Controversial Issues in Managing Locally Advanced Head and Neck Cancer

Thyroid Cancer

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Disclosures

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Controversial Issues in Managing Thyroid Cancer

- Risk of bleeding by VEGF-targeted TKI
Hemorrhagic complications

- One of the most severe and potentially life-threatening toxicities of anti-VEGF drugs
- Inhibition of VEGF
  - Interfere with the regenerative capacity of endothelial cells
  - Cause defects of the endothelial layer with exposure of the underlying matrix
  - Thrombosis and/or hemorrhage
Risk of bleeding with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials

• 23 trials were selected for the meta-analysis, yielding 6779 patients

• Incidence of bleeding events
  ➢ All grades: 16.7% (95% CI 12.7–21.5)
  ➢ High-grade events: 2.4% (1.6–3.9)

• Relative risk of all-grade bleeding events* was 2.0 (1.14–3.49; p=0.015)

*associated with sunitinib and sorafenib (for randomised controlled trials only)
## Incidence of bleeding with VEGF-targeted TKI

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Author</th>
<th>No.</th>
<th>Type of cancer</th>
<th>Rate of ≥ grade 3 bleeding (grade 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>Demetri ¹</td>
<td>207</td>
<td>GIST</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Socinski ²</td>
<td>63</td>
<td>NSCLC</td>
<td>(5%)</td>
</tr>
<tr>
<td></td>
<td>Motzer ³</td>
<td>375</td>
<td>RCC</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Machiels⁴</td>
<td>38</td>
<td>SCCHN</td>
<td>5% (11%)</td>
</tr>
<tr>
<td></td>
<td>Hui⁵</td>
<td>13</td>
<td>NPC*</td>
<td>28.6%:4pts (14.3%:2pts)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Ratin ⁶</td>
<td>202</td>
<td>RCC</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Abou-Alfa ⁷</td>
<td>137</td>
<td>HCC</td>
<td>(1pt: intracranial hemorrhage)</td>
</tr>
<tr>
<td></td>
<td>Escudier ⁸</td>
<td>451</td>
<td>RCC</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Brose ⁹</td>
<td>207</td>
<td>DTC</td>
<td>(1pt: myocardial infarction)</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Schlumberger¹⁰</td>
<td>261</td>
<td>DTC</td>
<td>(1pt: pulmonary embolism) (1pt: hemorrhagic stroke)</td>
</tr>
</tbody>
</table>

*previously received high dose radiation

1. Lancet 2006;368(9544):1329–38
5. Annal of Oncol 2010;22(6):1280-87
Baseline tumor cavitation as a significant risk factor for severe hemorrhage

- Retrospective multivariate analysis of clinical or radiological risk factors for pulmonary hemorrhage in two trials of bevacizumab-contained regimens
- Only baseline cavitation was associated with an increased risk (OR, 4.5; 95% CI, 0.73 to 28.33), although not significant ($P = .063$)

A left upper lobe cavitating mass that did not contact any vascular structure...

...developed further cavitation, and became contiguous with a vascular structure
Phase II study of sunitinib in R/M SCCHN: GORTEC 2006-01 (N=38)

• Head and Neck Bleeding

<table>
<thead>
<tr>
<th>Head and neck bleeding</th>
<th>Gr 1-2</th>
<th>Gr-3-4</th>
<th>Gr5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck bleeding</td>
<td>7 (18)</td>
<td>2 (5)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>with local relapse</td>
<td>7 (18)</td>
<td>2 (5)</td>
<td>3*(8)</td>
</tr>
<tr>
<td>with no local relapse</td>
<td>0</td>
<td>0</td>
<td>1#(3)</td>
</tr>
</tbody>
</table>

• *Tumor located less than 5 mm from carotid artery
• #A large ulcer with subsequent carotid rupture in an area that was previously irradiated

Machiels J H et al. JCO 2010;28:21-28
Grade 5 bleeding complications

Tumor located less than 5 mm from carotid artery

A large ulcer with subsequent carotid rupture in an area that was previously irradiated
Risk of bleeding with VEGF-targeted TKI

• Should patients with the following risk factors avoid VEGFR-targeted therapy?
  • Tumor located less than 5 mm from the carotid artery
  • Tumor located in an area that was previously irradiated
• Additional risk factors?
Case 1

- 59 yr male with recurrent PTC
- Prior treatment
  - Total thyroidectomy (1997)
  - RT for local recurrence (2004)
  - Total laryngectomy, ND (2007)
  - RT for bone metastasis (2008)
  - RAI for neck recurrence (2009)
- PS 1
- Symptoms: neck pain, bloody sputum
- No significant comorbidity
- No abnormal organ function
CT scan
Question 1

• Summary of Case 1
  ✓ Tumor that bleeds easily in an area that was previously irradiated, but not located less than 5 mm from the carotid artery
  ✓ Bloody sputum

• Does he have a high risk of bleeding?
• Should he avoid VEGFR-targeted TKI?
Clinical course after enrollment in the SELECT study

Before lenvatinib

2 weeks after lenvatinib

4 weeks after lenvatinib

10 weeks after lenvatinib

8 weeks after lenvatinib

6 weeks after lenvatinib
CT scan

Before study drug

4 month after study drug
Case 2

- 44 yr female with ATC
- Prior treatment
  - Subtotal thyroidectomy for PTC (2011)
  - ND for lt neck LN meta (2012)
  - RAI 100mCi (2013)
  - ND for paratracheal LN meta (2014)
  - ND for subclavicular LN meta (2015/2)
  - ND for rt neck LN meta (2015/8)
    - ATC transformation
- PS 1
- Symptoms: neck swelling
- No significant comorbidity
- No abnormal organ function
Question 2

• Summary of case 2
  ✓ Tumor invasion to the carotid artery
  ✓ Tumor reached very close to the skin surface
  ✓ No clear evidence of skin invasion
• Does she have a high risk of bleeding?
• Should she avoid VEGFR-targeted TKI?
Case 3

• A 73 yr male with recurrent PTC
• Prior treatment
  • Total thyroidectomy and ND (2005)
  • RAI 100mCi (2005)
  • Sorafenib (2014/7) for neck LN meta
    ➢ Discontinued due to neck tumor bleeding (2014/10)
  • RT (30Gy/10Fr) for neck LN meta (2015/3)
    • Mohs paste for neck bleeding (2015/3/27)
• PS 1
• Symptoms: neck swelling
• Comorbidity
  ✓ DM (HbA1c: 8.4%)
• No abnormal organ function
CT scan

carotid artery
Question 3

• Summary of Case 3
  ✓ Tumor invaded the carotid artery in an area that was previously irradiated
  ✓ Skin invasion
  ✓ History of neck bleeding due to sorafenib
  ✓ Poor control of diabetes

• Does he have a high risk of bleeding?

• Should he avoid VEGFR-targeted TKI?

• If he had no history of neck bleeding due to sorafenib, would you change your decision?
Clinical course

Before LEN

Day 11 after LEN

Day 24 after LEN

Slide courtesy of Dr Akifumi Suzuki
CT scan

Skin invasion and disintegration, like an ulcerative tumor, is a major high risk factor for bleeding

Slide courtesy of Dr Akifumi Suzuki
Risk of bleeding with VEGFR-targeted TKI

- High risk of bleeding with VEGFR-targeted TKI
  - Tumor located less than 5 mm from the carotid artery
  - Tumor located an area that was previously irradiated
- Major risk of bleeding
  - Skin invasion and disintegration
    - Avoid VEGFR-targeted TKI
  - Air infiltration (cavitation) around the carotid artery
    - Discontinuation of VEGFR-targeted TKI