The Application of Cytokine Therapy Following TKI Failure

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Objectives

- High Dose IL2 for RCC
- Anti- VEGF Therapy
  - Bevacizumab
  - Sunitinib malate
  - Sorafenib
- Retrospective analysis of IL-2 therapy as second line treatment after anti- VEGF resistance
High-Dose IL-2 Therapy:
Response Durations - 255 pts

FDA Approval
1992

15% response rate
with durable
responses in a small
percentage of
patients

Median Response
Duration – 50
months

But:

Significant toxicity
and cost*
High-Dose IL-2 vs IL-2 Plus IFN-α in mRCC: Phase 3 Study Design

**Primary end point:** 3-year PFS

Patients with mRCC (N=192)
ECOG PS 0/1
Without prior therapy

- **High dose IL-2 (n=96)**
  - 600,000 U/kg/dose every 8 hours on days 1-5 and days 15-19 every 12 weeks

- **IL-2 + IFN-α (n=96)**
  - 5M IU/m² IL-2 every 8 hours on day 1 then daily 5 days/week for 4 weeks; 5M IU/m² IFN-α 3×/week for 4 weeks every 6 weeks

### Phase III Trials in Metastatic RCC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>RR</th>
<th>p-value</th>
<th>Dur</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCI SB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD IV IL-2</td>
<td>156</td>
<td>21%</td>
<td>0.05</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>vs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD IV IL-2</td>
<td>150</td>
<td>13%</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>CWG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HD IV IL-2</td>
<td>95</td>
<td>23%</td>
<td>0.02</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>vs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD SC IL-2/IFN</td>
<td>91</td>
<td>10%</td>
<td></td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

More durable responses, especially CRs, with HD IL-2
No significant difference in OS or quality of life

Yang et al. JCO 2003; McDermott et al. JCO 2005
Grade 3 and 4 Toxicities

- Infection: 3.2%
- Hepatic: 11.6% (High-dose IL-2), 2.2% (IL-2 + IFN)
- Psychiatric: 1.1%
- Renal/electrolytes: 13.7% (High-dose IL-2), 3.3% (IL-2 + IFN)
- Pulmonary: 13.7% (High-dose IL-2), 1.1% (IL-2 + IFN)
- Cardiac: 8.4%
- Neurologic: 14.7% (High-dose IL-2), 3.3% (IL-2 + IFN)
- Hematologic: 13.7%
- Gastrointestinal: 14.3% (High-dose IL-2), 9.5% (IL-2 + IFN)
- Hypotension: 56.8% (High-dose IL-2)
- Constitutional: 14.3% (High-dose IL-2), 3.2% (IL-2 + IFN)

Immunotherapy Summary

- **Bottom line:**
  - Median survival ~13 months
  - HD-IL-2 RR 15-23% with 5% sustained response
  - Significant toxicity
  - Patient selection is important
    - No CNS metastases
    - Clear Cell histology
    - Good PS
    - ? No prior TKI therapy ?
A Paradigm Shift: Anti-Angiogenic Therapy
Targeted Therapy

VHL Pathway in RCC

- Von Hippel Lindau (VHL) gene product: oxygen sensor in renal tubular cells
- Majority of clear cell RCC characterized by biallelic VHL loss (60% of cases)
- Loss of function leads to upregulation of downstream targets due to increased levels of HIF
- Tumor suppressor gene
Bevacizumab in mRCC: Progression-Free Survival


- **High-dose bevacizumab** (10 mg/kg) (n=39)  
  - Median TTP (months): 4.8 ($P<.001$)
- **Low-dose bevacizumab** (3 mg/kg) (n=37)  
  - Median TTP (months): 3.0 ($P<.041$)
- **Placebo** (n=40)  
  - Median TTP (months): 2.5
## Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OR</strong></td>
<td>0</td>
<td>0</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>(All were PR)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Stable Disease**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>at 4 mo</td>
<td>20%</td>
<td>39%</td>
<td>64%</td>
</tr>
<tr>
<td>at 8 mo</td>
<td>5%</td>
<td>14%</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Side Effects**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Low dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>2</td>
<td>1</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>6</td>
<td>6</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>15</td>
<td>15</td>
<td>25 (64%)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>1</td>
<td>5 (13%)</td>
</tr>
</tbody>
</table>

Phase III RCT of Sunitinib v IFN demonstrated RR=37% by RECIST criteria with stable disease in 47% of pts.

Most frequent adverse events included fatigue, diarrhea, nausea, stomatitis, HTN, and hand-foot syndrome.

Improved PFS (11 vs 5 mo) compared with IFN

Survival data not mature

## Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Sunitinib (%)</th>
<th>IFN-α (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>53</td>
<td>5*</td>
</tr>
<tr>
<td>Nausea</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24</td>
<td>8*</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>20</td>
<td>5*</td>
</tr>
<tr>
<td>Ejection fraction decline</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Sorafenib in mRCC

- Phase III RCT of Sorafenib v placebo demonstrated RR=10% by RECIST criteria with stable disease in 74% of pts.

- Most frequent adverse events leading to discontinuation were hand-foot syndrome and hypertension

- Improved PFS (5.5 vs 2.8 mo) compared with placebo
  - Preliminary data suggest a trend towards increased overall survival

## Sorafenib in mRCC: Safety

<table>
<thead>
<tr>
<th>Category</th>
<th>Sorafenib</th>
<th>Placebo (n=384)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 3/4</td>
<td>Grades 3/4</td>
</tr>
<tr>
<td>Cardiac general</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (1%)</td>
<td>–</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (2%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>–</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mucositis</td>
<td>2 (1%)</td>
<td>–</td>
</tr>
<tr>
<td>Dermatology/skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash/desquamation</td>
<td>3 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Hand-foot skin reaction</td>
<td>20 (5%)</td>
<td>–</td>
</tr>
</tbody>
</table>
Conclusions

- Standard of care for advanced RCC has changed

- Angiogenesis inhibition: both Sunitinib and Sorafenib are approved for the treatment of advanced RCC

- Other anti-angiogenic agents including Bevacizumab are active as well
What is the Safety and Efficacy of IL2 after Anti-angiogenic Therapy?
Experience with IL-2 in TKI Failures

- Limited
- Referrals for IL-2 are declining at many centers
- TKI failure patients are often not well enough to meet IL-2 eligibility criteria
- Role of IL-2 following resistance to anti-angiogenic therapy remains unexplored
HD IL-2 for Anti-VEGF Failures at BIDMC

- Retrospective analysis
- 16 consecutive patients (7/04-5/07)
- All 16 eligible for IL-2 prior to anti-VEGF therapy, assumed they could get it later
- Treatment tolerability and toxicity compared to High Dose IL-2 arm of CWG Phase III trial (McDermott, et al JCO 2005)

Patient Characteristics

- Median Age 61 (range 48-70)

- ECOG PS
  - PS 0 - 9 patients
  - PS 1 - 6 patients
  - PS 2 - 1 patient

- Male:Female 12:4

- 15/16 pts met HD IL-2 eligibility
  - 15 received HD IL-2, 1 received LD IL-2

Prior Therapy

- Prior therapy:
  - Bevacizumab alone = 6
  - Sorafenib alone = 2
  - Sunitinib alone = 2
  - Sorafenib then Sunitinib = 2
  - Bevacizumab then Sunitinib = 3
  - Bevacizumab then Sorafenib = 1

- Duration of prior therapy ranged from 2 months to 28 months

- Interval between TKI and IL-2 ranged from 1-8 months
Results: Doses Received

- Median number of IL-2 doses received in our analysis
  - Course 1, Week 1 = 11 (79%)
  - Course 1, Week 2 = 8 (61%)
  - Median for course 1 was 18/28 (64%)

- Median number of IL-2 doses received in the CWG Trial
  - Course 1, Week 1 = 12
  - Course 1, Week 2 = 8
  - Median for Course 1 was 21 (68%)
Results: Doses Received

- **Our Analysis:**
  - 6/16 (37.5%) patients (95% CI 15.2% - 64.6%) did not receive C1 W2

- **CWG Phase III Trial:**
  - 12/89 (13.5%) patients (95% CI 7.2% - 22.4%) did not receive C1 W2 therapy
    - (p=.03)
Impact of TKI Therapy

- 6/10 pts (60%) with prior TKI did not receive week 2

- 0/6 pts (0%) with prior Bevacizumab alone did not receive week 2
  \[ p = 0.034 \]
Results: Toxicities

- Expected toxicities seen
- Toxicities that prevented further Rx
  - Bullous pemphigoid
  - Irreversible cardiomyopathy
  - Myocarditis
  - Severe angina
  - Atrial fibrillation with associated hypotension and bowel ischemia
  - Sudden fatal cardiac arrest
Results: Toxicities

- Incidence of severe (grade 3-5) cardiac toxicities in pts with prior TKI therapy was 50%
  - (95% CI 18.7% to 82.3%)

- Incidence is 8.5% in CWG Phase III trial

- No responses seen
Conclusions

- Small, retrospective analysis highlights unexpected and severe cardiac toxicity in TKI failures receiving IL-2.
- The assumption that IL-2 can be given safely to TKI failures may not be valid.
- Further examination of the safety of this approach is necessary and more cautious patient selection appears warranted.
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