The Platinum Study: Interdisciplinary and Translational Research in Survivors of Adult-Onset Cancer

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Cancer Survivorship: 2013

- U.S.: 13.7 million cancer survivors
  - 4% of population
  - 18 million by 2022

- Increases in cancer survival
  - Earlier diagnosis (screening)
  - More effective treatment (cisplatin)
  - Better supportive care

- Worldwide: 28 million

Cancer Survivorship
Consequences of Success

- Late effects of cancer and its therapy
  - Second malignant neoplasms
  - Cardiovascular disease
  - Renal, pulmonary
  - Neurologic
    - Chemotherapy-induced peripheral neuropathy; cognitive dysfunction
    - Hearing loss (e.g., cisplatin, cranial RT)
  - Fertility, many others
  - Psychosocial, economic, societal
Cancer Treatment
Turning Point: 1977

- Dr. Lawrence Einhorn, 1977: Introduction of cisplatin-based chemotherapy
- Einhorn LH, Donohue J. “Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer.” Annals of Internal Medicine 1977;87:293-298.
Cisplatin 
Importance

- Cure for metastatic solid cancer
- NCI’s List of Provocative Questions**
- Metallic agent with renal excretion
- Serum and urine levels: 20 years
- Platinating agents: *most commonly used group of cytotoxic drugs worldwide*
  - 5.8 million pts: cancers of colon, rectum, cervix, endometrium, bladder, stomach, head and neck, lung, esophagus, pancreas, ovary, testis

**http://provocativequestions.nci.nih.gov**
Cisplatin and Testicular Cancer Success

- Gain 37.9 years of life*
- Compare with other male urogenital cancers
  - Kidney: 16.5 years
  - Bladder: 12.0 years
  - Prostate: 10.1 years
- Result: lifetime for late effects of cancer and its therapy

*Li C, Ekwueme DU, Rim SH, Tangka FK. “Years of potential life lost and productivity losses from male urogenital cancer deaths – United States, 2004.” Urology 2010;76:528-535.
Adult-Onset Cancer Model: Long-Term Survivorship

- TC as model for curable cancer, and now…
- “Leading example of how the greater testicular cancer community can collaborate to provide **survivorship** studies that are of critical importance for the continued health of all patients cured of cancer”
  
Indiana (Larry Einhorn)
Norway (Sophie Fossa)
Great Britain (Alan Horwich)
Princess Margaret Hospital
(Mary Gospodarowicz)
Netherlands (F. van Leeuwen)
Mayo Clinic, Harvard-DFCI, U. Chicago
Memorial Sloan-Kettering
M.D. Anderson
U. Penn, others
Major Workshop Goals
Rochester: May 2009

1. Identify major unresolved issues
   • Long-term late effects of testicular cancer and its therapy
2. Mechanisms and interventions
3. Publish workshop summary
4. Undertake research agenda
Survivorship Workshop

✅ Action Items 1-3

- **JNCI Commentary 2010**
  - Team effort
  - Multidisciplinary approach
  - Pharmacogenomics, medical and psychosocial oncology, genetics, cardiology, nephrology, reproductive endocrinology, pathology, epidemiology, metal toxicology, radiation biology, bioinformatics, biostatistics
Late Effects of TC and Its Therapy*
JNCI 2010

1. Second malignant neoplasms
2. Cardiovascular disease
3. Renal
4. Neuropathy, ototoxicity, tinnitus
5. Pulmonary
6. Fertility
7. Psychosocial
8. Late relapse, others
9. *Genetic variants associated with toxicities*

Late Effects of Treatment Knowledge Gaps

- Sparse data: genetic variants\(^1\)
- Ideal group for study?
  - Young cancer patients, *homogeneous treatment*
  - Long-term survival, late toxicities
- Testicular cancer
  - Most common cancer: men age 18-39 yrs
  - Homogeneous cisplatin-based chemotherapy
  - 10-year relative survival: 95%
  - Long-term toxicities

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Late Effects of Cancer and its Therapy: Mechanisms

- Prevent, ameliorate, and treat late complications of cancer and its therapy
  - Understand biologic basis/risk
  - Define etiopathogenetic pathways
- Goal? Develop targeted prevention and intervention strategies
  - Optimize risk-based care
  - Minimize chronic morbidities; improve quality of life; decrease costs
The Platinum Study (RO1)
Action Item 4 of 4 (2009 Workshop)

**Indiana University**  
*Dr. Larry Einhorn*

**Princess Margaret Hospital**  
*Dr. Malcolm Moore*

**M.D. Anderson**  
*Dr. Lance Pagliaro*

**U. British Columbia**  
*Christian Kollmannberger*

**Memorial Sloan Kettering**  
*Dr. Darren Feldman*

**Harvard – Dana Farber**  
*Dr. Clair Beard*

**U. Pennsylvania**  
*Dr. David Vaughn*

**Mayo Clinic**  
*Dr. Robert Miller*

**URMC**  
*Lois Travis*

*Coordinating Center Biospecimen Repository*
The Platinum Study
Investigators (continued)

- Statistical genetics: Dr. Nancy Cox (U. Chicago)
- Pharmacogenomics: Dr. Eileen Dolan (U. Chicago)
- Hearing Science: Dr. Robert Frisina (USF)
- Neurology: Dr. David Herrmann (URMC)
- Cardiology: Dr. John Bisognano (URMC)
- Epidemiology: Dr. Howard Sesso (Harvard-BWH)
The Platinum Study (R01)
Primary Aims

- Establish well-characterized clinical cohort for lifelong follow-up to study genetics of long-term toxicities
- Identify SNPs associated with long-term neurotoxicity and ototoxicity
- Determine extent to which candidate SNPs (e.g. GST, COMT, TMPT) and those identified in cell-based assays are associated with clinical ototoxicity and neurotoxicity
Chemotherapy-Induced Peripheral Neuropathy (CIPN)*

- One of most common and potentially permanent side effects of modern chemotherapy
- Impact: quality of life
- Few preventive measures or interventions
- Few studies of genetic susceptibility to cisplatin-associated CIPN
  - Small candidate gene studies; inconclusive
- The Platinum Study: GWAS

Iatrogenic Ototoxicity*

- Bilateral sensorineural hearing loss, tinnitus
- Cisplatin: one of most ototoxic drugs in clinical use
  - Hearing loss in 500,000 new cancer patients each year**
- Few data: genetic variants (e.g., GST’s)
- Ross 2009, Nature Genetics
  - $TPMT$, $COMT$: 7 to-21 fold risks
  - Recommended GWAS as next step
- Yang 2013, Clin Pharm Therap (CPT)
  - $TPMT$ and $COMT$ not replicated
- The Platinum Study: GWAS

The Platinum Study (R01)
Secondary Aim

- Collect patient data including: demographics, medical status, vital signs, BMI, tobacco and alcohol use, diet, exercise and other variables for future studies of genetic risks of other long-term toxicities (e.g. cardiovascular disease [CVD], etc.)
The Platinum Study
CVD - Future Research*

- Contributions and interactions of:
  - Radiotherapy, *cisplatin-based* chemotherapy
  - BMI, family history of CVD, race, SES
  - Lifestyle factors; subclinical hypogonadism
  - *Genetic modifiers*

- Interventions
  - Smoking cessation, diet, activity
  - Treat biochemical parameters at threshold values before development of CVD
  - Information and communication technologies

- Risk prediction models**


**Freedman AN et al., JNCI 2005; 97: 715-23; and Freedman AN, et al., JNCI 2010;102:1698-1705.
Future Opportunities
Research Infrastructure*

- NOT-CA-14-013: “Core Infrastructure and Methodological Research for Cancer Epidemiology Cohorts;” includes cancer survivors
- Our consortium: 12,000+ germ cell tumors
  - Treatment distribution
    - 1/3 surgery only; 1/3 radiotherapy
    - 1/3 cisplatin-based chemotherapy
- Unique: germ cell tumors not in CCSS, NCCN, SPORES

The Platinum Study Expansion
Organization of UM1

Contributing Institutions

Working Groups
- Genetics (Co-Chairs: Drs. N. Cox & M.E. Dolan)
- Second Malignant Neoplasms (Chair: Dr. L. Travis)
- Chronic Diseases (Chair: Dr. L. Einhorn)
- Cohort Methods (Chair: Dr. H. Sesso)
- Psychosocial Outcomes (Chair: Dr. C. Beard)
- Interventions (Chair: Dr. D. Feldman)

Steering Committee
- Principal Investigator (Dr. Travis)
- Contributing Center PIs
- Working Group Chairs
- Data Management (C. Casacelli)
- Central Biospecimen Lab (Kris Kuryla)
- Radiation Dosimetry (Dr. Marilyn Stovall)
- NCI Extramural Program

Support Facilities
- Coordinating Center and Central Lab (URMC)
- Data Management Core (CTCC)
- Radiation Dosimetry Core (M.D. Anderson)

External Advisory Committee
(Drs. Lipshultz, Robison, Fossà, Gospodarowicz, and Oakes)

General Research Community
Thank you!
This is Team Science

The Platinum Study Investigators’ Meeting
(October 2013)
Clinical and Translational Sciences Institute
URMC, Rochester, NY

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