Germ Cell Testicular Tumors

Ignacio Duran, MD PhD
Instituto de Biomedicina de Sevilla,
Hospital Universitario Virgen del Rocío
Universidad de Sevilla
Why Germ Cell Cancer?

90% of tumors that develop from the testis arise from the Germ Cells. So Testicular Cancer is equivalent to Germ Cell Tumor.

Within the sem. Tubule: Sertoli Cells: The “nurse”. Nourish the cells in development. Germ Cells: Cells that are going to mature and become spermatogonia, spermatocytes.
Pathogenesis: A special disease

Initiation of pathogenesis occur intrautero

Primordial germ cells (PGC) would escape normal differentiation to become GCNI

GCNIS during puberty would gain invasive capacity


Epidemiology: A rare disease but...quite unique

- In 2012, ≈ 55,000 new cases worldwide
- Incidence increasing; variable distribution
- ≈ 800 new cases/year in Spain; Intermediate ASR [3.5 cases per 10^5]
- 1.5% of all cancer diagnosis
- Most frequent neoplasm in young adults
- Arrival of cisplatin, better surgical techniques and multidisciplinary work: The paradigm of curable neoplasm

Diagnosis: Symptoms/Signs

- Testicular lump (painless):
  **Testis ultra sound** to confirm diagnosis and explore contralateral

- Physical exam, cxr, blood work & pre- and post-orchiectomy serum **tumor markers**

- CT **abd-pelvis** [ chest (mandatory in non-seminoma)

Diagnosis: The med-onc patient

• When the patient arrives to the medical oncologist there is already an orchidectomy and a histological diagnosis

• The orchidectomy must be performed via inguinal

• In exceptional cases the orchidectomy might be postponed and systemic treatment started up front
Diagnosis: Symptoms/Signs

- Testicular lump (painless): **Testis ultrasound** to confirm diagnosis and explore contralateral

- Physical examination, blood work & pre- and post-orchietomy serum **tumor markers**

- **CT abd-pelvis** [chest (mandatory in non-seminoma)]

Diagnosis: Key Point

• Seminomas
  – Around 45%
  – On average appear 10 y later[40s]
  – Tend to be big masses
  – 15% of them produce HGC
  – NONE of them produce AFP
  – Typically rise LDH
  – More radio sensitive

Subtypes:
  • Seminoma
  • Seminoma with syncytiotrophoblast cells
  • Spermatocytic Seminoma* [spermatocytic tumour]

Diagnosis: Key Points

- **Non-Seminomas**
  - More frequent (≈55%)
  - Younger patients[30]
  - **Any marker** (HGC,AFP,LDH)
  - Less Radio sensitivity
  - Chemotherapy and surgery

**4 Types:**
- **EC** (the most frequent)
- **Yolk Sac Tumor** (AFP)
- **Choriocarcinoma** (HGC)
- **Teratoma**

Overview: Natural History

Natural history ranges from local growth to lymph node spread and visceral disease (Lung, Liver, Bone, Brain, etc ...)

I.Duran. Escorial 2014
Staging

- CT Chest-Abd-Pelvis
- CT /MRI CNS (if visceral mets/very high markers or neurological sympt)
- Bone Scan [only if symptoms suggesting bone mets]
- PET -FDGCT **should NOT** be used routinely
- Tumor markers (before & after orchiectomy)**
  - In advanced disease TM post-cx and **pre-chemo** are the ones used to classify patients
  - Attention to **half lives** of TM (AFP: A7P; HGC: 3 Dias)

I.Duran. Escorial 2014
**Stage I**: Tumor confined to the testis
- **Ia** No vascular invasion. **Ib** Vascular Invasion

**Stage II**: Retroperitoneal Lymph Nodes
- **Ila** [<2cm]; **Iib** [2-5cm]; **Ilc** [>5cm]

**Stage III**: Visceral disease or Lymph Nodes above the diaphragm
Treatment Decision

• **Histology:**
  – Seminoma
  – Non-Seminoma
  – Mixed Histologies (non sem mandates)

• **Staging:**
  – Localized Disease (Stage I)
  – Lymph Node Pelvic Disease (Stage II)
  – Visceral Disease (Stage III) (Risk Group)
Stage I Disease

- Over 50% of GCTs are clinical stage I disease at presentation
- Curability approaches 100% in this setting
- Multiple options have been traditionally considered

Cure without long term sequelae of treatment is the goal of management in Stage I disease

- Normal Tumor markers after orchiectomy
- No evidence of metastatic disease on imaging studies
Clinical Stage I- Seminomas

• Common presentation (≈ 80% of SGCT)
• Cure rates ≈ 100% regardless treatment option

• Different Strategies:
  – Adjuvant Radiation to retrop LN
  – Adjuvant Chemotherapy
    (Carboplatin AUC7 x 1-2)
  – Active Surveillance

• Risk adapted strategies?

• Attention to toxicity profiles (long survivors!!)

Chung P. Warde P. JNCI 2011; Albers P,.. Eur Urol. 2015 Dec;68(6):1054-68
SIU/ICUD Consensus. Seminomas

• “In stage I disease, the consensus conference recommended that patients should be informed of all treatment options (…)"

• In patients *willing and able to adhere to a surveillance program*, this should be considered the management option of *choice* [we are still defining the best surveillance schema]

Clinical Stage I NS-GCT

- Over 50% NS-GCT present with stage I
- Stage Ia-Ib (Lymphovascular invasion y/n)

**Treatment options after orchidectomy:**
- Primary RPLND
- Adjuvant Chemotherapy (BEP x2)
- Active Surveillance

**Equivalent outcomes:** 5-year OS~ 99%

**Objective:** Diminishing treatment related morbidity while keeping efficacy

SIU/ICUD Consensus 2009 Non Seminomas

✓ Patients should be made aware of all treatment options (surveillance, chemo, RPLND) and their potential side effects.

✓ For patients with low risk of occult metastasis surveillance is preferred.

✓ For those at high risk all 3 options can be considered

Stephenson AJ et al. Urology 2011
Seminomas Stage IIa-b

- Radiation to para Ao and ipsilateral iliac LN has been the standard treatment [Hockey stick radiation field] [30Gy]
- RFS 6 years 95%-86% in IIa-IIb
- OS close to 100%
- Recent studies justify as an alternative the use of 3 cycles of BEP/4 EP
- Equivalent efficacy and less toxicity in the long term

NSGCTs: STAGE IIa-IIb

- Two strategies:
  - LPRND-NS +/- ad.ttt
    * Low volume disease
    * Negative markers
  - CHEMOTHERAPY
    BEP x 3
    * High volume tumors
    * Positive markers

Advanced Disease IIc-III

We will classify our patients in PROGNOSTIC GROUPS according to predefined criteria (IGCCCG)

- 5862 pts with advanced GCTs
- 1975-1990 (F/u of 5 years)
- Analysis of prognostic factors
- **Non Seminomas:**
  - Markers, Location (Pr & Mets)
- **Seminomas:**
  - Only location of Mets


---

**TABLE 3: International Germ-Cell Collaborative Group Consensus Conference criteria for good- and poor-risk testicular cancer patients treated with chemotherapy**

<table>
<thead>
<tr>
<th>NONSEMINOMA</th>
<th>Good prognosis</th>
<th>All of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>marker &amp; location</td>
<td>AFP &lt; 1,000 ng/mL, β-hCG &lt; 5,000 IU/L, and LDH &lt; 1.5 × upper limit of normal</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>Nonmediastinal primary</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>No nonpulmonary visceral metastasis</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>Intermediate prognosis</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>All of the following:</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>AFP = 1,000-10,000 ng/mL, β-hCG = 5,000-50,000 IU/L, or LDH = 1.5-10 × normal</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>Nonmediastinal primary site</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>No nonpulmonary visceral metastasis</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>Poor prognosis</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>Any of the following:</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>AFP &gt; 10,000 ng/mL, β-hCG &gt; 50,000 IU/L, or LDH &gt; 10 × normal</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>Mediastinal primary site</td>
<td></td>
</tr>
<tr>
<td>marker &amp; location</td>
<td>Nonpulmonary visceral metastasis present</td>
<td></td>
</tr>
</tbody>
</table>

**SEMINOMA**

| Good prognosis | No nonpulmonary visceral metastasis |
| Intermediate prognosis | Nonpulmonary visceral metastasis present |

AFP = alpha-fetoprotein; hCG = human chorionic gonadotropin; LDH = lactic dehydrogenase
GOOD PROGNOSIS PATIENTS

3 Cycles of BEP

4 EP is an alternative

INTERMEDIATE OR POOR PROGNOSIS

- Manage as one group:
- Standard of care is:
  - BEP x 4

Recent studies by the French Group have tried to define a new standard for intermediate or poor prognosis however the results are not so solid as to change the standard

De Witt R. et al ASCO 2011: Fizazi K et al. ASCO GU 2017
ADVANCED DISEASE

CHEMOTHERAPY

COMPLETE RESPONSE
[neg. mms/no r.d.] F/U

PARTIAL RESPONSE
[neg mms/r.d.]

RESIDUAL MASS

RESOLUTION

PROGRESSIVE DISEASE
[NO neg mms/growing mass]

RESCUE TT.
Residual mass with negative mm [NS]

After chemotherapy we achieve a normalization of tumor markers with reduction of original tumor mass but still persistence of something > 1cm.

45% Fibrosis/necrosis
-35% Teratoma
-20% Tumor

When there is a residual mass after chemotherapy greater than 1 cm in NSGCT we have no clear data to support what is behind.

RESIDUAL DISEASE NON-SEMINOMATOUS GCT

NON-SEMINOMA

*Any residual mass >1cm in NSGCT should be resected
Residual Masses in Seminomas

Salvage Therapy

- Patients who relapse after first line or those who never respond to primary treatment
- They should be managed by expert teams (look for help)

**Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Primary site</td>
<td>Gonadal</td>
</tr>
<tr>
<td>Prior response</td>
<td>CR/PRm—</td>
</tr>
<tr>
<td>PFI, months</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>AFP salvage</td>
<td>Normal</td>
</tr>
<tr>
<td>HCG salvage</td>
<td>≤ 1,000</td>
</tr>
<tr>
<td>LBB</td>
<td>No</td>
</tr>
</tbody>
</table>

Score sum (values from 0 to 10)
- Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3
- Add histology score points: pure seminoma = —1; nonseminoma or mixed tumors = 0
- Final prognostic score (—1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)

Abbreviations: CR, complete remission; PRm—, partial remission, negative markers; PRm+, partial remission, positive markers; SD, stable disease; PD, progressive disease; PFI, progression-free interval; AFP, alpha fetoprotein; HCG, human chorionic gonadotrophin; LBB, liver, bone, brain metastases.

- **Location** of primary
- **Prior response**
- **Progression Free Interval**
- **Markers** at the time of rescue
- Liver, Bone or Brain mets
Conclusions

- **Testicular cancer** is a rare but quite relevant tumor

- If well managed is a **curable disease** in most cases

- Early stages can be handled with less aggressive strategies with excellent outcomes
  
  [Long survivors/potential toxicity]

- **Advanced Disease** requires stratification into prognostic groups before treatment

- Refractory disease should ideally be treated in institutions with large experience
Tiempo para más?

Si no para esas noches de insomnio
Brain Metastases

• Brain metastases (BM) can be present at the initial diagnosis or at relapse, although is a poor prognosis population some of these patients can still be potentially cured

• Adverse risk factors for both groups are:
  – (1) The multiplicity of BM
  – (2) The presence of liver or bone metastases concurrently

• BM synchronous [better prognosis]
  – BEP X 4 +/- consolidation [attention to late tox]

• BM metachronous [worse prognosis]
  – HDCT +/- surgery or rads

Special Scenarios

• **Very high tumor burden:** “Cooling schemas”
  – Normal renal function:
    • 2 days of EP & on day +11. BEP or VIP
    • Mini BOP
  – Abnormal renal function:
    • Avoid Bleomycin. Carbo +/- etop & on day +11 BEP or VIP

• **HIV patients:**
  – Identical management but HAART should be given concurrently +/- prophylaxis if CD4<200
Special Situations

• **Marker Elevation with no clinical/radiological evidence of disease:**
  – Rule out disease in **Sanctuaries** (brain, testis)
  – High **BHGC**:
    • Rule out hypogonadism\(^1\)
    • Rule out drugs (Marihuana might increase BHGC)
  – High **AFP**:
    • Liver damage: 2ary to toxis, virus, anaesthetics\(^2\)

Late toxic effects

- **Hypogonadism:**
  - Testosterone < 8 nmol/L
  - 11-35%
  - Testost determination recommended during fu

- **Cardiovascular Toxicity:**
  - 2-3 increased risk of CV toxicity: Raynaud Sdm

- **Metabolic Syndrome:**
  - 20-30% long term GCT survivors
  - Aprox 3-5 years after treatment

- **Second Tumors:** Double RR. GI/GU
  - Solid tumors > 10 years after
  - Leukemias 0.5%-2% (Etoposide dose <2<)
The near future


MUCHAS GRACIAS
Y FELIZ VERANO!!