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

Siegel R, et al. Cancer treatment and survivorship statistics, 2012. Ca Cancer J Clin 2012;62:220-241.

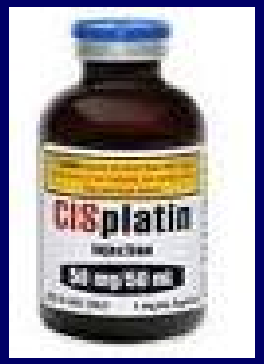
Cancer Survivorship
Consequences of Success

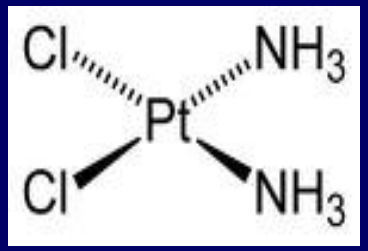
- Late effects of cancer and its therapy
  - Second malignant neoplasms
  - Cardiovascular disease
  - Renal, pulmonary
  - Neurologic
    - Chemotherapy-induced peripheral neuropathy; cognitive dysfunction
    - Hearing loss (e.g., cisplatin, cranial RT)
  - Fertility, many others
  - Psychosocial,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

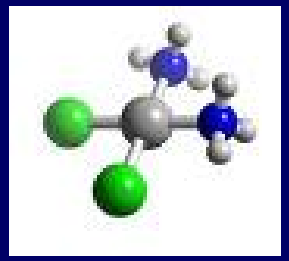
Cancer Treatment
Turning Point: 1977

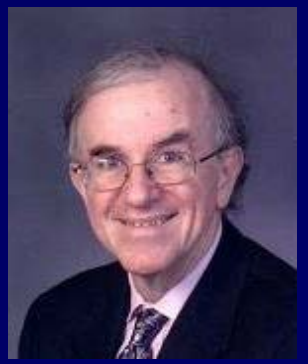
- Dr. Lawrence Einhorn, 1977:
  Introduction of cisplatin-based chemotherapy

- Einhorn LH, Donohue J. "*Cis-diamminedichloro-platinum, 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"
  - *Source: Bajorin DF. The graying of testis cancer patients: what have we learned? J Clin Oncol 2007;28:4341-3.*

International Workshop: 2009

Rochester, NY

- 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

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COMMENTARY

Testicular Cancer Survivorship: Research Strategies and Recommendations

Lois B. Travis, Clair Beard, James M. Allan, Alv A. Dahl, Darren R. Feldman, Jan Oldenburg, Gedske Daugaard, Jennifer L. Kelly, M. Eileen Dolan, Robyn Hannigan, Louis S. Constine, Kevin C. Oeffinger, Paul Okunieff, Greg Armstrong, David Wiljer, Robert C. Miller, Jourik A. Gietema, Flora E. van Leeuwen, Jacqueline P. Williams, Craig R. Nichols, Lawrence H. Einhorn, Sophie D. Fossa

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Testicular cancer represents the most curable solid tumor, with a 10-year survival rate of more than 95%. Given the young average age at diagnosis, it is estimated that effective treatment approaches, in particular, platinum-based chemotherapy, have resulted in an average gain of several decades of life. This success, however, is offset by the emergence of considerable long-term morbidity, including second malignant neoplasms, cardiovascular disease, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, decreased fertility, and psychosocial problems. Data on underlying genetic or molecular factors that might identify those patients at highest risk for late sequelae are sparse. Genome-wide association studies and other translational molecular approaches now provide opportunities to identify testicular cancer survivors at greatest risk for therapy-related complications to develop evidence-based long-term follow-up guidelines and interventional strategies. We review research priorities identified during an international workshop devoted to testicular cancer survivors. Recommendations include 1) institution of lifelong follow-up of testicular cancer survivors within a large cohort setting to ascertain risks of emerging toxicities and the evolution of known late sequelae, 2) development of comprehensive risk prediction models that include treatment factors and genetic modifiers of late sequelae, 3) elucidation of the effect(s) of decades-long exposure to low serum levels of platinum, 4) assessment of the overall burden of medical and psychosocial morbidity, and 5) the eventual formulation of evidence-based long-term follow-up guidelines and interventions. Just as testicular cancer once served as the paradigm of a curable malignancy, comprehensive follow-up studies of testicular cancer survivors can pioneer new methodologies in survivorship research for all adult-onset cancer.

J Natl Cancer Inst 2010;102:1114–1130

Testicular cancer is the most curable solid tumor, with an overall 10-year relative survival rate of more than 95% (1,2). Given the young average age at diagnosis, it is estimated that successful treatment approaches, in particular, platinum-based chemotherapy (3–5), have resulted in an average gain of several decades of life for patients with advanced disease. The high cure rate of patients with testicular cancer, however, is offset by the emergence of considerable long-term morbidity (6–8). The late effects of testicular cancer and its treatment include second malignant neoplasms, cardiovascular disease, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, decreased fertility, psychosocial disorders, and possibly cognitive impairment (3–8). An international study of more than 40 000 testicular cancer survivors that included those diagnosed before the cisplatin era showed that the 40-year cumulative incidence of second malignant neoplasm may reach approximately one in three (7). Moreover, second malignant neoplasms and cardiovascular disease are important causes of premature death in long-term testicular cancer survivors (8).

A compelling need exists to expand the research base into the late effects of testicular cancer and its treatment, especially with regard to factors that confer an enhanced susceptibility to the long-term toxicities of cisplatin-based chemotherapy and radiotherapy. Furthermore, an understanding of the mechanisms that underlie the development of long-term adverse sequelae after cisplatin-based therapy has broader implications because platinating agents are now one of the most widely used groups of cytotoxic drugs worldwide. The persistence of platinum-DNA adducts in numerous tissues (eg, kidney or brain) (9,10) for up to several years after treatment also causes concern. For example, whether platinum-DNA adducts in brain (11) might result in premature cognitive impairment in survivors as they age has not been evaluated, although central nervous system progenitor cells are targeted by cisplatin-based therapy in preclinical studies (12). Circulating platinum, which remains partly reactive (13), is detectable for more than 10 years after treatment completion (11), with urine and serum concentrations that are up to 1000 times higher in patients than in unexposed control subjects (14). Whether platinum might have an impact on the actions of essential trace elements (eg, calcium, copper, magnesium, iron, and zinc) or result in chronic endothelial activation and vascular damage has not been comprehensively addressed.

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*

*Travis LB, Beard C, Allan JM, Dahl AA, Feldman DR, Oldenburg J, … Einhorn LH, Fossa SD. Testicular cancer survivorship: research strategies and recommendations. J Nat Cancer Inst 2010;102:1114-1130.

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

[1] Bhatia S. Role of genetic susceptibility in development of treatment-related adverse outcomes in cancer survivors. CEBP 2011;20:2048-67.

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 Kollsmannberger

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)


Dr. Cox


Dr. Dolan


Dr. Frisina


Dr. Herrmann


Dr. Bisognano


Dr. Sesso

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

*Travis LB, Fossa SD, Sesso HD , …. Einhorn LH, Cox NJ, Dolan ME. Chemotherapy-induced peripheral neurotoxicity and ototoxicity: new paradigms for translational genomics. J Nat Cancer Inst 2014 (in revision).

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

*Travis LB, Fossa SD, Sesso HD , …. Einhorn LH, Cox NJ, Dolan ME. Chemotherapy-induced peripheral neurotoxicity and ototoxicity: new paradigms for translational genomics. J Nat Cancer Inst 2014 (in revision). ** Mukherjea D, et al. J Neuroscience 2008; 28:13056-64.

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**

*Travis LB. Beard C, Allan J, et al.;. JNCI 2010;102:1114-1130.

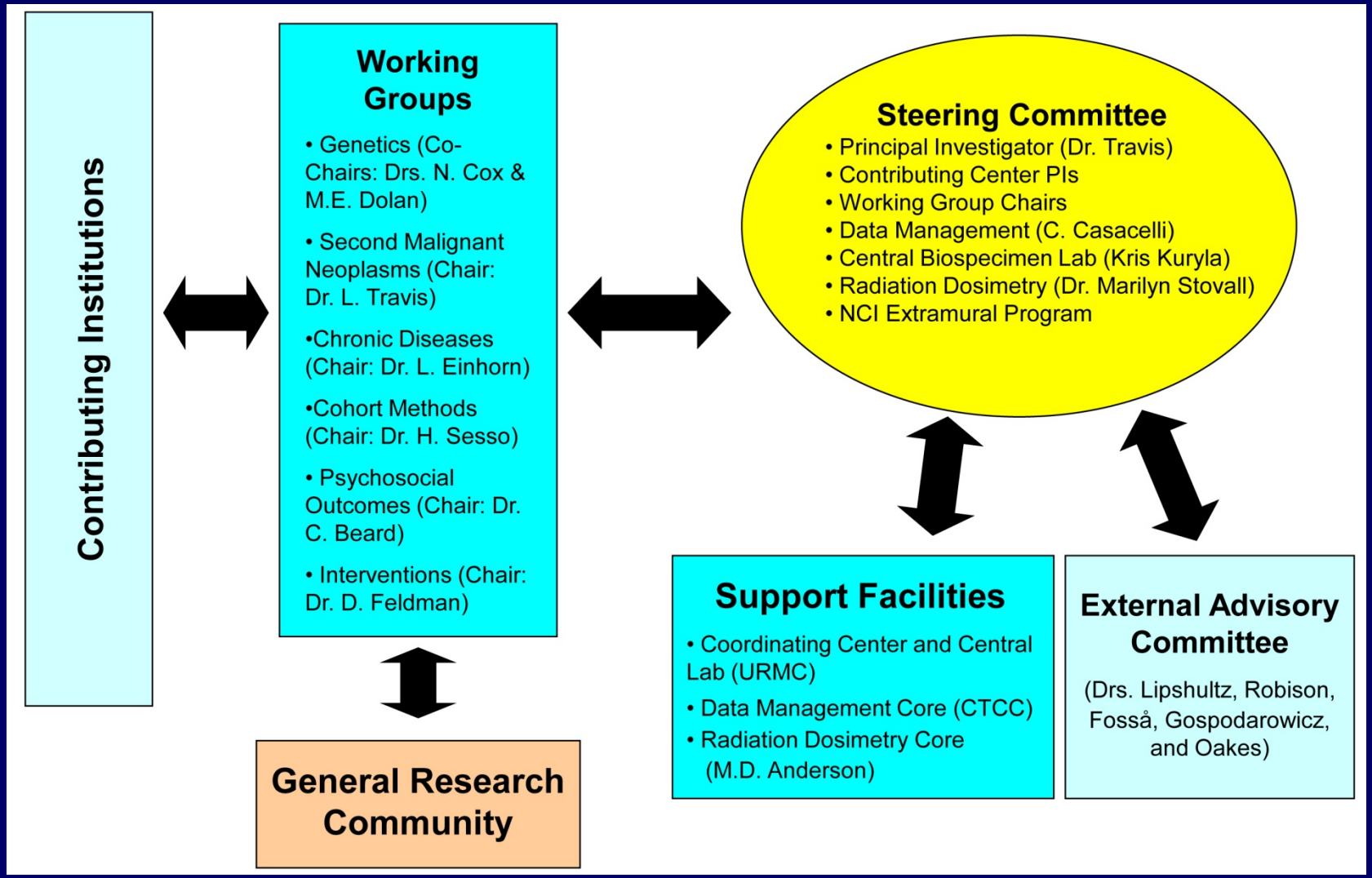
**Freedman AN et al., JNCI 2005; 97: 715-23; and Freedman AN, et al., JNCI 2010;102:1698-1705.

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

*Elena J, et al. Leveraging Epidemiology and Clinical Studies of Cancer Outcomes; Recommendations and Opportunities for Translational Research, JNCI 2012: Khoury M et al. Transforming Epidemiology for 21st Century Medicine and Public Health. CEBP 2013.

The Platinum Study Expansion
Organization of UM1



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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