**IMPORTANCE OF TESTIS CANCER**

- Most common carcinoma in men 15-35
- Value of combined modality therapy
- Model for randomized studies
- New drug discovery
- Goal of therapy cure

**SEQUENTIAL PVB STUDIES AT INDIANA UNIVERSITY**

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Pts.</th>
<th>C.R.</th>
<th>Surg.</th>
<th>NED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1974-76)</td>
<td>47</td>
<td>33 (70%)</td>
<td>5 (11%)</td>
<td>27 (57%)</td>
</tr>
<tr>
<td>2 (1976-78)</td>
<td>78</td>
<td>51 (65%)</td>
<td>13 (17%)</td>
<td>57 (73%)</td>
</tr>
<tr>
<td>3 (1978-81)</td>
<td>147</td>
<td>92 (63%)</td>
<td>31 (21%)</td>
<td>117 (80%)</td>
</tr>
</tbody>
</table>

**SEG GU 332**

**RANDOMIZE**

Cisplatin 20 mg/M² x 5
Vinblastine 0.15 mg/kg, days 1 and 2
Bleomycin 30 units days 2, 9, and 16

Courses repeated every 3 weeks for 4 courses

**SECSG GU332: PVB VERSUS PVP16B**

<table>
<thead>
<tr>
<th></th>
<th>PVB</th>
<th>PVP16B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number patients</td>
<td>121</td>
<td>123</td>
</tr>
<tr>
<td>C.R.</td>
<td>74 (61%)</td>
<td>74 (60%)</td>
</tr>
<tr>
<td>NED with surgery</td>
<td>15 (12%)</td>
<td>28 (23%)</td>
</tr>
<tr>
<td>Continuously NED</td>
<td>80 (66%)</td>
<td>96 (78%)</td>
</tr>
</tbody>
</table>
SECSG GU 306 – MINIMAL AND MODERATE DISSEMINATED GERM CELL TUMORS

**Randomize**
- **PVP₁₆B – 4 courses (12 weeks)**
- **PVP₁₆B – 3 courses (9 weeks)**

Cisplatin 20 mg/M² daily x 5 every 3 weeks
VP₁₆ 100 mg/M² daily x 5 every 3 weeks
Bleomycin 30 units weekly

COMPARISON OF MINIMAL PLUS MODERATE: 3 VERSUS 4 COURSES PVP₁₆B

<table>
<thead>
<tr>
<th></th>
<th>PVP₁₆B ×3</th>
<th>PVP₁₆B ×4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number entered:</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>NED status achieved:</td>
<td>86 (98%)</td>
<td>93 (97%)</td>
</tr>
<tr>
<td>Relapse:</td>
<td>6 (6%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Continuously NED:</td>
<td>81 (92%)</td>
<td>88 (92%)</td>
</tr>
<tr>
<td>NED with salvage chemotx:</td>
<td>1 (1%)</td>
<td>4 (4%)</td>
</tr>
</tbody>
</table>

LONG-TERM FOLLOW-UP OF 3 VERSUS 4 COURSES OF PVP-16B IN GOOD-RISK GERM CELL TUMORS

- 118 patients at Indiana University randomized on this SEG study
- Median follow-up 10 years and all have > 5 year follow-up
- 4 deaths in each arm, including 1 drug toxicity, 1 acute leukemia and 1 suicide

3 VERSUS 4 (cont’d)

- No survival difference between 3 and 4 courses (p = 0.79)
- There were only 2 disease-related deaths in 104 patients with HCG < 1,000; there were 5 disease-related deaths in 14 patients with HCG > 1,000 (risk ratio 21:4)

“INTERNATIONAL GERM CELL CONSENSUS”

**Advanced (14%)**
- PMNSGCT
- Non-pulm. visc mets
- AFP > 10,000
- HCG > 50,000
- LDH > 10XULN

Chemotx: BEP x 4 or VIP x 4

**Intermediate (26%)**
- Seminoma with non-pulmonary visc mets
- AFP 1,000 to 10,000
- HCG 5,000 to 50,000
- LDH 1.5 to 10 x ULN

Chemotx: BEP x 4 or BEP x 3 and EP x 1

ETOPOSIDE + CISPLATIN FOR METASTATIC GOOD-RISK GCT*

- Retrospective review of EP x 4 in 289 good-risk patients by IGCCG criteria treated 1982-2002
- 98% C.R.s; 6% relapsed
- SECSG phase III study of BEP x 3 versus BEP x 4 achieved 92% cures (JCO 7:387-391, 1989)
  - some of these patients were actually intermediate or poor risk
  - 118 Indiana patients from Indiana University; 102 of 104 with serum HCG < 1,000 continuously NED

REASONS TO CHOOSE EP X 4

- Concern about pulmonary fibrosis
- Difficulty doing post-chemo RPLND
- Perception that EP x 4 has a higher cure rate than BEP x 3

REASONS TO CHOOSE BEP X 3

- Cisplatin remains the most toxic drug due to cumulative anorexia, nausea, vomiting, neurotoxicity, ototoxicity and sterility
- Rare cases of etoposide induced leukemia – dose dependent
- Data

BEP x 3 VERSUS EP x 4: GOOD-RISK DISEASE

- Standard “American” BEP x 3 versus EP x 4 in 251 patients in a multi-institution French study conducted 1994 to 1999
- More Grade 3-4 neutropenia with EP (62% versus 47%; p < 0.001) and more Grade 1-3 neurotoxicity (7% versus 2%; p < 0.001) and dermatitis (16% versus 3%); p < 0.001) with BEP x 3
- “Adverse events” defined as CA in post-chemo resection, incomplete response or relapse from favorable response

<table>
<thead>
<tr>
<th>BEP x 3</th>
<th>EP x 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 127)</td>
<td>(N = 124)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>PFS</td>
<td>90%</td>
</tr>
<tr>
<td>4 yr. surv.</td>
<td>96%</td>
</tr>
</tbody>
</table>

“Adverse events” defined as CA in post-chemo resection, incomplete response or relapse from favorable response

The only standard of care in good-risk patients is BEP x 3


OVERALL SURVIVAL

- Median follow-up = 51 months
- Logrank p = 0.14

BEP
- 5 deaths
- EP
- 10 deaths

251 good-risk IGC CCG patients

Logrank p = 0.06
90% CI: 0.80–0.96
EUROPEAN CONSENSUS ON DIAGNOSIS AND TREATMENT OF GERM CELL CANCER*

“For patients with good prognosis disease, according to IGCCCG criteria, standard treatment is BEP x 3”


INTERNATIONAL GERM CELL CONSENSUS CLASSIFICATION: POOR PROGNOSIS DISEASE

• Non-seminoma
  - Mediastinal primary
  - Non-pulmonary visceral metastases
  - AFP > 10,000 ng/ml
  - hCG > 50,000 iu/l
  - LDH > 10 x normal

JCO 15:594-603, 1997

ADVANCED GERM CELL TUMOR

RA

RANDOMIZE

BEPE x 4

BEPE x 2 followed by 2 courses of high dose chemotherapy with Carboplatin 600 mg/M^2 x 3 + CTX 50 mg/kg x 3

1. Study activated 9-95 and ended 9-03
2. Participants MSKCC, SWOG, ECOG, Dana Farber and University of Chicago

SURGICAL RESULTS AFTER FIRST-LINE CHEMOTHERAPY (cont’d)

Five Prognostic Groups
a) C.R. – no surgery
b) Unresectable P.R. – no surgery
c) Teratoma positive orchiectomy – PC surgery
d) Teratoma negative, but < 90% regression
e) Teratoma negative, > 90% regression, no surgery

2. Divided into 5 groups, based upon status, histology and post-chemotherapy surgery
ULTIMATE OUTCOME (295 PATIENTS)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cont. No.</th>
<th>Cont. NED (%)</th>
<th>Curr. NED (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.R.</td>
<td>78</td>
<td>72 (92)</td>
<td>72 (92)</td>
</tr>
<tr>
<td>Unres. P.R.</td>
<td>50</td>
<td>20 (40)</td>
<td>25 (50)</td>
</tr>
<tr>
<td>Teratoma +</td>
<td>90</td>
<td>78 (87)</td>
<td>85 (94)</td>
</tr>
<tr>
<td>Teratoma – &lt; 90% P.R.</td>
<td>50</td>
<td>43 (86)</td>
<td>46 (92)</td>
</tr>
<tr>
<td>Teratoma – &gt; 90% P.R.</td>
<td>27</td>
<td>20 (74)</td>
<td>21 (78)</td>
</tr>
</tbody>
</table>

RESULTS OF POSTCHEMOTHERAPY SURGERY*

<table>
<thead>
<tr>
<th>Germ Cell</th>
<th>No. Necrosis</th>
<th>Teratoma</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group C (teratoma +)</td>
<td>375</td>
<td>36 (9%)</td>
<td>321 (86%)</td>
</tr>
<tr>
<td>Group D (teratoma neg. but &lt; 90% P.R.)</td>
<td>269</td>
<td>115 (43%)</td>
<td>130 (48%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>644</td>
<td>151 (25%)</td>
<td>451 (68%)</td>
</tr>
</tbody>
</table>


PREDICTION OF PULMONARY HISTORY POST-CHEMOTHERAPY

- International retrospective review from centers at MSKCC (39), Oslo (22), Groningen (23), Indiana University (71), Munich (26), and Netherlands (4 centers – 34 patients)

PREDICTION OF PULMONARY (cont’d)

- Resected pulmonary mass histology necrosis in 116 (54%), teratoma in 70 (33%) and cancer in 29 (13%)
- Fifty-four patients had a prior or simultaneous RPLND revealing only necrosis; 48 of 54 (89%) had necrosis at thoracotomy, 4 (7%) teratoma and 2 (4%) cancer

SURGICAL OUTCOME (% CURRENTLY NED)*

<table>
<thead>
<tr>
<th>Path</th>
<th>First-line</th>
<th>Salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrosis</td>
<td>43/50 (86%)</td>
<td>21/28 (75%)</td>
</tr>
<tr>
<td>Teratoma</td>
<td>65/75 (87%)</td>
<td>13/25 (52%)</td>
</tr>
<tr>
<td>Non-GCT</td>
<td>7/12 (58%)</td>
<td>3/14 (21%)</td>
</tr>
<tr>
<td>Persistent GCT</td>
<td>7/17 (41%)</td>
<td>6/30 (20%)</td>
</tr>
<tr>
<td>TOTAL:</td>
<td>122/154 (79%)</td>
<td>43/97 (44%)</td>
</tr>
</tbody>
</table>


SALVAGE THERAPY OPTIONS FOR CURABLE PATIENTS

- VeIP or TIP for 1-2 courses followed by high dose chemotherapy
- VeIP or TIP x 4
- Salvage surgery
PITFALLS IN SALVAGE THERAPY

- Elevated HCG or AFP as only evidence of relapse or progressive disease
- Plateau in decline of HCG
- Sanctuary sites

PITFALLS IN SALVAGE THERAPY (cont’d)

- Growing teratoma
- Pseudonodules on chest x-ray or CT due to bleomycin
- Special consideration: PMNSGCT or late relapse

ABMT IN GERM CELL TUMORS

- G-CSF
- Carboplatin 700 mg/M² x 3 (2100 mg/M²)
- VP-16 750 mg/M² x 3 (2250 mg/M²)
- Double transplant

SALVAGE CHEMOTHERAPY WITH HIGH DOSE CARBOPLATIN + ETOPOSIDE AND PERIPHERAL BLOOD STEM CELL TRANSPLANT (PBSCT)

- Retrospective review of 184 consecutive patients treated from February, 1996 to December, 2004
- Cytoreduction with 0-2 courses of vinblastine + ifosfamide + cisplatin followed by tandem transplant carboplatin 700 mg/M² x 3 + etoposide 750 mg/M³
- Since switching from marrow (1986-1996) to PBSCT, more rapid engraftment; median time to second course 28 days (range 20 to 42)
- PBSCT done primarily as an outpatient
- 3 transplant related mortalities and 3 cases of AML (2 fatal)

SALVAGE CHEMOTHERAPY WITH PBSCT: RESULTS*

<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>116 (63%); 114 &gt; 1 yr. cont. NED 92 (68%)</td>
</tr>
<tr>
<td>Second-line Tx</td>
<td>136</td>
<td>92 (68%)</td>
</tr>
<tr>
<td>Third-line or later</td>
<td>48</td>
<td>23 (48%)</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>


POST BMT TREATMENT RESULTS*

- Between 1986-1997, 101 germ cell tumor patients progressed after BMT
- Median time to relapse 10 months (range 1-17 months)
- BMT was first salvage in 29 and second or later salvage in 72 patients
- 54 of 101 received post-BMT therapy, including 7 with surgery alone
POST BMT (cont’d)

- Only 3 C.R. and 9 P.R. for 66 chemotherapy regimens in 47 patients (response rate 18.2%)
- Only 1 of 15 responses with platinum-based chemotherapy
- Five patients (4.9%) are NED at 30-93 months after relapse (4 oral VP-16 plus surgery and 1 surgery alone)


PACLITAXEL + GEMCITABINE AFTER PROGRESSION FOLLOWING SALVAGE CHEMOTHERAPY HIGH DOSE CHEMOTHERAPY*

- Retrospective study of paclitaxel 100 mg/M² + gemcitabine 1000 mg/M² days 1, 8, and 15 q 4 weeks (maximum 6 months) after initial cisplatin combination chemotherapy and salvage therapy with high dose carboplatin + etoposide
- 33 patients treated from 2001 to 2004
- Toxicity primarily myelosuppression and neuropathy; no treatment-related mortality
- 10 of 33 responses (30%) including 4 P.R. (2-6 mos. duration) and 6 (18%) C.R.
- 4 of 33 continuously NED with paclitaxel + gemcitabine alone, including 3 patients continuously NED 3+ years; 1 additional patient NED 4+ years following resection germ cell cancer


OPTIONS FOR PROGRESSIVE INCURABLE PATIENTS

- Clinical trial
- Daily oral etoposide
- Single agent paclitaxel or gemcitabine
- Oxaliplatin, alone or in combination
- Epirubicin

WHO SHOULD GET CHEMOTHERAPY?

- All patients with stage III disease
- Stage II with > 3 cm. retroperitoneal disease
- Newly diagnosed clinical stage I, but elevated hCG and/or AFP postorchiectomy
- ?? High risk clinical stage I patients
## Non-Seminomatous Testicular Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Incidence</th>
<th>Cure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>40%</td>
<td>100%</td>
</tr>
<tr>
<td>Stage II</td>
<td>40%</td>
<td>98%</td>
</tr>
<tr>
<td>Stage III</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>95%</strong></td>
<td></td>
</tr>
</tbody>
</table>