
  - Ischemia time = 20 minutes, all on ice
  - Preserved 70% of the kidney, actually removed very little functioning kidney
  - Postop uneventful
  - Peak Scr: 2.33, down to 1.70 POD 4
  - Final Scr: 1.80, eGFR 37, 3 weeks out
  - Final Pathology: clear cell, G3, margins neg, pT1b

**Consolidative Surgery after TKI’s**

- Concerns: blocking VEGF
  - Wound healing/tissue integrity
  - Vascular Integrity
- Data limited but suggests minimal increased morbidity
- Recommendations
  - Hold TKI for 2 half lives before and after surgery
  - Meticulous hemostasis, postop DVT/PE prophylaxis
  - Consider retention sutures selectively
- PNx as the ultimate test of postoperative healing, good results thus far

**Case 2**

**TKI may be ineffective**

- 64-year-old woman from East Coast
- Solitary kidney, hilar tumor
- PMH/PSH: HTN, CKD, COPD, extensive tobacco, Hx Breast CA
- FH: no GU cancer or syndromes
- Hx severe atrophy L kidney
- Labs: Scr 1.34 (eGFR = 40)
- CT: hilar mass, contralateral atrophy
- Met evaluation: negative
RMB then TKI Trial

- Clear Cell RCC, G2
- RENAL = 11X

- TKI trial with Pazopanib: 2 month course
- CT with necrotic tumor: No change in size or location!
  - RENAL still 11X
  - Has not pulled away from hilum
- Met evaluation still negative
Management Options: Your choice?

- 20% A. Thermal ablation
- 20% B. Lap Partial Nx
- 20% C. Open Partial Nx
- 20% D. Lap Radical Nx
- 20% E. Continue TKI and then reassess

Answer Now

Surgery

- Open PNx (possible Rad Nx)
- Held Pazopanib for 7 days preop
  - Tumor well encapsulated, dissected away from hilum, extensive dissection prior to clamping
  - Ischemia time = 46 minutes, all on ice
  - Peak SCr: 2.16, down to 1.82 POD 4
Surgery

- Recovery and follow-up
  - Postop urine leak, left JP in, healed over 2-3 weeks with no further intervention
  - Final Pathology: clear cell, G3, margins neg, pT1b (5.0 cm)
  - Final SCr: 1.73 a year later, eGFR 31

Case 3
Imaging after TKI may be misleading

- 55-year-old man
- 11 cm R renal mass, atrophy on L
- CKD: SCr 1.56, eGFR 46; RFS: 8L, 92R
- Afib, HTN, BMI 26, tobacco use
- RENAL 12X
- Met eval negative
- Bx: G3 clear cell
Management Options: Your choice?

A. Follow-up with repeat imaging in 6-12 months
B. Thermal ablation
C. Lap Partial Nx
D. Open Partial Nx
E. Lap Radical Nx
F. TKI and reassess

Answer Now
After 2 months of TKI

- Mass decreased to 7.2 cm (previously 11 cm)
- RENAL 10X, pulled away from hilum
- Somewhat indistinct in some areas, margins of mass difficult to pin down?
- SCR 1.80, eGFR 39
- Next step?

Surgery

- Open R renal exploration, attempted PNx
- Intraoperative US indistinct in some areas
- Mass appeared to be about 7 cm, but at initial incision tumor encountered
- This was repeated 2x, 1 and 2 cm higher
- Tumor present that was not evident on CT/US
- Presumed satellite lesions, Rad Nx performed

Initial Incision

Second Incision

Final Report: pT3a, N0
Satellite lesions in middle pole and extending into lower portion of upper pole Clear cell, still 10 cm
**Outcome**

- Peak SCr about 3.7, then decreased
- 3 months later, SCr 2.41, no dialysis
- Other kidney functioning better than anticipated
- Will likely progress to ESRF, then will consider for renal transplantation at about 2 year point
- Hopefully will not need to be on dialysis for long prior to this
- Disconnect between imaging and path findings, tumor regressed but satellite lesions still present

**Surgery after VEGF Targeted Therapies**

**Recommendations**

- Wait 2-3 half lives before/after surgery if possible
  - Sunitinib (active metabolite) T1/2: 80-100 hours
  - Pazopanib: 31 hours
  - Bevacizumab T1/2: 17 days
  - Temsirolimus: 17 hours
- Careful and meticulous surgical technique
  - Meticulous hemostasis, aggressive VTE prophylaxis
  - Careful wound closure, selective use of retention sutures
- Still experimental, best done on protocol
- Monitor these experiences closely as we proceed

**Conclusions**

- Locally-advanced RCC is less common today, but prognosis is poor and aggressive surgical mgmt should be undertaken if feasible
- Debulking nephrectomy still routinely applied based on OS benefit
- There is currently no effective adjuvant therapy; several trials of VEGF-targeted tx ongoing
- Neoadjuvant VEGF-targeted therapy may lead to enhanced feasibility of resection of locally-advanced RCC; still investigational at present
  - Likely to be most useful in *specific* surgical circumstances to be defined
  - Surgical safety: limited data but appears to be reasonable
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