Testicular Cancer and Mediastinal Germ Cell Tumors

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DISCLOSURES

Off-Label Usage
  • None

Interests
  • None
Germ Cell Tumors

- Background
- Disseminated Disease
  - Good Risk
  - Intermediate and Poor risk
- Mediastinal GCT
- Salvage Therapy
- Clinical Stage I disease
Germ Cell Tumors

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Testicular Cancer: Incidence and Mortality

- Estimated New Cases in 2014: 8,820
- % of All New Cancer Cases: 0.5%

New Cases and Deaths from 1992 to 2011:
- Number of new cases per 100,000 males:
- Deaths over the years:

Survival Rate:
- 5 Years: 95.3%

SEER
Surveillance, Epidemiology, and End Results Program
Turning Cancer Data Into Discovery
### Histology and Serum Markers

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>BHCG</th>
<th>AFP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seminoma</strong></td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Non-Seminoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teratoma</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Yolk Sac Carcinoma</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Embryonal Carcinoma</td>
<td>++/-</td>
<td>++/-</td>
</tr>
</tbody>
</table>
Germ Cell Tumors: Primary Sites

- Testis
- Ovaries
- Mediastinum
- Retroperitoneum
- Pineal Gland
Clinical Presentation

- Painless unilateral intrascrotal mass (>50%)
- Back or flank pain (11%)
- Gynecomastia (7%)
- Uncommon:
  - Hemoptysis
  - Dyspnea
  - CNS Symptoms
  - Bone metastasis
Staging

- Stage I – Testicle alone
  - Is – Marker elevation alone after orchiectomy
• Stage I – Testicle alone
  \( l_s \) – Marker elevation alone after orchiectomy

• Stage II – Retroperitoneal Lymph node involvement
Staging

• Stage I – Testicle alone
  Is – Marker elevation alone after orchiectomy

• Stage II – Retroperitoneal Lymph node involvement

• Stage III – Disseminated disease (lungs, liver, brain, bone) or marker positive disease after RPLND
Isochromosome 12p: i(12p)
Treatment Recommendations: Stage I

**Stage I: Testicle alone**

- Serum markers
  - Normal
  - Falling consistent with $T^{1/2}$ *

- CT scans
  - Normal Abdominal and Chest
Treatment Recommendations: Stage I

**Stage I: Testicle alone**

- **Serum markers**
  - Normal
  - Falling consistent with $T^{1/2}$ *

- **CT scans**
  - Normal Abdominal and Chest

* Serum half lives:
  - BHCG - ~24 hours
  - AFP - ~ 5 days
Stage I: Testicle alone

- Serum markers
  - Normal
  - Falling consistent with $T^{1/2}$ *

- CT scans
  - Normal Abdominal and Chest

Therapeutic options:

- Surveillance
- RPLND
- Chemotherapy

* Serum half lives:
  - BHCG - ~24 hours
  - AFP - ~ 5 days
Treatment Recommendations: Stage II

Stage II:

- Serum markers:
  - Normal or abnormal

- CT scans:
  - Normal Chest
  - +/- Abnl. Abdominal
Treatment Recommendations: Stage II

**Stage II:**
- Serum markers:
  - Normal or abnormal
- CT scans:
  - Normal Chest
  - +/− Abnl. Abdominal

**Therapeutic options:**
- Clinical Stage II
  - RP mass < 3 cm
    - RPLND
    - Chemotherapy
  - RP mass > 3 cm
    - RPLND
    - Chemotherapy
- Serologic Stage II
  - RPLND
  - Chemotherapy
Treatment Recommendations: Stage III

**Stage III:**

- Serum markers:
  - Normal or abnormal
- CT scans:
  - Abnormal Chest
  - +/- Abnl. Abdominal
  - Disease outside Abdomen (e.g. bone, brain, liver, SCLN)
- PET Scans not helpful in NSGCT
Treatment Recommendations: Stage III

**Stage III:**
- Serum markers:
  - Normal or abnormal
- CT scans:
  - Abnormal Chest
  - +/- Abnl. Abdominal
  - Disease outside Abdomen (e.g. bone, brain, liver, SCLN)
- PET Scans not helpful in NSGCT

**Therapeutic options:**
- Chemotherapy
- Following chemotherapy:
  - Surgical resection of residual disease (NSGCT):
    - Teratoma (40-45%)
    - Necrosis (40-45%)
    - Cancer (10%)*
  - If residual disease in Seminoma:
    - Consider PET
Germ Cell Tumors

• Background
• Disseminated Disease
  – Good Risk
  – Intermediate and Poor risk
• Mediastinal GCT
• Salvage Therapy
• Clinical Stage I disease
Original PVB Regimen

**Induction**

- **Cisplatin**: 20 mg/m² IV x 5 days
- **Vinblastine**: 0.2 mg/kg IV x 2 days (repeat every 3 wks x four courses)
- **Bleomycin**: 30 IU IV push weekly

**Maintenance**

- **Vinblastine**: 0.3 mg/kg IV monthly x 21 mos.
SEG GU 332

Cisplatin 20 mg/m² X 5
Vinblastine 0.15 mg/kg days 1 & 2
Bleomycin 30 units days 2, 9, 16

Cisplatin 20 mg/m² x 5
VP-16 100 mg/m² x 5
Bleomycin 30 units days 1, 8, 15

Courses repeated every 3 weeks for 4 courses
International Consensus Classification*

- "Good Prognosis"
  60% of all patients;
  91% 5 year survival and 87% PFS

- "Intermediate Prognosis"
  26% of all patients;
  79% 5 year survival and 74% PFS

- "Poor Prognosis"
  14% of all patients (all with NSGCT)
  48% 5 year survival and 41% PFS

* JCO 15:594-603, 1997
IGCTCC Classification: NSGCT

Good Prognosis (56% of NSGCT)

- All of the following:
  - AFP < 1,000 ng/ml
  - BHCG < 5,000 IU/L
  - LDH ≤ 1.5 x normal
  - Non-mediastinal primary
  - No non-pulmonary visceral metastasis

* JCO 15:594-603, 1997
Carboplatin inferior to Cisplatin in Good Risk Disease

- **PE x 4 versus CE x 4** *(MSKCC, J. Clin Oncol 11:598, 1993)*
  - 265 patients entered
  - Carboplatin arm inferior with respect to:
    - Event Free (IR or Relapse) Survival (p=0.002)
    - Progression Free Survival (p=0.005)
    - Toxicity (Myelosuppression, GCP fever)

- **BEP x 4 vs. BEC x 4** *(MRC/EORTC, J Clin Oncol 15:1844, 1997)*
  - 598 patients entered
  - Carboplatin arm inferior with respect to:
    - Complete Response rate (94% vs. 87%; p=0.009)
    - Survival (p=0.003)
EST 4887

Randomize

Cisplatin 20 mg/m² days 1-5
Etoposide 100 mg/m² days 1-5

Cisplatin 20 mg/m² days 1-5
Etoposide 100 mg/m² days 1-5
Bleomycin 30 units/week

{ } x 3 cycles

{ } x 3 cycles
**EST 4887**

**Randomize**

- Cisplatin 20 mg/m² days 1-5
- Etoposide 100 mg/m² days 1-5
  \[ \times 3 \text{ cycles} \]

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- Etoposide 100 mg/m² days 1-5
- Bleomycin 30 units/week
  \[ \times 3 \text{ cycles} \]

**Results:**

<table>
<thead>
<tr>
<th></th>
<th>BEP (n=86)</th>
<th>EP (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total NED</td>
<td>82 (95%)</td>
<td>78 (90%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>8 (9%)</td>
<td>18 (23%)</td>
</tr>
<tr>
<td>Dead</td>
<td>3 (3.4%)</td>
<td>7 (8.1%)</td>
</tr>
<tr>
<td>Continuously NED</td>
<td>74 (88%)</td>
<td>80 (70%)</td>
</tr>
</tbody>
</table>
BEP x 3 vs. EP x 4: Good Risk

• Standard “American” BEP x 3 versus EP x 4 in 251 patients in a multi-institution French study (1994 to 1999)

• “Adverse events” defined as CA in post-chemo resection, < CR, or relapse from (CR or PR)

• Results with BEP:
  – Less Grade 3-4 neutropenia (62% vs. 47%; p < 0.001)
  – Less Grade 1-3 neurotoxicity (7% vs. 2%; p < 0.001)
  – More dermatitis (16% vs. 3%; p < 0.001)

*Culine S, et al.: Proc ASCO 22;382, 2003*
EVENT-FREE SURVIVAL

- 4EP; 84% at 4 years
- 3BEP; 90% at 4 years

BEP
EP

251 good-risk IGCCCG patients

Logrank $p = 0.06$
(84% vs. 88%, $p = 0.08$ in ineligible pts)
OVERALL SURVIVAL

- BEP
- EP

4EP; 92% at 4 years
3BEP; 96% at 4 years

Median follow-up = 51 months

BEP
5 deaths
EP
10 deaths

Logrank
p = 0.14
Historical Perspective: Good Risk Disease

- BEP superior to PVB
- BEP x 3 is similar to BEP x 4
- Cisplatin is superior to carboplatin
- BEP x 3 is superior to PE x 3
- BEP x 3 is less toxic than PE x 4
Intermediate Prognosis (28% of NSGCT)

- Non-seminoma
  - No non-pulmonary visceral metastases
  - AFP \(\geq 1,000\) and \(\leq 10,000\) ng/ml
  - BHCG \(\geq 5,000\) and \(\leq 50,000\) IU/L
  - LDH \(> 1.5\) x normal and \(\leq 10\) x normal

* JCO 15:594-603, 1997
Poor Prognosis (16% of NSGCT)

- Non-seminoma
  - Mediastinal primary
  - Non-pulmonary visceral metastases
  - AFP > 10,000 ng/ml
  - BHCG > 50,000 IU/L
  - LDH > 10 x normal

* JCO 15:594-603, 1997
Historical Perspective: Poor Risk Disease

- BEP superior to PVB
- $P_{200}VBE$ superior to PVB
- $BEP_{100}$ superior to $BEP_{200}$
- BEP similar to VIP
- BEP superior to BOP/VIP
- BEP x 4 is superior to high dose chemotherapy plus stem cell transplant
ADVANCED GERM CELL TUMOR

- Study activated 9-95; Closed September 2003
- Participants MSKCC, SWOG, ECOG, Dana Farber and University of Chicago

BEP x 4

BEP x 2 followed by two courses of high dose chemotherapy (HDT):
- Carboplatin 600 mg/M² x 3
- Etoposide 600 mg/M² x 3
- Cyclophosphamide 50 mg/kg x 3
BEP vs BEP + High-dose Chemotherapy

**Event-Free Survival**

- **BEP alone (110 Pts, 60 Failures)**
- **BEP + HDT (107 Pts, 55 Failures)**

**Survival**

- **BEP alone (111 Pts, 77 Alive)**
- **BEP + HDT (108 Pts, 73 Alive)**

* C.R. rates similar (55% versus 45%)
* One year durable C.R. rate 48% versus 52%
* Two year overall survival 72% versus 71% respectively

Motzer et al: J Clin Oncol Jan, 2007
Germ Cell Tumors

- Background
- Disseminated Disease
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- Mediastinal GCT
- Salvage Therapy
- Clinical Stage I disease
Differential Diagnosis: Anterior Mediastinal Neoplasms

- Thymoma/ Thymic Carcinoma
- Lymphoma (Hodgkin’s and NHL)
- Endocrine (Thyroid and Parathyroid)
- Germ Cell Neoplasms
Thymic Hyperplasia

• **True Hyperplasia**
  - Increased weight and volume
  - Complication of chemotherapy (e.g., Hodgkin's Disease, GCT)
  - Thermal burns (after stopping corticosteroids)

• **Lymphoid Hyperplasia**
  - Increased lymphoid follicles, but not weight or volume
  - Myasthenia Gravis
  - Other autoimmune disorders (SLE, PSS, rheumatoid arthritis, thyrotoxicosis, allergic vasculitis)
Case Report

- A 31 year old WM presents with cough and chest pain.

- Physical exam reveals a thin, tall man appearing somewhat pale. VS were WNL LN: normal; CV: distant heart sounds; Abd: soft and non-tender; GU: atrophic testis
Labs:

- BHCG - 50,000 IU/l
- AFP - 251 ng/ml

- CBC:
  - Hg - 10.1
  - Ht - 29.7
  - WBC - 7.4
  - Platelet Ct - 74,000
Case Report: (cont’d)

• The patient is begun on BEP and sent to his local physician for second and third courses.
Case Report: (cont’d)

- The patient is begun on BEP and sent to his local physician for second and third courses.
- Nine weeks later he presents with chest wall mass.
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Case Report: (cont’d)

• The patient is begun on BEP and sent to his local physician for second and third courses.
• Nine weeks later he presents with chest wall mass.

• His BHCG is now 32 mIU/L and his AFP is normal.
• CBC has Hb= 9.7, WBC = 3.2 and Platelet count = 23,000/ml
What’s going on?
Mediastinal Germ Cell Tumors

- Most common extragonadal site
- Older age onset
- Male preponderance (equal for teratoma)
- Elevated BHCG and/or AFP
- i12p
- Associated Syndromes:
  - Hematologic disorders
  - Non-germ cell malignancies
  - Klinefelter's (younger onset)
Mediastinal NSGCT: Hematologic Malignancies

- Acute megakaryocytic leukemia
- Myelodysplastic syndrome
- Refractory thrombocytopenia
- Refractory Anemia with Excess Blasts
- Malignant histiocytosis
- Systemic mastocytosis
Mediastinal NSGCT: Non-Germ Cell Malignancies

- Rhabdomyosarcoma
- Synovial Cell Sarcoma
- PNET
- Nephroblastoma
- Adenocarcinoma
Extragonadal Germ Cell Tumors: A Meta-analysis

- Retrospective review of 628 cases treated 1975 to 1996 at 10 centers in Europe plus IUMC (n = 216)
- 524 were NSGCT and 104 pure seminoma
- Twelve patients with retroperitoneal and 4 with PMGCT developed a subsequent testis primary (median time interval was 60 months)
- Seventeen of 287 (6%) patients with PMGCT developed hematologic disorder:
  - usually of platelet lineage
  - i12p often present in leukemia blasts
<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>5 yr. PFS</th>
<th>5 yr. Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediastinal seminoma</td>
<td>51</td>
<td>88%</td>
<td>89%</td>
</tr>
<tr>
<td>Retroperitoneal seminoma</td>
<td>52</td>
<td>77%</td>
<td>88%</td>
</tr>
<tr>
<td>Mediastinal NSGCT</td>
<td>287</td>
<td>44%</td>
<td>49%</td>
</tr>
<tr>
<td>Retroperitoneal NSGCT</td>
<td>227</td>
<td>45%</td>
<td>63%</td>
</tr>
</tbody>
</table>
Germ Cell Tumors

- Background
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- Salvage Therapy
- Clinical Stage I disease
A 21 year old man presented with a testicular mass. He underwent an right orchiectomy which revealed a mixed germ cell tumor (embryonal carcinoma and immature teratoma).

The workup reveals:
- Chest CT: normal
- Abdominal CT: 4 cm para-aortic lymphadenopathy with mild hydronephrosis
- AFP = 200 ng/ml; BHCG = 1,200 IU/L; LDH = 256
- BUN = 16 and Creatinine = 1.4 mg/dl
• He was treated with 3 cycles of BEP and returns for follow up. His repeat markers are normal. His abdominal CT shows no change in the size of his mass.
• Physical exam now reveals a 3 cm left supraclavicular lymph node.
• Physical exam now reveals a 3 cm left supraclavicular lymph node.

• Fine needle aspiration of the lymph node reveals: “cells consistent with germ cell tumor”
What do you now recommend?

- Two more cycles of BEP
- Switch to VeIP x 4
- TIP x4
- Refer for high dose chemo with tandem transplant
- Surgical resection of disease
- Phase II trial
Pitfalls in Salvage Chemotherapy

- Elevated HCG or AFP as only evidence of relapse or progressive disease
  - Elevated LH
  - Marijuana
  - Hepatitis
- Second primary
- Pseudo-nodules on chest x-ray or CT
- “Growing Teratoma” Syndrome
Salvage Therapy Options: Curable Patients

- VeIP x 4 (30% cure in NSGCT, 50% in Seminoma)
- TIP x 4
- High dose chemotherapy with Stem cell transplant
- Salvage surgery
Forty six patients treated at MSKCC

TIP Regimen:
- Paclitaxel 250 mg/M² over 24 hours,
- Ifosfamide 6 grams/M²
- Cisplatin 100 mg/M²

Eligibility:
- All were testis primary
- All had prior C.R. or P.R. with normal markers for > 6 months

Results: 29 (63%) continuously disease-free after TIP alone or with surgery.

*Kondapunta et al: JCO 6549-6555, 2005*
Salvage Chemotherapy with High Dose Carboplatin and Etoposide with peripheral Stem Cell Transplant (PBSCT)

- 184 consecutive patients treated from February, 1996 to December, 2004
- Cytoreduction with 0-2 courses of VeIP followed by tandem transplant: carboplatin 700 mg/M2 x 3 + etoposide 750 mg/M3

<table>
<thead>
<tr>
<th></th>
<th>No. pts.</th>
<th>No cont. NED (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire series</td>
<td>184</td>
<td>117 (64%); 114 &gt; 1 yr. cont.</td>
</tr>
<tr>
<td>NED:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-line Tx</td>
<td>133</td>
<td>92 (69%)</td>
</tr>
<tr>
<td>Third-line or later</td>
<td>51</td>
<td>25 (49%)</td>
</tr>
<tr>
<td>Hcg &gt; 1,000</td>
<td>20</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>AFP &gt; 1,000</td>
<td>7</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Platinum refractory</td>
<td>30</td>
<td>15 (50%)</td>
</tr>
</tbody>
</table>

High Dose Salvage Chemotherapy in Germ Cell Tumors

Late Relapse of Germ Cell Tumors

- Retrospective analysis of 81 patients treated for late relapse at Indiana University 1979-1992

- Forty-seven (58%) relapsed after being disease free for more than five years, the remaining 34 relapsed at 2 - 5 years.

- Approximately 2-3% of patients disease free for 2 or more years will have a late relapse.
Late Relapse (con’t)

- **Characteristics:**
  - Elevated AFP in 44 (58%)
  - Elevated HCG in 21 (28%) patients
  - Both markers elevated in 11 patients

- **Continuously NED after treatment (n=21):**
  - Teratoma: 8/15 (53%)
  - Germ Cell Carcinoma: 10/59 (17%)
  - Teratoma plus Sarcoma: 3/7 (43%)

- 19 of these 21 had surgery as a component of salvage therapy

\[ p=0.002 \]
Second Malignant Neoplasms in Testicular Cancer Survivors*

- SEER Registry data of 12,691 survivors of testicular NSGT managed with surgery or chemotherapy alone (no radiation)
- No increase risk of second malignancies in patients undergoing surgery alone
- A 26% to 62% increase in secondary solid cancers in those receiving chemotherapy,
- Increase in leukemia incidence (2%) seen in patients receiving 2,000 mg/m² of etoposide
- Cumulative dose of 650 mg of cisplatin is associated with 3 fold increase of leukemia

*Travis LB et al JNCI (2005)
Germ Cell Tumors

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Clinical Stage I NSGCT: Surveillance

- Follow up includes: markers, CXR and Abdominal CT scans
- Approximately 30% recurrence rate

- Predictive factors:
  - Presence of Embryonal Carcinoma
  - Absence of yolk sac carcinoma
  - Vascular invasion
  - Lymphatic invasion

- LVI:
  - If present: ~ 50% recurrence rate after orchiectomy
  - If absent: ~ 15% recurrence rate after orchiectomy
  - Relapses may occur 3-5 years post orchiectomy

99% Cure rate
Clinical Stage I NSGCT: RPLND

- Following RPLND, patients do not need abdominal CT in follow-up
- Virtually 100% normal ejaculation with nsRPLND

- If pathology negative: 10% relapse rate
- If pathology is positive: 30% relapse rate (without adjuvant) <1% with adjuvant BEP

99-100% Cure rate
Clinical Stage I NSGCT: Options (BEP, RPLND or surveillance)

- **Albers P (2008):** 346 evaluable patients randomized to RPLND or one cycle of BEP
- **Recurrences:**
  - Fourteen of 188 (7.5%) with RPLND
  - 2 of 178 (1.1%) with BEP x 1 ($p = 0.0025$)
- **Tandstad T (2009):** 745 patients were randomized to surveillance vs. one (or 2) cycles of BEP and stratified by absence or presence of Vascular Invasion (VAS)

<table>
<thead>
<tr>
<th>Options</th>
<th>No of Pts</th>
<th>VAS+</th>
<th>VAS-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance</td>
<td>350</td>
<td>41.7%</td>
<td>13.2%</td>
</tr>
<tr>
<td>BEP X1</td>
<td>312</td>
<td>3.2%</td>
<td>1.3%</td>
</tr>
<tr>
<td>BEP x 2</td>
<td>72</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Note: no deaths from progressive testicular cancer in either study*
Options for Clinical Stage I Seminoma

- XRT (Overtreatment in 70-80%)
  - 20 Gy same as 30 Gy (JCO, 2005)
  - Extended field not required (JCO, 1999)
- Chemotherapy (Overtreatment in 70%, still need follow up with Abdominal CT scans)
  - Carboplatin
  - BEP, EP, or cisplatin
- Surveillance (Treat only the truly needy)
Common Problems: Summary

- Clinical Stage I: Know options and limitations
Common Problems: Summary

- Clinical Stage I: Know options and limitations
- Stage III: Good risk
  - Carboplatin inferior
  - BEP x 3 or PE x 4
Common Problems: Summary

- Clinical Stage I: Know options and limitations
- Stage III: Good risk
  - Carboplatin inferior
  - BEP x 3 or PE x 4
- Stage III: Poor risk
  - BEP x 4 (may substitute ifosfamide for bleomycin)
Common Problems: Summary

• Clinical Stage I: Know options and limitations
• Stage III: Good risk
  – Carboplatin inferior
  – BEP x 3 or PE x 4
• Stage III: Poor risk
  – BEP x 4 (may substitute ifosfamide for bleomycin)
• Salvage therapy
  – Pseudo-progression (false markers, growing teratoma)
  – High dose chemotherapy with tandem transplants
  – Late relapses