Challenges in Treating Pregnant Cancer Patients

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Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation

Learning Objectives

- Describe dosing strategies for chemotherapeutic agents in the pregnant and postpartum patient
- Review monitoring parameters and clinical outcomes of chemotherapeutic agents in the pregnant and postpartum patient
- Integrate concepts for management of chemotherapy of pregnant and postpartum/lactating patients into case vignettes
- Describe ethical considerations surrounding chemotherapy in the pregnant patient

Development

- First Trimester (0 – 13 weeks)
  - Organogenesis: heart, neural tube, limbs, palate, & ears
  - Development of hematopoietic system, CNS, eyes, and genitalia continues into 2nd & 3rd trimesters.
- Second Trimester (14 – 26 weeks)
- Third Trimester (27 – 40 weeks)

Epidemiology

- Maternal cancer develops in approximately 1:1000 pregnancies.
  - Approximately 5000 cases a year in USA
- The incidence will probably increase as women delay having children until older ages.
- The most frequently diagnosed cancers:
  - breast, cervical, lymphoma, & melanoma

Diagnostic Dilemma

- Changes in women’s body during pregnancy makes cancer diagnoses difficult.
  - Breast enlargement during pregnancy normal but confuses the w/u for breast cancer.
  - Delay in w/u for melanoma because of hyperpigmentation during pregnancy.
- Cervical inspection part of routine pregnancy care
  - Increased opportunity to diagnose early stage cervical cancer.
PHARMACOKINETIC CHANGES - MATERNAL

- Increased plasma volume
- Increased third spacing
  - Amniotic fluid
- Increased renal clearance
- Decreased plasma albumin
  - Increased amount of active drug
  - Other plasma proteins increased
- Faster hepatic oxidation


BREAST CANCER in PREGNANCY

- Histopathological & immunohistochemical findings are similar between pregnant breast cancer patients & non-pregnant premenopausal women.
  - High incidence of grade III tumors, ER (-) status, & lymph node positivity
  - Approximately 30% HER-2 amplified


TIMING OF CHEMOTHERAPY

- First Trimester
  - Associated with spontaneous abortions, fetal death, & major malformations
  - 10 – 20% risk of major malformations

- 2nd & 3rd Trimester
  - Less teratogenic than 1st trimester
  - Increased risk for intrauterine growth retardation & low birth weight compared to non-chemotherapy treated women


PROGNOSIS in WOMEN with BREAST CANCER

- Belief that breast cancer diagnosis during pregnancy portends a poor prognosis

- Cohort study from European registry
  - 311 pregnant pts
  - 865 non-pregnant pts
  - All with newly dx breast cancer

J Clin Oncol 2013;31:2532-9

BREAST CANCER in PREGNANCY

- Approximately 0.2 – 2.6% of all breast cancers are diagnosed during pregnancy.

- Physiological changes to the breasts associated with pregnancy delay in diagnosis & treatment.
  - Engorgement, nipple discharge, & hypertrophy


PROGNOSIS in WOMEN with BREAST CANCER

- Prognostic factors
  - Age - Pregnant: 33 yrs vs. Non-pregnant: 41 yrs
  - Stage – more stage II & III in pregnant pts
  - ER/PR status – 46% + in pregnant vs. 75% + non-pregnant
  - HER-2 amplified – 32% in pregnant vs. 17% non-pregnant

J Clin Oncol 2013;31:2532-9
PROGNOSIS in WOMEN with BREAST CANCER

<table>
<thead>
<tr>
<th></th>
<th>Pregnant</th>
<th>Non-pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr DFS</td>
<td>65%</td>
<td>71%</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>78%</td>
<td>81%</td>
</tr>
</tbody>
</table>

HR 1.34 (0.93-1.91)  
p=0.14

HR 1.19 (0.73-1.93)  
p=0.51

J Clin Oncol 2013;31:2532-9

OTHER CONSIDERATIONS in PREGNANT BREAST CANCER PATIENTS

- Do not use radiation therapy during any trimester of pregnancy.
- Sentinel node biopsy
  - Use of blue dye is discouraged
  - Radiolabeled sulfur colloid appears to be safe


CHEMOTHERAPY in PREGNANT BREAST CANCER PATIENTS

- Do not use chemotherapy in 1st trimester
- Doses should be calculated on actual body weight


Lancet 2012;379:570-9

CHEMOTHERAPY in PREGNANT BREAST CANCER PATIENTS

- Utilize regimens similar to non-pregnant patients
  - Avoid methotrexate regimens (e.g. CMF) due to third spacing
  - Limited data with taxanes in pregnancy
    - If used, consider weekly dosing
  - Trastuzumab & Pertuzumab contraindicated in pregnancy


Lancet 2012;379:570-9
HORMONAL AGENTS & BISPHosphonates in PREGNANT BREAST CANCER PATIENTS

- Tamoxifen
  - Pregnancy Category D
  - If indicated, use after delivery
- Bisphosphonates
  - Pregnancy Category D
  - Hypocalcemia associated with bisphosphonates can affect contractility of the uterus

LEUKEMIA in PREGNANCY

- Occurs 1 in 75,000 – 100,000 pregnancies
- Usually AML or ALL
- Usually diagnosed in 2nd or 3rd trimester
- Requires immediate treatment

TREATMENT of AML

<table>
<thead>
<tr>
<th>Approach</th>
<th>Treatment</th>
<th>Maternal Outcome</th>
<th>Fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trimester</td>
<td>Pregnancy termination then conventional treatment</td>
<td>Daunorubicin plus cytarabine then consolidation</td>
<td>Unaffected</td>
</tr>
<tr>
<td>2nd or 3rd trimester</td>
<td>Treat like non-pregnant women</td>
<td>Daunorubicin plus cytarabine then consolidation</td>
<td>Probably unaffected</td>
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</tbody>
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Lancet 2012;379:580-7

TREATMENT of APML

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<th>Approach</th>
<th>Treatment</th>
<th>Maternal Outcome</th>
<th>Fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st trimester</td>
<td>Pregnancy termination then conventional treatment</td>
<td>Daunorubicin plus ATRA then consolidation</td>
<td>Might be affected</td>
</tr>
<tr>
<td>2nd or 3rd trimester</td>
<td>Treat like non-pregnant women</td>
<td>Daunorubicin plus ATRA then consolidation</td>
<td>Probably unaffected</td>
</tr>
</tbody>
</table>

Lancet 2012;379:580-7

TREATMENT of ALL

<table>
<thead>
<tr>
<th>Approach</th>
<th>Treatment</th>
<th>Maternal Outcome</th>
<th>Fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20 weeks gestation</td>
<td>Pregnancy termination then conventional treatment</td>
<td>Multi-drug chemotherapy</td>
<td>Unaffected</td>
</tr>
<tr>
<td>&gt; 20 weeks gestation</td>
<td>Treat like non-pregnant women</td>
<td>Multi-drug chemotherapy</td>
<td>Probably unaffected</td>
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Lancet 2012;379:580-7

FETAL MONITORING

- Fetal ultrasound at diagnosis
- Estimate date of delivery
- If systemic therapy utilized, fetal monitoring prior to each cycle

**SUPPORTIVE CARE**

- Prevention of N/V – ondansetron & corticosteroids + lorazepam
- Treatment of N/V – metoclopramide
- Neutropenia
  - Filgrastim appears safe
- Infections
  - Safe: penicillin, cephalosporins, metronidazole, & macrolides
  - Avoid: sulfonamides, tetracyclines, quinolones


**FETAL OUTCOMES**

- Long-term outcomes after prenatal chemotherapy exposure is limited
- 84 children born to mothers treated for hematological malignancy
  - Median follow-up 19 years (6 – 29 yrs)
  - Learning & educational performance normal
  - No congenital, neurological, or psychological abnormalities observed

&Clin Lymphoma 2001;2:173-7

**DELIVERY of the CHILD**

- Chemotherapy should not be given after 35 weeks.
- Avoid delivery of the child during the anticipated nadir of counts.
- If possible, delivery should be 3 weeks or more after chemotherapy to allow mother and child to eliminate the drugs & recover counts.


**FETAL OUTCOMES**

- 236 cycles of chemotherapy administered in 68 patients
- No increased risk CNS or auditory morbidity
- Growth & intelligence within normal limits

<table>
<thead>
<tr>
<th>Ejection Fraction (%)</th>
<th>Chemotherapy exposure</th>
<th>Control</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (60 – 75)</td>
<td>71 (57 – 83)</td>
<td>-6.0%</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

&Lancet Oncol 2012;13:256-64

**FOLLOW-UP on the CHILD**

- Metastatic spread to the placenta & fetus is extremely rare
  - Associated with melanoma, leukemia & lymphoma
- Pathological examination of placenta
  - Negative: follow-up similar to healthy infants
  - Positive: considered high-risk
    - Follow every 6 months for 2 years
    - Monitoring relevant to primary malignancy in mother

&Cancer Treat Rev 2008;34:302-12

**BREAST FEEDING**

- Chemotherapy drug concentrations in human breast milk are not well-studied.
- Anti-cancer chemotherapy concentrations are dose & schedule dependent.
- Recommended to not breastfeed while receiving chemotherapy or tamoxifen.

ETHICS

LIMITATIONS of DATA PRESENTED

• Small sample sizes, case series, or case reports
• Tendency to report good outcomes not poor outcomes
• Limited long-term maternal and fetal follow-up

CONCLUSIONS

• Future studies should assess toxic effects of chemotherapy in pregnant patients and also pharmacokinetics.
• Future research should better assess the long-term maternal & fetal outcomes of those receiving chemotherapy during pregnancy.
• Publish your experience, particularly with new agents
• Recommend having your patient to consider joining an international registry.
  • http://www.pregnantwithcancer.org/

ETHICS

• The risk of cancer increases with age.
• Women are waiting later to begin childbearing.
• In both of these cases the women were in their mid-thirties and struggled with infertility.
• Both desperately wanted to have a child.

KEY REFERENCES