Germ Cell Testicular Tumors

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Outline

• Testis Anatomy-Pathogenesis
• Epidemiology
• Diagnosis & Natural History
• Approaching the patient (treatment decision)
• Treatment by stage
• Summary & Conclusions
• Appendix
Testis and Testis Cancer

Cell types in the testis:
- Macrophages
- Myoid Cells: Muscle cells

90% of tumors that develop from the testis arise from the Germ Cells. So Testicular Cancer equivalent to Germ Cell Tumor development. Germ Cells: Cells that are going to mature and become spermatogonia, spermatocytes.
Pathogenesis: A special disease

- Aberrant Chromatid exchange in early meiosis
- Cyclin D2
- Iso- chromosome 12


Epidemiology: A rare disease but...quite unique

- GCTs represent 1% of all cancers

- \( \approx 8,000 \) new cases/year (US)  
  \( (\approx 700 \text{ in Spain}) \)

- It is the most frequent neoplasm in young adults (15-35 y/o)

- Arrival of cisplatin, better surgical techniques and multidisciplinary work: CURABLE NEOPLASM
Diagnosis: Symptoms/Signs

- Testicular lump (painless)

- Symptoms mimicking infection

- Symptoms related to advanced disease
  - Dyspnea /Cough/ Hemoptysis
  - Lower Back Pain
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: 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:**
- Classic Seminoma
- Atypical Seminoma
- Spermatocytic Seminoma*

Classic Seminoma

Spermatocytic Sem
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**

Non Seminomatous Tumor (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 brain (if visceral mets/very high markers or neurological sympt)
- PET CT **should NOT** be used routinely
- **Tumor markers** (before & after orchidectomy)**
  - In advanced disease TM **pre-chemo** are the ones used to classify patients
  - Attention to **half lives** of TM (AFP: A7P; HGC: 3 Dias)
Staging

Stage I: Tumor confined to the testis
   Ia No vascular invasion. Ib Vascular Invasion
Stage II: Retroperitoneal Lymph Nodes
   Ila [<2cm]; Iib [2-5cm]; Iic [>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 Treatment Strategies
  - Adjuvant **Radiation** to retrop LN
  - Adjuvant **Chemotherapy** (Carboplatin)
  - Active **Surveillance**

- Risk adapted strategies?

- Attention to toxicity profiles (long survivors!!)

Chung P. Warde P. JNCI 2011
I.Duran. Escorial 2014
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


I.Duran. Escorial 2014
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 Ila-IIb

Enfermedad retroperitoneal ≤ 5 cm(N1,N2)

-Tratamiento estándar: Radioterapia

-Dosis y campos han sido comparados


- Campo de radiación “HOCKEY STICK FIELD”

- RFS 6 años 95% y 86% en Ila y IIb

- OS próxima al 100%

*Si contraindicación para radioterapia: BEP x 3

NSGCTs
STAGE  IIa-IIb

-Two strategies:

-LPRND-NS +/- ad.tt  →  *Low volume disease
   *Negative markers

-CHEMOTHERAPY  BEP x 3  →  *High volume tumors
   *Positive markers

Rabbani F, Sheinfeld J et al: Low volume nodal metastases detected at retroperitoneal lymphadenectomy for testicular
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

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

**Nonseminoma**

Good prognosis

All of the following:
- AFP < 1,000 ng/mL, β-hCG < 5,000 IU/L, and LDH < 1.5 × upper limit of normal
- Nonmediastinal primary
- No nonpulmonary visceral metastasis

Intermediate prognosis

All of the following:
- AFP = 1,000-10,000 ng/mL, β-hCG = 5,000-50,000 IU/L, or LDH = 1.5-10 × normal
- Nonmediastinal primary site
- No nonpulmonary visceral metastasis

Poor prognosis

Any of the following:
- AFP > 10,000 ng/mL, β-hCG > 50,000 IU/L, or LDH > 10 × normal
- Mediastinal primary site
- Nonpulmonary visceral metastasis present

**Seminoma**

Good prognosis
- No nonpulmonary visceral metastasis

Intermediate prognosis
- Nonpulmonary visceral metastasis present

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

BEP 500/5
Cisplatin 20mg/m2/day x 5 days
Etoposide 100mg/m2 day x 5 days
Bleomycyne 30 U days 2,9 and 16

Recent studies at ASCO 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 2013
RESIDUAL DISEASE

NON-SEMINOMA

- 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-SEMINOMA

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

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RESIDUAL DISEASE

SEMINOMAS

< 3 cm

> 3 cm

Surveillance

PET 8 Weeks after

Other opt

Surgery

Surveillance

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)
- Relapse after Surveillance; Treat adv disease
- Relapse after 1\(^{st}\) line: **Stratification Systems:**

<table>
<thead>
<tr>
<th>Table 4. Prognostic Score for Patients With Nonseminoma and Seminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score Points</strong></td>
</tr>
<tr>
<td><strong>Parameter</strong></td>
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<tr>
<td>---</td>
</tr>
<tr>
<td>Primary site</td>
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<tr>
<td>Prior response</td>
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<tr>
<td>PFI, months</td>
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<tr>
<td>AFP salvage</td>
</tr>
<tr>
<td>HCG salvage</td>
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<tr>
<td>LBB</td>
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<tr>
<td>Score sum (values from 0 to 10)</td>
</tr>
<tr>
<td>Regroup score sum into categories: (0) = 0; (1 or 2) = 1; (3 or 4) = 2; (5 or more) = 3</td>
</tr>
<tr>
<td>Add histology score points: pure seminoma = —1; nonseminoma or mixed tumors = 0</td>
</tr>
<tr>
<td>Final prognostic score (-1 = very low risk; 0 = low risk; 1 = intermediate risk; 2 = high risk; 3 = very high risk)</td>
</tr>
</tbody>
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- **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

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

- **Refractory disease** should ideally be treated in institutions with large experience

- Don’t forget the **long survivors & potential toxicity**
SAVE THE DATE:
NOV 2014

IF YOU WANT TO LEARN MORE.............

SIMPOSYUM SOGUG 2014
Tiempo para más?
Special Scenarios

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

- **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

- **Brain Metastases**:
  - Start with full chemotherapy +/- Rad/Surg
Special Situations

• **Marker Elevation** with no clinical/radiological evidence of disease:
  – Rule out disease in **Sanctuaries** (brain, testis)
  – High **BHGC**:
    • Rule out hypogonadism¹
    • Rule out drugs (Marihuana might increase BHGC)
  – High **AFP**:
    • Liver damage: 2ary to toxics, virus, anaesthetics²

Late toxic effects

• Hypogonadism:
  – Testosterone $< 8$ nmol/L
  – 11-35%
  – Testost determination reccomended 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!!