Introduction, Methods and Limitations of the Data

Cancer Chemotherapy Use during Pregnancy
Introduction

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Introduction

• ~17 to 100 per 100,000 women are diagnosed with cancer during pregnancy

• Patient and her medical team must determine course of treatment optimal for mom with minimal risk to fetus
  – Most treatments for cancer involve chemotherapy
  – Nearly all cancer chemotherapeutic agents have possible or demonstrable risk to the fetus

• Current medical paradigm suggests:
  – Avoid treatment during the 1st trimester, when possible
  – Treatment in 2nd and/or 3rd trimester does not appear to increase risk of major congenital malformations observed at birth
Sources of literature

• Majority of data on pregnancy outcomes are reported in case reports and case series, which have small sample sizes

• There are efforts to obtain larger patient samples by systematically collecting data via registries and prospective studies
  – Registries include:
    • Cooper University Hospital in Camden, New Jersey, USA
    • University of Oklahoma Health Sciences Center in Oklahoma City, Oklahoma, USA
    • Toronto Hospital of Sick Children in Ontario, Canada
    • University of Frankfurt and German Breast Group, Germany
  – Clinical trials (www.clinicaltrials.gov):
    • MD Anderson Cancer Center, Houston, Texas, USA
    • Katholieke Universiteit, Leuven, Belgium
Purpose

• Purpose of draft NTP monograph:
  – To summarize the effects of gestational exposure to cancer chemotherapy on pregnancy outcomes in the peer-reviewed literature
    • Of 113 chemotherapy agents currently in use, the draft NTP monograph includes data on all 52 agents for which pregnancy outcomes were documented
  – To serve as a tool for physicians and their patients in making clinical decisions
    • Not intended as a medical advice or clinical guidance
Health outcomes

• Draft NTP monograph focuses on 5 health outcomes:
  – Primary outcomes:
    • Major congenital malformations associated with treatment during the 1st trimester versus the 2nd and/or 3rd trimester only
    • Early and late spontaneous fetal death
  – Secondary outcomes:
    • Pregnancy complications (e.g., reduction in amniotic fluid and spontaneous preterm labor)
    • Newborn weight and health (e.g., small for gestational weight, fetal/neonatal cardiotoxicity, and transient myelosuppression)
    • Growth and development of gestationally-exposed offspring
Background information

• To provide context, the draft NTP monograph provides background information on:

  – Prevalence and prognosis of 7 frequently diagnosed cancers in women of reproductive age

  – Individual cancer chemotherapeutic agents, including data on:
    • Mechanism of action
    • Indications
    • Evidence of transfer to fetus or breast milk
    • Developmental toxicity in laboratory animal studies

  – Background information was collected from both primary and secondary sources; it is not the main focus of this evaluation
Concept development

• Concept for this evaluation was developed following discussion with scientists and clinicians in the United States at the:
  – National Cancer Institute (NCI)
  – National Institute of Child Health and Human Development (NICHD)
  – Food and Drug Administration (FDA) Center for Drug Evaluation and Research
  – National Comprehensive Cancer Network (NCCN)

• Concept was reviewed by the NTP Board of Scientific Counselors on June 21, 2010
Technical advisors

- Technical advisors provided guidance on sections of the draft monograph, including the content of the appendix tables and agent specific chapters

- Technical advisors for the draft NTP monograph:
  - **Hatem Azim Jr, MD**; Department of Medical Oncology, Jules Bordet Institute, Brussels, Belgium
  - **Elyce Cardonick, MD**; Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Cooper Health System, Camden, NJ
  - **Richard Theriault, DO**; Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
Methods

Cancer Chemotherapy Use during Pregnancy
Literature Search Strategy

• Focused on 4 key concepts:
  – Chemotherapy, pregnancy, pregnancy outcomes, and human studies

• Screening criteria for literature search results
  – Inclusion:
    • Pregnancy outcomes of female cancer patients treated with cancer chemotherapy during pregnancy
  – Exclusion:
    • Male cancer patients
    • Non-English language
    • Absence of data on pregnancy outcome
    • Chemotherapy administered for non-cancer health conditions
    • Drugs used to treat side-effects of cancer or its treatments
Literature Search Results

- Database searched:
  - PubMed
  - Web of Science
  - Scopus
  - Embase
  - Toxnet
- Initial search – through June 7, 2010
- Total references, n=1425

References with pregnancy outcomes included in the Appendix Tables, n=452

- Other databases searched:
  - Cochrane Reviews
  - NIH Consensus Documents
  - REPROTOX database
  - MOTHERRISK website
- Review of bibliographies of ~75 review articles

Screening and Data Extraction

References excluded from final analysis:
- Abstracts, n=6
- Multiple reporting of same case, n=9
- Studies without individual patient data, n=6

Main findings based on 431 references (1271 conceptuses)
### Number of publications by type

<table>
<thead>
<tr>
<th>Study types</th>
<th>Number of publications</th>
<th>Number of conceptuses per study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>case reports</td>
<td>321</td>
<td>335</td>
</tr>
<tr>
<td>case series</td>
<td>84</td>
<td>385</td>
</tr>
<tr>
<td>case series, retrospective</td>
<td>9</td>
<td>93</td>
</tr>
<tr>
<td>cohort, retrospective</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>survey, retrospective</td>
<td>13</td>
<td>267</td>
</tr>
<tr>
<td>survey, registry</td>
<td>1</td>
<td>160</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>431</strong></td>
<td><strong>1271</strong></td>
</tr>
</tbody>
</table>

- Differences in the number of case reports and conceptuses per study due to twin pregnancies and some patients have more than one pregnancy.
Distribution of Cases by Country Regions

- North America: 45.14%
- Europe: 44.18%
- Asia: 7.63%
- Australia: 0.88%
- South America: 1.61%
- Africa: 0.56%
Data extraction

• Individual agent tables (Appendices C, D): Description of pregnancy outcomes of individual cases

<table>
<thead>
<tr>
<th>Chemotherapy agent</th>
<th>Study type</th>
<th># of cases</th>
<th>Cancer type</th>
<th>Timing of treatments</th>
<th>Co-treatment (timing)</th>
<th>Delivery route</th>
<th>Gestational age at delivery, weeks</th>
<th>Pregnancy complications and outcome</th>
<th>Follow Up</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab (loading dose, then 2 mg/kg every 3 weeks)</td>
<td>Case report</td>
<td>1</td>
<td>Breast</td>
<td>PC, 1st</td>
<td>None</td>
<td>NA</td>
<td>6</td>
<td>Induced abortion due to ectopic pregnancy. No histological examination of embryo was performed.</td>
<td>NA</td>
<td>(Berveiller, 2008)</td>
</tr>
<tr>
<td>Trastuzumab (4 mg/kg loading dose, then 2 mg/kg every 3 weeks)</td>
<td>Case report</td>
<td>1</td>
<td>Breast</td>
<td>2nd, 3rd</td>
<td>Vinorelbine</td>
<td>Vaginal, induced</td>
<td>34</td>
<td>Oligohydramnios; amniotic fluid remained low despite intravenous fluids to mother. Male infant: 5 lb, 11oz [2580 g], Apgar scores 9, 9 and 10. Newborn was healthy at birth.</td>
<td>At 6 months, healthy with normal development.</td>
<td>(Fanale, 2005)</td>
</tr>
</tbody>
</table>

• Master file: Tally of pregnancy outcomes by publication to calculate total conceptuses evaluated in the draft NTP monograph
Definitions of the 5 health outcomes

• Congenital malformations (Correa et al 2007; Rasmussen et al 2003)
  – Major: defects that adversely affect health or development
  – Minor: defects that do not adversely affect health or development

• Spontaneous fetal death
  – Early (≤22 weeks of gestation; spontaneous abortion)
  – Late (>22 weeks of gestation; stillbirth)

• Pregnancy complications
  – Reduction in amniotic fluid - any report of anhydramnios, oligohydramnios, or reduced amniotic fluid volume during pregnancy
  – Intrauterine growth restriction (IUGR) - developing fetus’ estimated weight is <10\textsuperscript{th} percentile of other fetuses at the same gestational age
  – Spontaneous preterm labor: spontaneous labor occurring at <37 weeks gestation
Definitions of the 5 health outcomes (cont'd)

• Newborn weight and health:
  – Small for gestational size (Olsen et al. 2010)
    • Infants with birth weights at <10th percentile of other infants at the same gestational age
  – Transient myelosuppression
    • Blood measurement of pancytopenia (anemia), leukopenia, neutropenia, and/or thrombocytopenia at birth
  – Fetal/neonatal cardiotoxicity
    • Diagnosis of arrhythmia, cardiomyopathy, tachycardia, and/or heart failure in utero or at birth
  – Growth and development of gestationally-exposed children
    • Focus on physical growth, development of the central nervous system, reproductive system, vision, hematopoietic system, cardiotoxicity, and occurrence of cancer
Data analysis

- Descriptive statistics
- Data calculated as apparent rates of occurrence
  - Major malformations, spontaneous fetal death per total conceptuses*
  - Reductions in amniotic fluid, spontaneous preterm labor per stillborn and live born pregnancies
  - Intrauterine growth restriction per stillborn and liveborn conceptuses
  - Small for gestational age per live born conceptuses (newborns)
- Data analyzed in two ways:
  - Overall pooled analysis of any chemotherapy exposure
  - Individual agent exposure (singly and in combination therapy)
- For major malformation data, exposure during the 1st trimester was compared to exposure only in the 2nd and/or 3rd trimester
- Data were compared to general population values to provide context for results

*Included all fetal deaths. Studies lacking fetal autopsy data were considered normal.
Limitations of the Data

Cancer Chemotherapy Use during Pregnancy
Limitations of the data

- There were a number of limitations to the NTP’s interpretation of the literature on pregnancy outcomes
  - Lack of a referent group
  - Small number of cases for most chemotherapeutic agents
  - Lack of long-term follow up evaluations
  - Publication bias
Charge Questions

A. Introduction, Methods and Limitations of the Data

a. Please comment on whether the scientific information in the text is technically correct, clearly stated, and objectively presented. Please comment on whether the tabular information and its format are easily understandable. Please identify any needed improvements.

b. Please comment on whether the methods for compiling and presenting the data are appropriate. Please identify any needed improvements.