Indiana University Health

Tandem Transplant for Germ Cell Tumors

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Presentation Outline

- IU Health and IU BMT Program
- Germ cell cancer overview
- Referral process and work-up procedures
- Stem cell collection and high dose chemotherapy
- Follow-up care

Indiana University Health

- Indiana University Health (formerly Clarian Health) is Indiana's most comprehensive healthcare system.
- A unique partnership with Indiana University School of Medicine, one of the nation's leading medical schools, offers patients access to innovative treatments and therapies.
- Within the Indiana University Medical School campus:
  - IU Health University Hospital
  - Riley Hospital for Children at IU Health
  - Richard L. Roudebush VA Medical Center
  - Wishard Memorial Hospital

History of IU BMSCT Program

1985	Four-bed unit at Riley Hospital for Children at IU Health
1986	Autologous program initiated
1987	Adult program moved to IU Health University Hospital
1987	First unrelated donor transplant
1988	First peripheral blood stem cell transplant
1994	Riley Hospital for Children at IU Health opens Transplant unit
2003	Adult BMT Unit upgraded to new unit at current location
2007	Renovated Cellular Therapy Laboratory and Adult Apheresis
2008	IU Simon Cancer Center opened a 28-bed heme/onc/BMT unit
2011	Simon Family Tower at Riley Hospital for Children

Adult IU BM/SCT Facility

- 13-bed adult inpatient HEPA-filtered unit (ICU monitoring capabilities) at University Hospital
- 28-bed adult inpatient heme/onc/BMT unit in the IU Simon Cancer Center
- Dedicated HEPA-filtered BMT Outpatient Clinic

MD's on Staff

Dr. Rafat Abonour
Former Medical Director

Dr. Sherif Farag
Medical Director

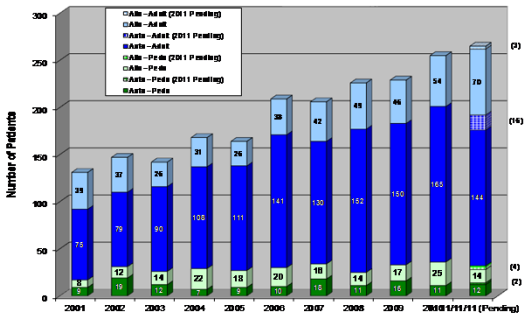
Dr. Michael Robertson
Dr. Robert Nelson
Dr. Jennifer Schwartz
Dr. Shivani Srivastava

Dr. Kenneth Cornetta
Former Medical Director

Adult Clinical Team

	Adult
Attending Physicians	7
Transplant Coordinators	4.5
Nurse Practitioners	3.5
Pharm D	2
Nutritionist	1
Financial Coordinator	0.5
Social Workers	1
Research Nurse	1.5
Data Management	4

Transplantation Activity 2001-2011



Germ Cell Tumors

Lawrence Einhorn, MD

Distinguished Professor of Medicine
Lance Armstrong Foundation Chair in Oncology

- Joined the IU Faculty in 1973, named Distinguished Professor in 1987 and became Lance Armstrong Foundation Professor of Oncology in 2006
- In 1974 developed a chemotherapy regimen for disseminated testis cancer that revolutionized treatment and success
- Internationally recognized not only for GCT, but other types of urological cancers, lung cancer and other malignant tumors
- Publications number in the hundreds

Germ Cell Tumor Definition

- A tumor arising from sperm or the eggs within the ovary
- Extragonadal primary
  - Primary mediastinal
    - Poor prognosis
  - Retroperitoneal
    - Similar prognosis as primary testicular cancer
- Ovarian cancer is different than Ovarian GCT
- Primary testicular GCT

Introduction

- The most common solid malignancy affecting males between the ages of 15 and 35
- Germ cell tumors account for 95% of testicular cancers
- Prior to the late 70s, five-year survival was 64%
- In 2011, five-year survival is over 95%

Epidemiology

- Relatively uncommon - 1% of male malignances in the United States
- Scandinavian countries have the highest incidence
- Rare in African-Americans
- Primary age group is 15-35 for non-seminomatous germ cell tumor (NSGCT) and a decade older for seminoma
- For 2011 estimated new cases 8,290, deaths 350
  (American Cancer Society.: Cancer Facts and Figures 2011. Atlanta, GA: American Cancer Society, 2011)

Risk Factors

- Cryptorchidism (undescended testis)
- A family history of testis cancer
- Personal history of testicular cancer
- HIV infection

Clinical Manifestations

- Nodule or painless swelling of one testicle
- Dull ache or heavy sensation in the lower abdomen
- Symptoms of metastatic disease relate to site of disease
  - Neck mass
  - Cough, dyspnea and hemoptysis
  - Gastrointestinal symptoms
  - Back pain (bulky retroperitoneal disease)
  - CNS symptoms

Fertility

- At time of diagnosis 10-35% are sterile
  - Treatment induced sterility:
    Abdominal radiotherapy, RPLND, chemotherapy
- Chemotherapy = 71% rate of fathering a child
- Chemotherapy + radiation = 67%
- Risk factors for azoospermia:
  - Radiation therapy
  - Age > 30 years
  - Chemotherapy duration > 6 months
- SPERM BANKING DISCUSSION!!!!

Pliarchopoupou K, et al. *Cancer Treat Rev.* 2010; 36:262-67.

Initial Staging and Disease Evaluation

- Scrotal ultrasound
- Serum tumor markers
  - Beta-hCG
  - AFP
  - LDH
- Radiographic imaging
  - Abdominal/pelvic CT scan
  - CXR then CT if indicated
  - PET scans
- Radical inguinal orchiectomy
- Pathology evaluation of tumor

Pure Seminoma

- Slightly older age group
- AFP is not elevated
- Beta-hCG is elevated in fewer than 20% of cases
- Good and intermediate prognostic categories only
- Treatments may include:
  - Surgery
  - Chemo
  - Radiotherapy

Non-Seminomatous Germ Cell Tumors (NSGCT)

- Five pathological classifications
  - Teratoma
  - Embryonal carcinomas
  - Yolk sac tumors
  - Choricarcinomas
  - Mix cell type
- Elevated AFP or Beta-hCG
- Good, intermediate and poor prognostic categories
- Treatments include:
  - Surgery
  - Chemotherapy

Risk Classification

Risk Status	Non-Seminoma	Seminoma
Good risk	Testicular or retroperitoneal primary No non-pulmonary mets **AFP < 1,000 ng/mL** **hCG < 5, 000 IU/L** **LDH < 1.5 ULN**	Any site, no non-pulmonary mets **Normal AFP** **Any hCG** **Any LDH**
Intermediate risk	Same as above with: **AFP 1, 000-10,000 ng/mL** **hCG 5, 000-50,000 IU/L** **LDH 1.5-10 x ULM**	Same as above, with non-pulmonary visceral metastases
Poor risk	Non-pulmonary visceral metastases present (i.e. bone, liver, brain): **AFP > 10,000 ng/mL** **hCG > 50,000 IU/L** **LDH < 10 x ULN**	No patients classified as poor risk

Adapted from International Germ Cell Cancer Collaborative Group. *J Clin Oncol.* 1997;15:594-603.

Preliminary Treatments

- Orchiectomy followed by active surveillance
- Chemotherapy (BEP or EP)
  - Bleomycin
  - Cisplatin
  - Etoposide
- Radiation
  - Used primarily in pure seminoma patients, NSGCTs are less radiosensitive
- Retroperitoneal lymph node dissection (RPLND)
  - Used to identify nodal micrometastases
  - Provides accurate pathological staging of the retroperitoneum

Salvage Therapy Options

- Observation-false elevation of tumor markers
- Surgical resection of tumors
- Conventional dose chemotherapy regimens
- Radiation Therapy
- High dose chemotherapy with peripheral blood stem cell transplant

Question

Which of the following is the best answer regarding the use of high dose chemotherapy and stem cell transplant in testicular cancer?

1. High dose chemotherapy prolongs DFS, but not OS.
2. Tandem transplant is standard of care for recurrent disease.
3. Induction chemotherapy for stem cell transplant includes VIP for 2 cycles.
4. Stem cell transplant is considered after failing 2 salvage chemotherapy regimens

Answer: 2

HEALTH

Tandem Transplant

Referral Process

- Patients are evaluated by our oncology germ cell team
  - Lawrence Einhorn, MD
  - Nasser Hanna, MD
- Preliminary contact by telephone or email
- All clinical records including:
  - Serial tumor markers
  - Surgery reports
  - Pathology reports and slides for review
  - Radiology reports and films
- Weekly meetings between BMT and GCT team

Transplant Consultation: *Building a Foundation*

- Insurance, insurance, insurance!!!
- Oncology team decision:
  - Cytoreduction prior to HDSCT
  - Direct to transplant ASAP
    - Platinum refractory patients (defined as disease progression on therapy or within four weeks of completing therapy)
    - Third-line therapy
- Education
- Family support
- Travel
- Housing options
  - ProCare Concierge: www.procarenetwork.com/hotels
  - Fair Haven Foundation: www.fairhavenfoundation.org
  - Ronald McDonald House

Housing: Fair Haven Foundation

- Provides free housing to patients in need
- Foundation started by an IU Health employee
- Currently leases six apartments
- It is a Christian-based mission effort
- The **Fair Haven Foundation** name comes from the Mediterranean island of Fair Havens, where a storm-tattered ship once took refuge in the midst of terrible winds (Acts 27:8). Their prayer is that you would find refuge in the midst of the storm that you are facing.
- Contact information: www.fairhavenfoundation.org

Insurance Approval

- Contact insurance company immediately and identify the decision maker
- Educate the insurance provider
- Have a form letter prepared to send to the insurance company with supporting articles and bibliography
- Make certain they understand it is a tandem transplant and obtain approval for both
- Submit an SOP and consult note
- Peer-to-peer reviews

Stem Cell Transplant Work-up

- Local versus Indiana University Health
- Tests to be completed - in a timely fashion:
  - 12-lead EKG
  - PA and lateral CXR
  - 24-hour urine collection for creatinine clearance
  - Pulmonary functions with spirometry and diffusing capacity
  - Sickle cell screen
  - Infectious disease panel
  - CMP, CBC, PT/PTT, INR
  - Dental evaluation * (red flag)
- Transplant MD consultation
- Information sheet and consent signatures

HDCT - Treatment Schema

Mobilization of peripheral blood stem cells (PBSC): G-SCF (10 µg/kg/d)

↓

Apheresis (adequate number for 2 autologous transplants)

↓

Cycle 1 high dose chemotherapy:
Carboplatin days -5, -4, -3
Etoposide days -5, -4, -3

↓

PBSC re-infusion day 0 and Filgrastim starting day 0

↓

Perform additional mobilization and PBSC collection if needed

↓

Cycle 2 high dose chemotherapy as given in cycle 1

Bhatia S, et al. *J Clin Oncol.* 2000;18:3346-51; Einhorn LH, et al. *NEJM.* 2007;357:340-8.

Mobilization and Stem Cell Collection

- Filgrastim mobilization only
- Our dose is 10 mcg/kg/day rounded up to the nearest vial size
- A tunneled 28 cm 14 French double lumen catheter is placed for the collection and remains through out the tandem transplant process
- Collection of stem cells is initiated on day 5 of Filgrastim

Mobilization and Stem Cell Collection
(continued)

- Our collection target cell dose is $5x10^6$ CD34+ cells/kg with a minimum of $1x10^6$ CD34+ cells/kg per transplant
- Most collections are completed in one or two days
- Plerixifor (Mozobil® Genzyme Corporation, Cambridge, MA) has been used at a dose of .24mg/kg on 10 poor mobilizing patients and our collection goal was met
- The plan is to collect enough cells for both transplants with the initial collection process

Let the Chemo Begin

- Outpatient vs inpatient transplant:
  - Caregiver issues
  - Housing options
  - Compliance
  - Physical contraindications

Preparative Regimen

- Carboplatin 700 mg/m2/day IVPB over 30 minutes on days -5, -4, -3.
- Etoposide 750 mg/m2/day over 2 hours on days -5, -4, -3.
  - (For comparison purposes: Our BEP regimen dose of Etoposide is 100mg/m2/day x 5 doses)

Regimen-related Toxicities

- Significant lower GI toxicity – diarrhea, cramping, neutropenic enterocolitis
- **Carboplatin** - renal dysfunction, ototoxicity, peripheral neuropathy
- **Etoposide** - infusion-related reactions, increased LFTs, rash, peripheral neuropathy

Supportive Care

- Ciprofloxacin 500 mg po daily (start day -1)
- Fluconazole 400 mg po daily (start day -1)
- Vancomycin 1500 mg IV daily (start day -1)
- Antiemetics
  - Aprepitant, 5-HT_3 antagonist, dexamethasone
- Adequate hydration
- Chlorhexadine Gluconate 10 – 15 mL orally, swish and spit four times daily
- Filgrastim beginning on day 0

Routine Lab Work

- Beta-hCG and AFP on admission and weekly
- Daily CBC, CMP, magnesium and phosphorus
- Blood product transfusion:
  - Transfuse PRBC to keep Hgb >7
  - Transfuse platelets to keep > 10K

Chemo Cycle #2

- Typically begins 23-28 days after initiation of cycle #1
- Disease response to cycle #1 to qualify for cycle #2
- Preparative regimen is identical
- Dose modifications for toxicities
- Delays between cycles should be avoided

Special Considerations

- Progressive/refractory disease
  - Not a contraindication to HDC
  - "Induction" chemo not required to document chemo sensitivity
- Brain metastasis
  - Not a direct contraindication to HDC
  - Monitor platelet count closely during transplant
- Neuropathy
  - Peripheral
  - Otologic abnormalities
- Monitoring labs between cycle 1 and cycle 2
  - Magnesium and potassium levels
  - CBC

Follow-up Care

- They do not require re-vaccination
- They are returned to their primary oncologist
- Follow-up with the IU GCT team about one month after recovery of blood counts
- Consideration at that time for:
  - Observation
  - Surgical resection of residual disease
  - Maintenance oral VP-16 in the NSGCT population

Case Study: Eric

- Eric is a 22 y.o. male college student in CA that presented to the local hospital with severe weakness
  - Hgb 5.0
  - Endoscopy to r/o GI bleed revealed a nodule in gastric area
  - CT demonstrated involvement of the lungs, liver and spleen
  - Brain MRI revealed 2 lesions
- Pathology from left orchiectomy confirmed the diagnosis of NSGCT
- Beta-hCG = 694,000 and AFP = 33.9
- Eric underwent four cycles of BEP: first cycle administered in CA, then he returned home to TN to complete his chemo
- At the end of chemotherapy Beta-hCG = 27

Case Study: Eric (continued)

- One month later his Beta-hCG had risen to 297
- Eric presented to IU for second opinion one day after the elevated tumor marker
- Transplant work-up completed locally
- Stem cell collection delayed one week due to insurance issues
- The day prior to initiating high dose chemo, patient seized due to progression of brain mets and was coded in the cafeteria
- After evaluation by neuro oncology, radiation oncology and medical oncology it was decided to proceed with the preparative regimen
- Beta-hCG had gone up to 2,362 in just 2 weeks

Case Study: Eric (continued)

- Uneventful tandem transplant course with the second cycle being done as an outpatient
- Platelets were kept above 50K
- At completion of tandem transplant Beta-hCG, fell to 10.8 and brain metastasis improved
- He completed three cycles of oral VP-16
- Eight months out from chemo he had normal Beta-hCG
- One 2 cm lesion was treated with gamma knife radiosurgery 10 months after transplant

Case Study: John

- 49 y.o. male computer programmer who went to dinner and ate a lot of chicken wings March 2009
  - Presented with severe right sided abdominal pain
  - CT scan revealed left sided mass
  - Testicular ultrasound + for left testis mass
- Pathology from mass and testicle were pure seminoma
- Beta-hCG unusually high at 8,000
- Received three cycles of BEP and one cycle EP ending in June 2009
- Beta-hCG normalized and had an appropriate radiographic response by CT and PET scan

Case Study: John (continued)

- December 28, 2009 consult with Dr. Einhorn due to Beta-hCG elevation and PET scan + for recurrent disease
- Options:
  - Four courses SDC = 70% cure rate
    - Tandem transplant offering a 50% cure rate as third line therapy
  - One course VeIP followed by tandem transplant
    - 24/26 disease-free (two-year minimum follow-up)

Case Study (continued)

- Received cycle one February 7th-28th, 2010
- Received cycle two March 11th-28th, 2010
- May 23, 2010 = normal PET scan and normal Beta-hCG
- June 20, 2010 follow-up visit with Dr. Einhorn
  - Continued peripheral neuropathy
  - Slight hearing impairment
  - RTC in one year - CT scans every four months, CXR every two months with tumor markers

Quoted a 90% cure rate at this juncture

Take-Home Points

- Testicular cancer is a rare disease
- Be proactive with the insurance
- Timing is of the essence
- Oncology germ cell team should have an integral role throughout the transplant process
- Tandem transplant is the goal
- Widespread metastatic and refractory disease can be cured

Contact Information

- **Website**
  www.iuhealth.org
- **General telephone to schedule a consultation**
  317.944.0920
- **GCT program contact information**
  - Lawrence Einhorn, MD leinhorn@iupui.edu
  - Nasser Hanna, MD hanna@iupui.edu
  - Jackie Brames, RN mjbrames@iupui.edu
- **Transplant program contact information**
  - Rafat Abonour, MD rabonour@iupui.edu
  - Jay Baute, RN jbaute1@iuhealth.org

Tandem High Dose Caboplatin and Etoposide is the Most Effective Salvage Therapy for Relapsed Testicular Tumors

Rafat Abonour, M.D.

Epidemiology of Testicular Cancer

- 1% of all cancers in men
- Most common carcinoma in men (15-35)
- 8,480 cases in 2010 and only 350 deaths
- Goal of therapy is cure and most are cured with first line therapy
- Model for multi-disciplinary approach to cure.

ACTINOMYCIN-D-50 years ago

- 50% response rate, including 10-20% C.R.'s
- Most relapses occurred within one year
- 5-10% cure rate

HISTORICAL PERSPECTIVES

- Single agent studies with Vinblastine + Bleomycin achieved results similar to Actinomycin-D
- Vinblastine + Bleomycin synergistic in pre-clinical systems; initial studies in testicular cancer produced a 25% cure rate
- Platinum (cisplatin) produced 3 complete and 3 partial responses in 11 patients with refractory testicular cancer

"ORIGINAL" PVB

- Cisplatin 20 mg/M^2 x 5 q 3 weeks x 4
- Vinblastine 0.2 mg/kg x 2 q 3 weeks x 4
- Bleomycin 30 units weekly x 12

maintenance Vinblastine
0.3 mg/kg monthly x 21

RESULTS – FIRST PVB STUDY
40 years ago

Complete remission	33/47 (70%)
Partial remission	14/47 (30%)
Disease-free with PVB + surgery	5/47 (11%)

30/47 (64%) 5 year survival
27/47 (57%) NED

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

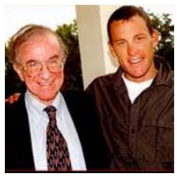
JCO 15:594-603, 1997

Poor Risk Disease Results, Is more intense regimen better in First Line Therapy?

Response (%)	BEP x 4	VIP x 4
CR	31	37
PFS	58	64
OS	67	69
Toxicities (%)	**BEP x 4**	**VIP x 4**
Overall toxicities	79 P = 0.0002	93
Hematologic	76 P = 0.003	90

Hinton S, et al. *Cancer*.2003;97(8):1869-75.
CR = Complete response; PFS = Progression free survival; OS = overall survival

- A Formula for winning



SEG GU 332

RANDOMIZE

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

BEP: Cisplatin 20 mg/M² x 5
VP-16 100 mg/M² x 5
Bleomycin 30 units day 1, 8, and 15

Courses repeated every 3 weeks for 4 courses

SECSG GU332: PVB VERSUS BEP

	PVB	BEP
Number patients	121	123
C.R.	74 (61%)	74 (60%)
NED with surgery	15 (12%)	28 (23%)
Continuously NED	80 (66%)	96 (78%)

SEG TESTIS STUDY: ADVANCED DISEASE

RANDOMIZE

Cisplatin 20 mg/M² x 5 q 3 weeks x 4
VP-16 100 mg/M² x 5 q 3 weeks x 4
Bleomycin 30 units weekly x 12

Cisplatin 40 mg/M² x 5 q 3 weeks x 4
VP-16 100 mg/M² x 5 q 3 weeks x 4
Bleomycin 30 units weekly x 12

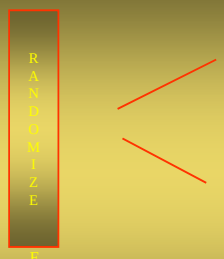
RESULTS with double dose Cisplatin

	Standard Dose (%)	Double Dose (%)
Number evaluable	77	74
C.R.	36 (46.8)	35 (47.3)
NED – Teratoma	15 (19.5)	14 (18.9)
NED – CA	5 (6.5)	1 (1.4)

RESULTS (cont'd)

	Standard Dose (%)	Double Dose (%)
Relapse	7 (12.5)	3 (6.0)
Continuously NED	49 (63.6)	46 (62.2)
Presently NED	51 (66.2)	49 (66.2)

HDCT in Newly Diagnosed ADVANCED GCT



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

BEP VERSUS HIGH DOSE CHEMOTHERAPY*

- 174 poor risk and 45 intermediate risk patients (n= 219)
  - randomized to BEP x 4 versus
  - BEP x 2 followed by 2 courses of high dose chemotherapy with stem cell transplant
- C.R. rates identical (55% versus 54%) with 1 year durable C.R. rate 48% versus 52%
- 2 year overall survival 72% versus 71%

*Motzer, et al: JCO 25: 247-256, 2007

CISPLATIN PLUS VP-16 AS INITIAL SALVAGE CHEMOTHERAPY-The Early days

- SECSG Protocol: Induction chemotherapy PVB
- 19 of 44 patients (43%) achieved an NED status
- 10 of 44 (23%) continuously NED 20-39 months

J Clin Oncol 3:666, 1985

SALVAGE THERAPY OPTIONS FOR

- High dose chemotherapy with peripheral blood stem cell transplant
- VeIP or TIP x 4 cycles
- 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

Prognostic Factors for High Dose Chemotherapy

- Those likely to not benefit from HDC:
  - Primary mediastinal GCT refractory to initial and salvage chemotherapy
  - Refractory disease
    - Rising markers or radiographic evidence of progression within 4 weeks of cisplatin
    - High β-HCG levels

Bosl GJ. Cancer of the Testis. In: DeVita eds. (Title of book): edition.

The case for HDC as Salvage therapy

- Poor risk patients = not the same high rate of cure as good and intermediate risk (50%)
- GCT's are highly responsive to chemotherapy
- High dose chemo as 3rd line salvage therapy
  - 10-20% cure rate
- Improved supportive care
- Patient's age permits use of high dose chemotherapy with improved safety profile

History of High Dose Chemotherapy

1986

1997

Nichols CR, et al. *J Clin Oncol.*1989;7:932-9.
- Phase I/II

Broun ER, et al. *J Clin Oncol.*1997;79:1605-10.
- 2 cycles of high dose chemotherapy- carboplatin/etoposide

2000

Bhatia S, et al. *J Clin Oncol.*2000;18:3346-51.
- Review of 65 patients

2000

Motzer RJ, et al. *J Clin Oncol.*2000;15:2546-52.
- High dose carboplatin/etoposide/cyclophosphamide in poor risk patients

2007

Einhorn LH, et al. *NEJM.* 2007;18:3346-51.
- Review of 184 patients

HDC - Treatment Schema

Mobilization of peripheral blood stem cells: G-SCF (10 µg/kg/d)

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Apheresis (adequate number for autologous transplants)

↓

Cycle 1 high dose chemotherapy:
Carboplatin days -5, -4, -3
Etoposide days -5, -4, -3

↓

PBSC re-infusion day 0 and Filgrastim starting day 0

↓

Perform additional mobilization if needed

↓

Cycle 2 high dose chemotherapy as given in cycle 1

Bhatia S, et al. *J Clin Oncol.* 2000;18:3346-51; Einhorn LH, et al. *NEJM.* 2007;357:340-8.

High Dose Chemotherapy (HDC)

- Retrospective review of 184 patients with cisplatin-resistant, progressive GCT's
- 173 received 2 cycles of VeIP, then HDC
- 11 received 1 cycle of VeIP, then HDC
- Primary endpoint
  - Disease Free Survival
- Secondary endpoint
  - Overall survival

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

Patient Characteristics

Patient Characteristics	Number of patients (%)
# of previous chemo regimens	
1	135 (73.4)
2	45 (24.4)
3	4 (2.2)
Response to initial chemotherapy	
CR	75 (40.8)
PR	9 (4.9)
< CR or PR with normal tumor markers	100 (54.3)
Initial IGCCCG stage (risk)	
Low	71 (38.6)
Intermediate	38 (20.7)
High	75 (40.8)

Einhorn LH, et al. *NEJM.* 2007;357:340-8. CR = Complete remission; PR = partial remission; IGCCCG = International Germ Cell Cancer Collaborative Group.

High Dose Chemotherapy

- HDC consisted of:
  - Carboplatin 700 mg/m^2 on days -5, -4, -3
  - Etoposide 750 mg/m^2 on days -5, -4, -3
- 1 million or more CD34+ cells/kg were required for each cycle of HDC
- No planned reductions/escalations of doses
- 2nd cycle given after recovery of counts, unless toxicities (grade 4 non-hematologic), or no response to the 1st cycle

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

Toxicities

Grade 3 and higher toxicities	# of Patients
Late Hematologic (leukemia)	3
Renal (creatinine ↑'d 3-6 x ULN)	4
Gastrointestinal	30
Hepatic	6
Neurologic	9
Pulmonary	3

2 deaths were associated with leukemia
2 deaths were associated with hepatic dysfunction
1 death was associated with pulmonary toxicities

HDC with PBSCT can cure metastatic GCT's when used as 2nd line and even as 3rd line therapy

Einhorn LH, et al. *NEJM.* 2007;357:340-8. ULN = Upper limit of normal

SALVAGE CHEMOTHERAPY WITH PBSCT: RESULTS*

	No. pts.	No cont. NED (%)
Entire series	184	116 (63%); 104 > 2 yr. cont. NED
Currently NED	122 (66%) (4 Tax+Gem and 2 surg)	
Second-line Tx	135	94 (70%)
Third-line or later	49	22 (45%)
hCG > 1,000	22	14 (64%)
Seminoma	35	26 (74%)
Platinum refractory	40	18 (45%)

*Einhorn LH, et al.: NEJM 357:10-18, 2007

PROGNOSTIC VARIABLES

Variable	Pts.	Cont. NED (%)	p value
Second-line Tx	135	94 (69.6)	0.003
Third-line or later	49	22 (44.9)	
Seminoma*	35	26 (74.3)	0.17
Nonseminoma	149	90 (60.4)	
Platinum refractory	40	18 (45.0)	0.01
Platinum sensitive	144	98 (68.1)	

*14 of 15 cont. NED as initial salvage therapy

PROGNOSTIC VARIABLES (cont'd)

Variable	Pts.	Cont. NED (%)	p value
Response to initial chemo			
C.R. or P.R. marker neg > 6 mos.	84	61 (72.6)	0.015
< C.R. or P.R. marker neg	100	55 (55.0)	
Initial IGCCC stage			
Good-risk	71	54 (76.1)	0.006
Intermediate	38	24 (63.2)	
Advanced	75	38 (50.7)	

Results

- Prognostic variables associated with statistical improvement in PFS
  - HDC as second line therapy vs. 3rd line
  - Platinum sensitivity
  - Response to initial chemotherapy
  - Favorable prognosis
  - Favorable IGCCCG score

Einhorn LH, et al. *NEJM.* 2007;357:340-8.

STRATIFICATION USING 3 VARIABLE RULE

- Score of 3 for third-line or later chemotherapy, 2 for advanced IGCCG stage, and 2 for platinum refractory

	Good (0)	Intermediate (2-3)	Poor (4-7)
Number pts.	73	64	47
DFS (%) (40%)	80 (79%)	26 (62%)	10

HDC vs. CDC

- Retrospective review of 1,594 patients
  - 773 received conventional dose chemotherapy (CDC)
  - 821 received HDC
- Evaluated use of second line therapy in patients who received prior cisplatin
- Patients were classified according to risk:
  - Very low, low, intermediate, high, very high
- Estimated 2 year PFS and 5 year OS

Lorch A, et al. *J Clin Oncol.* 2010;28:15S:4513.

HDC vs. CDC

(Number of patients)	2 year PFS (%)	5 year OS (%)
All patients (1594) HDC vs. CDC	49.6 vs. 27.8 P < 0.001	53.2 vs. 40.8 P < 0.001
Very low risk (76) HDC vs. CDC	91.6 vs. 58.4 P < 0.008	88.7 vs. 64.5 P < 0.007
Low risk (257) HDC vs. CDC	64.3 vs. 40 P < 0.001	64.5 vs. 66.2 P = 0.901
Intermediate risk (546) HDC vs. CDC	53.5 vs. 31.9 P < 0.001	58.3 vs. 45.5 P < 0.002
High risk (351) HDC vs. CDC	33.3 vs. 17.2 P < 0.001	35.2 vs. 23 P < 0.001
Very high risk (105) HDC vs. CDC	22 vs. 1.9 P < 0.001	27 vs. 3.4 P < 0.002

Lorch A, et al. *J Clin Oncol.* 2010;28:15S:4513.

FIRST-LINE SALVAGE CHEMOTHERAPY*

	No. Pts.	2 yr. PFS (%)	5 yr. survival (%)
Conventional dose	773	27.8	40.8
		p< 0.001	p< 0.001
High dose	821	49.6	53.2
	1,594		

HIGH DOSE CHEMOTX – FIRST RELAPSE*

	No. Pts.	2 yr. PFS (%)	5 yr. survival (%)
Single transplant	408	44.1	46.3
		p< 0.001	p< 0.001
Sequential transplant	413	55.0	60.6
Carbo + etoposide (CE)	301	57.6	62
CE + Ifos	95	30.9	34.9
CE + Thiotepa	102	40.0	43.9
CE + Cyclophosphamide	212	53.5	55.9
Other	111	45.1	49.4

*Lorch A, et al.: JCO 29:2178-2184, 2011

SINGLE VERSUS TRIPLE TRANSPLANT*

- Between 11/99-11/04, 211 pts. with relapsed or refractory GCT were randomized to VIP x 1 followed by
  - 3 cycles of high dose carboplatin (1,500 mg/M$^{2)}$ + etoposide (1,500 mg/M^2)
  - vs. 3 cycles of VIP + 1 cycle of high dose carboplatin (2,200 mg/M^2) + etoposide (1,800 mg/M^2) + cyclophosphamide (6,400 mg/M^2)
- Treatment related mortality 4% versus 16% (p = 0.01)
- 5 year PFS 47% vs. 45% (p = 0.456)
- 5 year overall survival 49% vs. 39% (p = 0.057)

*Lorch A, et al.: Proc ASCO 29:290, 2011

SINGLE VERSUS TRIPLE TRANSPLANT*

- Sequential Versus Single High-Dose Chemotherapy in Patients With Relapsed or Refractory Germ Cell Tumors: Long-Term Results of a Prospective Randomized Trial
- Anja Lorch, et al JCO.2011.40.4160
- CONCLUSION: Patients with relapsed or refractory GCT achieve durable long-term survival after single as well as sequential HDCT. Fewer early deaths related to toxicity translated into superior long-term OS after sequential HDCT.

SALVAGE HIGH DOSE CHEMOTHERAPY: SEMINOMA

- Retrospective review of 48 consecutive patients with pure seminoma who received high dose chemotherapy with carboplatin + etoposide with peripheral blood stem cell transplant from 2/96 to 6/06
- 36 of 48 (75%) continuously NED, including 22 of 24 receiving this therapy as initial salvage chemotherapy.MFU 46 months (range 25-131 months)
- 4 of 48 (8%) treatment-related mortality, all in patients with 2 or more prior chemotherapy regimens

Agarwala et al: Amer J Clin Oncol 34:286-288,2011

• HDCT for Testicular Tumors

- HDCT is a curative options for large number of patients with relapse GCT.
- HDCT can be curable in 25% of patients with platinum refractory disease.
- High dose Caboplatin and Etoposide are the mean drugs shown to be effective.
- Patients selection and post transplant surgical and maintenance therapy plays an important role in curing these patients.

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