Palliative Care in Kidney Cancer

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Medical Director, WRHA Adult and Pediatric Palliative Care
The presenter has no conflicts of interest to disclose
Objectives

• To review select palliative care issues in advanced kidney cancer

• To consider the specific implications of metastases to the bone and brain

• To review the implications of impaired renal function on analgesic use in metastatic kidney cancer
Some Considerations In Renal Cell Carcinoma

- Overall 5 yr survival approx 45%
- Approx 1/3 present with locally invasive or metastatic disease
- About another 1/3 develop metastases during disease progressions following nephrectomy
- Potential high symptom burden from pulmonary, brain, bone, and spinal cord/nerve root involvement
- Renal function may be a consideration in medication choices
Distribution of metastatic sites in renal cell carcinoma: a population-based analysis


$n = 11,157$ patients
Bony Metastases In Renal Cell Carcinoma

- Reported incidence of 20 – 35%
- Aggressive, lytic process
- Most frequent sites: pelvis, spine, ribs
- Patients with bone-metastatic RCC have one of the highest rates of SREs (Skeletal Related Events) of any solid tumor (fractures, hypercalcemia, spinal cord or nerve root compression, RadTx, surgery)

“Particularly destructive”
- Approx 80% of those with bone mets require RadTx
- Up to 40% suffer fracture of long bones
Skeletal complications and survival in renal cancer patients with bone metastases

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\textsuperscript{d} Cancer Research Centre, University of Sheffield, Weston Park Hospital, Sheffield, UK
• included all patients (N=803) with advanced/metastatic RCC from 1998–2007

• 32% presented with (N=131) or later developed (N=123) bone mets

• Of the 254 with bone mets:
  - 83% also developed metastases elsewhere
  - 28.3% experienced spinal cord or nerve root compression
  - 78.3% had RadTx
  - 20.9% experienced a fracture
  - 12.2% developed hypercalcemia

Considered Skeletal Related Events (SREs)
Palliative Approach To Bone Mets

• Prevent SREs – Zoledronate (may also help pain); perhaps denosumab in future

• Analgesia
  - RadTX
  - Perhaps acetaminophen, though likely not potent enough. NSAIDs should likely be avoided
  - Opioids – consider renal function in selection
  - Neuropathic adjuvants for neuropathic or challenging pain
  - Perhaps corticosteroids

• Fracture risk?
  - Plain films of involved areas
  - Consider orthopedic opinion RE fracture risk, prophylactic surgery
### Table 3. The Mirels Scoring System for Impending Pathologic Fractures

<table>
<thead>
<tr>
<th>Score</th>
<th>Size</th>
<th>Site</th>
<th>Radiographic Nature of Lesion</th>
<th>Degree of Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1/3 of cortex</td>
<td>Upper extremity</td>
<td>Osteoblastic lesions</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>1/3 to 2/3 of cortex</td>
<td>Lower extremity</td>
<td>Mixed osteolytic and osteoblastic lesions</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>More than 2/3 of cortex</td>
<td>Peritrochanteric region</td>
<td>Purely osteolytic lesions</td>
<td>Limits function</td>
</tr>
</tbody>
</table>

*aProphylactic surgical intervention indicated for patients with a score of 9 or above.*
# Prevention Of SREs

**Table 4 – Evidence-based use of osteoclast inhibition for genitourinary cancers**

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Evidence-based use</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell or bladder/urothelial carcinoma metastatic to bone</td>
<td>In the absence of contraindications, either of the following two options:</td>
<td>Efficacy of the two drugs was similar in head-to-head study within a heterogeneous population of patients with metastatic solid tumors (nonbreast, nonprostate). RCC metastatic to bone carries a particularly high risk for SREs, making this a strong indication for osteoclast inhibition.</td>
</tr>
<tr>
<td></td>
<td>- Denosumab 120 mg every 4 wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Zoledronic acid every 4 wk</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3 – Kaplan-Meier estimates of time to first skeletal-related event in patients with bone metastases from renal cell carcinoma during a 9-mo trial of zoledronic acid. Data presented are for those who received 4 mg zoledronic acid (n = 27) or placebo (n = 19).
SRE = skeletal-related event; NR = not reached.

**RANKL:**
- *receptor activator of nuclear factor-κB ligand*
- a tumor necrosis factor (TNF) family member that activates RANK on osteoclast precursors and stimulates the:
  - fusion of pre-osteoclasts
  - the attachment of osteoclasts to bone
  - their subsequent activation
  - their survival

**OPG (osteoprotegerin):**
- inhibits the above activities of RANKL
- ↓ osteoclast numbers and ↑ osteoclast apoptosis
  - The ratio of RANKL:OPG may be the ultimate determinant of bone resorption
  - PTH causes ↑ in serum RANKL and RANKL:OPG ratio, with ↑ Ca^{++} levels

**Denosumab:** a fully human monoclonal antibody which binds to RANKL, preventing stimulation of RANK receptor and thus inhibiting RANKL mediated bone resorption
Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials

Allan Lipton a,*, Karim Fizazi b, Alison T. Stopeck c, David H. Henry d, Janet E. Brown e, Denise A. Yardley f, Gary E. Richardson g, Salvatore Siena h, Pablo Maroto i, Michael Clemens j, Boris Bilynskyy k, Veena Charu l, Philippe Beuzeboc m, Michael Rader n, Maria Viniegra o, Fred Saad p, Chunlei Ke q, Ada Braun q, Susie Jun q
Fig. 1. CONSORT diagram.
Fig. 2a. Time to first on-study skeletal-related event (SRE).

Fig. 2b. Time to first and subsequent on-study skeletal-related event (SRE) (multiple event analysis).
<table>
<thead>
<tr>
<th>Type of SRE</th>
<th>Zoledronic Acid (N = 2861)</th>
<th>Denosumab (N = 2862)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SRE</td>
<td>1081</td>
<td>934</td>
<td>0.83 (0.76 to 0.90), P&lt;0.001</td>
</tr>
<tr>
<td>Pathological fracture</td>
<td>605</td>
<td>528</td>
<td>0.86 (0.76 to 0.96), P=0.009</td>
</tr>
<tr>
<td>Radiation to bone</td>
<td>625</td>
<td>509</td>
<td>0.77 (0.69 to 0.87), P&lt;0.001</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>86</td>
<td>76</td>
<td>0.89 (0.65 to 1.21), P=0.46</td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>72</td>
<td>63</td>
<td>0.86 (0.61 to 1.21), P=0.38</td>
</tr>
</tbody>
</table>

Fig. 3a. Time to first on-study skeletal-related event (SRE) by SRE type.
Overview Of Adverse Events (AEs)

- At Least One AE
- Serious AE
- Study D/C due to AE

Legend:
- Denosumab
- Zoledronic Acid
Adverse Events (AEs) - Differences

- Acute Phase Reaction
- Grade 3-4 hypocalcemia
- Renal AE

<table>
<thead>
<tr>
<th>Condition</th>
<th>Denosumab</th>
<th>Zoledronic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Phase Reaction</td>
<td>8.0%</td>
<td>20.0%</td>
</tr>
<tr>
<td>Grade 3-4 hypocalcemia</td>
<td>3.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Renal AE</td>
<td>10.0%</td>
<td>15.0%</td>
</tr>
</tbody>
</table>
Kidney function following nephrectomy: Similitude and discrepancies between kidney cancer and living donation

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Received 4 March 2010; received in revised form 9 April 2010; accepted 12 April 2010
Fig. 1. Kidney function according to time since nephrectomy. MDRD-eGFR = estimated glomerular filtration rate calculated using Modification of Diet in Renal Disease equation. After 4 years, mean decrease in MDRD-eGFR was of 30.4% in group 1 and 32.4% in group 2 (standard deviation = 10.9).
Opioids

- 3-glucuronide metabolites of morphine & hydromorphone can accumulate in renal insufficiency; thought to be neurotoxic
- May result in opioid-induced neurotoxicity (OIN), with delirium, myoclonus, hyperalgesia
- Hydromorphone generally preferred over morphine in renal insuff, though fentanyl and methadone have no active metabolites and are preferred in moderate/severe renal impairment

**NSAIDs:** avoid in vulnerable/tenuous renal function

**Zoledronate:** follow manufacturer’s recommendations

**Denosumab:** “represents an improvement over zoledronic acid as it demonstrates no effect on renal function and can be used in patients without the need to adjust doses or monitor renal status” (Lipton et al.; Eur J Cancer 48 (2012) 3082–3092)
Brain Metastases In Renal Cell Carcinoma

- Maastricht Cancer Registry (Schouten et al; Cancer 2002):
  - 5-year cumulative incidence of brain mets was 9.8%
  - 2nd after lung carcinoma; higher than melanoma, breast

- Retrospective reports from other studies range 4 – 48%

- Incidence of occult metastases at time of diagnosis may range from 15 – 33%

- Should routine imaging be done? Not according to guidelines from the National Comprehensive Cancer Network (2013); European Association of Urology (2013), or European Society for Medical Oncology (2012)

Impact of Brain Metastases

- median survival with untreated RCC brain mets 3 – 4 mo
- KPS < 80%, Dx to targeted therapy <1 year, and >4 mets was associated with worse survival (Vickers et al (Renal Database Consortium); Clin Genitourin Cancer. 2013)
Management of Brain Metastases

- selection for aggressive local treatment (neurosurgery and stereotactic radiosurgery) based on RPA Class (recursive partitioning analysis):

<table>
<thead>
<tr>
<th>Class</th>
<th>Prognostic factors</th>
<th>Survival, median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>PS ≥70%</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>Age &lt;65 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controlled primary tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No extracranial metastases</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>PS &lt;70%</td>
<td>2.3</td>
</tr>
<tr>
<td>II</td>
<td>All other patients</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Adapted from Gaspar et al.\(^{30}\)
PS: Performance status.
**Recommendations**

**Asymptomatic brain metastases patients without mass effect**
Insufficient evidence exists to make a treatment recommendation for this clinical scenario.

**Brain metastases patients with mild symptoms related to mass effect**
*Level 3* Corticosteroids are recommended to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema secondary to brain metastases. It is recommended for patients who are symptomatic from metastatic disease to the brain that a starting dose of 4–8 mg/day of dexamethasone be considered.

**Brain metastases patients with moderate to severe symptoms related to mass effect**
*Level 3* Corticosteroids are recommended to provide temporary symptomatic relief of symptoms related to increased intracranial pressure and edema secondary to brain metastases. If patients exhibit severe symptoms consistent with increased intracranial pressure, it is recommended that higher doses such as 16 mg/day or more be considered.

**Choice of Steroid**
*Level 3* If corticosteroids are given, dexamethasone is the best drug choice given the available evidence.

**Duration of Corticosteroid Administration**
*Level 3* Corticosteroids, if given, should be tapered slowly over a 2 week time period, or longer in symptomatic patients, based upon an individualized treatment regimen and a full understanding of the long-term sequelae of corticosteroid therapy.
Opportunity To Discuss Goals Of Care

Consider 59 yo man with multiple brain mets from RCC, no further options for surgery, RadTx, chemoTx. Anticipated course is likely to include:

- Ongoing treatment with dexamethasone; varying dose
- Functional decline
- In final week or so will be mostly sleeping, have poor intake, may have delirium/agitation, may have pain (headaches)
- Not uncommon to develop pneumonia as final event – treatment with antibiotics and O2 will arise as a consideration
- May also include a sudden change e.g. CNS bleed
What are his wishes with regards to:

• Caloric and fluid support if he is unable to take orally?

• Should dexamethasone be aggressively pulsed with each decline?

• Should dexamethasone be continued when he is unconscious and death is imminent?

• Should a probable pneumonia near end-of-life be treated? Will that impact on chosen care setting?

• Should O2 be continued if he is unconscious, comfortable and death is near?

• If the balance between comfort and alertness is challenging, what is the preferred default?

• Is aggressive sedation OK for agitated delirium near EOL?