MANAGEMENT OF CS I SEMINOMA

Discussion of MRC TE19/EORTC 30982

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Clinical Stage I Seminoma

What questions are my patients asking?

What should I recommend to the next patient that I see in consultation?
Clinical Stage I Seminoma
What Do We Know?

2. RT and surveillance: Widely accepted standards.
   A. ~4% relapse rate from RT.
   B. 15-20% relapse during surveillance.
3. Carboplatin seems to be a reasonable 3rd option.
   A. Carboplatin relapse = 5.3%. RT=4%.
   B. 2nd 1° GCT reduced from 1.7% to 0.3%
   C. 1° tumors >4 cm have worse RFS.
   D. Dosing matters. AUC<7 has worse RFS.
4. Second malignant neoplasms (SMN) and cardiovascular disease (CVD) known to occur after RT and chemotherapy for GCT.
Clinical Stage I Seminoma

What Questions Should I Ask So I Can Advise My Patient?

1. What does the trial design tell me?
2. How do surveillance, RT, and carboplatin differ?
3. How much should I worry about 2nd 1° GCT?
4. Can I identify “high risk” patients?
5. How do I factor in late toxicity?
What is a “Non-inferiority” Trial?

“Non-inferiority” is not the same as “Equivalence”

<table>
<thead>
<tr>
<th></th>
<th>Superiority</th>
<th>Non-inferiority</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Goal</strong></td>
<td>Difference exists between RT and Carbo</td>
<td>Carbo not less effective than RT by a specified amount</td>
</tr>
<tr>
<td><strong>α=.05; power=.90</strong></td>
<td>2-sided</td>
<td>1-sided</td>
</tr>
<tr>
<td>Assume difference</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Sample Size</td>
<td>2647</td>
<td>1869</td>
</tr>
</tbody>
</table>

**Equivalence**

Confirm absence of difference between RT and Carbo

3%

6090

∴ Equivalence has not been demonstrated.
Randomized Trial Design

*(Lancet 366: 293, 2005; ASCO 2008)*

**Non-inferiority design**

90% power “to exclude an absolute increase in 2-year relapse rate of > 3.0%” (e.g., 4% vs >7.0%).

**Implication of Design among 1000 patients:**

1. After RT, a maximum of **40 relapses (events)** expected. With carboplatin, no more than **70 relapses**.

2. Clinically important differences between arms will be **VERY small**, and, therefore, **HARD** to detect.
CURRENT RESULTS (ASCO, 2008):

5 yr RFR: Carboplatin = 94.7%; RT = 96%
Absolute Difference = 1.3%
Relative Difference = 32%
90% CI (-0.7%, 3.5%)
95% confidence that difference is <3.6%.

∴ The trial hasn’t met its endpoint (<3%).
The carboplatin relapse rate could be >7%.

For 1000 patients, these data imply that:

40 events (RT) increases to 53 (Carboplatin),
but could be >70.
### Surveillance, RT, and Carboplatin

%Sites of Relapse in CS I Seminoma

<table>
<thead>
<tr>
<th>Relapse Sites</th>
<th>Surveillance#</th>
<th>RT-DL*#</th>
<th>RT-PA*#</th>
<th>1 or 2 Carbo#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retroperitoneum</td>
<td>84%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>81%</td>
</tr>
<tr>
<td>“Abd”</td>
<td>---</td>
<td>&lt;1%</td>
<td>17%</td>
<td>---</td>
</tr>
<tr>
<td>Pelvis</td>
<td>11%</td>
<td>&lt;1%</td>
<td>40%</td>
<td>2%</td>
</tr>
<tr>
<td>Systemic</td>
<td>5%</td>
<td>99%</td>
<td>43%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*DL: dogleg; PA: para-aortic

### Issues to Consider:

1. DL port ≈ PA port, but PA means pelvic/“abd” relapses.
2. Carboplatin reverts to surveillance relapse pattern.
3. Carboplatin, RT-PA, Surveillance need long-term CT F/U.

Second Primary GCT

1. 2\textsuperscript{nd} GCT: Carboplatin: 2 (0.3\%) vs. RT 15 (1.7\%)

2. Pre-treatment FSH level correlated with 2\textsuperscript{nd} GCT.

However:

• No data on balance of FSH in each arm.
• 43\% have ↑FSH before any Rx. (Huddart, Br J Cancer 2005)
• ~2\% of patients have 2\textsuperscript{nd} 1\textsuperscript{o} GCT.

Median time to 2\textsuperscript{nd} GCT 6.3 years (range <1 - 18). (Géczi, J Cancer Res Clin Oncol, 2003; Fossa, JNCI, 2005)

Is 2\textsuperscript{nd} GCT reduction sufficient for using carboplatin?

I do not believe that this is sufficient reason. %2\textsuperscript{nd} GCT reduction is = %increase in relapse rate
Can I treat only “high risk” patients?
Seminoma Prognostic Factors

<table>
<thead>
<tr>
<th>Risk Factors*</th>
<th>Group</th>
<th>%Rel</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;4cm, Rete (-)</td>
<td>0 risk factors</td>
<td>12%</td>
<td>176 (39)</td>
</tr>
<tr>
<td>T&gt;4cm, Rete (-)</td>
<td>1 risk factor</td>
<td>16%</td>
<td>182 (40)</td>
</tr>
<tr>
<td>T&lt;4cm, Rete (+)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&gt;4cm, Rete (+)</td>
<td>2 risk factors</td>
<td>32%</td>
<td>95 (21)</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>19%</td>
<td>453</td>
</tr>
</tbody>
</table>

(*Warden, JCO 20:4448, 2002)

1. MRC/EORTC: ≥4 cm higher relapse rate.
2. Highest risk group is not very common.
3. Carboplatin and RT overtreat 0-1 risk factor groups.
Should I use a risk-adapted approach?
Seminoma Prognostic Factors

Ideal approach. Similar to CS I NSGCT.

Limitation: Factors not validated prospectively.

- Aparicio (JCO, 2005)
  Nearly all relapses occur in rete (+) group. Supports Rete testis risk factor, not size.

- A consortium effort is needed to identify and validate risk factors.
Future of Risk Identification: Standard Criteria + Molecular Signature?

IGCCCG and molecular signature (Korkola et al, ASCO 2008, Abstract #5084)

1. Identify and validate standard histologic criteria
2. Adapt molecular assay to paraffin tissue.
Does acute toxicity allow a direct choice?

1. Carboplatin causes less ↓WBC and more ↓Plt than RT.
2. Dyspepsia may or may not be different from RT.
3. Return to work >80% by 12 weeks for both RT and carboplatin, but slower recovery after RT.
4. Sperm count recovers by 2 years for RT, but unknown for carboplatin.
5. Paternity ~70% at 15 years after RT, unknown for carboplatin, and 92% with surveillance.  
   *(Brydøy et al, JNCI 2005)*

Acute Toxicity tolerable but surveillance = no toxicity.
Survivorship

What should I tell my patient about late toxicity?

1. **Second Malignant Neoplasms (SMN).**
   After RT and chemo. 50% of SMN outside RT port.
   
   (van Leeuwen, JCO, 2001; Travis, JNCI 2005; van den Belt-Dusebout, JCO 2007;

   **MRC/EORTC Trial**
   
   RT : 0.9% SMN  \[\text{\{6.5 years median F/U}\]}
   Carbo : 1.1% SMN  \[\text{\{6.5 years median F/U}\]}
   Surveillance: 5.9% SMN  \[\text{\{16.5 years median F/U}\]}
   RPLND: 4.3% SMN  \[\text{\{16.5 years median F/U}\]}

2. **Cardiovascular Disease (CVD).**
   Particularly after cisplatin-based chemotherapy.
   
   (Meinardi, JCO, 2000; Huddart, JCO, 2003).
Late Toxicity After GCT Treatment
Competing Risks: 2nd Cancers and Heart Disease

Cumulative risk of 2nd malignant neoplasm (SMN) or cardiovascular disease (CVD) by treatment among NSGCT survivors

1. **RPLND.**
   Both SMN and CVD in the absence of therapy.

2. **Chemo or RT:**
   Risk of SMN or CVD greater than after RPLND.

3. **RT+Chemo**
   Risk greater than either Chemo or RT.

van den Belt-Dusebout, JCO; 25:4370, 2007
Does Carboplatin Cause CVD or SMN?

Cardiovascular Disease:
2. 4% CS I seminoma patients who received carboplatin had fatal AMI. All were older, had H/O of CVD, and an event 7 - 29 months after carboplatin. Related? (Reiter et al, JCO 2001).

Second Malignant Neoplasm (SMN)
3. Carboplatin and RT: ~1% SMN at 6.5 yrs median F/U.

Conclusion
More long term carboplatin experience required.
MANAGEMENT OF CS I SEMINOMA

How do I integrate these data into my practice?

WHAT IS THE GOAL?
Maximum cure rate with least toxicity for the patient population.

HOW TO ACCOMPLISH THIS GOAL?
Focus on the relative risk/benefit ratio for the population.
### Treatment Assignment Among 1000 CSI Seminoma Patients

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>RT only</th>
<th>Chemo only</th>
<th>RT+ Chemo</th>
<th>Chemo x2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surveillance</strong></td>
<td>80%</td>
<td>13%</td>
<td>6%</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Surveillance &amp; RT for 2 Risk Factors</strong></td>
<td>68%</td>
<td>27%</td>
<td>4%</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>0</td>
<td>96%</td>
<td>0</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Carbo</strong></td>
<td>0</td>
<td>0</td>
<td>95%</td>
<td>0</td>
<td>5%</td>
</tr>
</tbody>
</table>

Assume: Surveillance Relapse = 20%; 2/3 of Surveillance Relapse get RT; RT Relapse=4%; Carboplatin Relapse=5%; 2 Risk Factor Relapse = 32%; No Relapse after (B)EP.
Conclusions

Your patient needs a recommendation.

1. **Surveillance is an option.**
   - Least treatment for greatest number of patients.
   - With or without risk adapted approach.

2. **RT is an option.**
   - Becoming less preferred due to fear of SMNs.
   - 50% of SMNs occur outside RT portal
   - Dogleg port clears the pelvis—no long-term CT F/U.
   - PA port — Long-term CT F/U. Patient compliance.
Conclusions

Your patient needs a recommendation.

3. **Carboplatin is an option.**
   Carboplatin is not THE standard of care.
   Retroperitoneal and pelvic relapse dominate.
   More chemo exposure.
   Long-term CT F/U. Patient compliance.
   Remember carboplatin is inferior to cisplatin.
   Late toxicity of carboplatin cannot be evaluated.

4. **Each choice has known and unknown risks.**
   To achieve best outcome, the patient needs to understand his options and risk profile.
   Long-term CT followup requires a compliant patient.
Conclusions

**MSKCC preferences.**

1. Surveillance-based management. Least exposure to RT, Chemo, and especially RT+Chemo.

2. Favor RT-DL when RT is given.

3. A risk adapted approach, as in CS I NSGCT, is likely the best approach. More research needed on CS I prognostic factors.