GnRH Analogs for Fertility Preservation: What are the Data?

AHN-JH SKCCC Current Topics in Breast Cancer Symposium
Karen Lisa Smith MD MPH
Assistant Professor
Johns Hopkins Breast and Ovarian Cancer Program

March 22, 2019

Educational Objectives

• To understand the effect of chemotherapy on ovarian function
• To review the available evidence regarding temporary ovarian suppression with GnRH analogs during chemotherapy as a strategy for ovarian protection
• To discuss current United States fertility preservation guidelines

Outline

• Rationale for GnRH analog use during chemotherapy
• Mechanism of action of GnRH analogs for ovarian protection
• Trials evaluating temporary ovarian suppression with GnRH analogs during chemotherapy
• Where do GnRH analogs fit into US fertility preservation guidelines?
**Background: Chemotherapy-Induced Amenorrhea**

- Menstrual cycles often cease during chemotherapy. May be temporary or permanent. Recovery dependent on:
  - **Age** (chemo accelerates age-related decline in follicle reserve; older age \(\rightarrow\) less recovery)
  - **Baseline AMH** (lower AMH \(\rightarrow\) less recovery)
  - **Duration/Dose/Regimen:**
    - Greater recovery with AC than CMF
    - Addition of taxanes, trastuzumab and use of dose dense therapy do not increase risk
    - Lower rates of amenorrhea with regimens without alkylating agents (e.g. paclitaxel/trastuzumab). (Alkylating agents \(\rightarrow\) primordial cell death)

---

**Background: Bleeding After Chemotherapy by Patient Age**

-Recovery of menses usually within 1 year (if amenorrhea is temporary)

---

**Background: Infertility due to Breast Cancer Treatment**

- **Chemotherapy is gonadotoxic:** induces DNA breaks in primordial follicles \(\rightarrow\) apoptosis \(\rightarrow\) reduced ovarian reserve
  - Recovery of menses not a reliable indicator of ovarian reserve. Even if menstrual cycles resume, younger menopause
- Fertility declines during the 5-10 year course of endocrine therapy
- Delayed childbearing in western countries \(\rightarrow\) many young women have not completed their families at diagnosis
- Estimated number of young women with breast cancer at risk for infertility (based on receipt of chemotherapy and/or adjuvant endocrine therapy) each year: \(\sim\)19000
- Estimated number of young women with breast cancer at risk for infertility who may want children and who could benefit from fertility counseling/preservation interventions each year: \(\sim\) 9000
Background: Fertility Concerns

- Web-based survey of survivors 40 or younger at diagnosis, n=657
  - 57% concerned about possibility of infertility due to treatment
  - 29% said concern about infertility impacted treatment decisions
  - 72% reported discussing fertility concerns with doctor
    - Only 1/2 felt their concerns were adequately addressed
- Follow-up prospective survey revealed similar findings – high rates of concern, impact of fertility concerns on treatment decisions
- Additional studies demonstrate that the majority of female cancer survivors have reproductive concerns and that many desire children
- Reproductive concerns in female cancer survivors associated with lower quality of life, increased depression, increased distress


Infertility and Other Aspects of Premature Ovarian Insufficiency After Chemotherapy

Chemotherapy
Reduced Ovarian Reserve/ Premature Ovarian Insufficiency
Infertility
Signs/symptoms of Menopause

Effects of Premature Ovarian Insufficiency Besides Infertility

- Hot flashes
- Vaginal dryness
- Loss of bone density
- Cognitive Dysfunction
- Reduced QOL/Wellbeing
- CV disease
- Other…

Lambertini Cancer Treatment Reviews 2019
Temporary Ovarian Suppression with GnRH Analogs During Chemotherapy

- May consider temporary ovarian suppression with GnRH analogs during chemotherapy as an option for ovarian protection
  - To prevent menopause
  - May help preserve fertility
- Rationale for investigating GnRH analogs for ovarian protection:
  - Reduced ovarian activity at time of chemotherapy associated with reduced risk of gonadal failure (based on data in pre-pubertal children exposed to chemotherapy suggesting less ovarian failure)

Mechanism of Action of GnRH Analogs for Ovarian Protection

- Mechanism of action uncertain
  - Some have questioned the biologic rationale because the majority of follicles in adult ovaries are at the primordial stage (quiescent) and primordial follicles do not have gonadotropin receptors

Possible Mechanisms of Action of GnRH Analogs for Ovarian Protection

<table>
<thead>
<tr>
<th>Indirect Effects</th>
<th>Direct Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppress FSH →</td>
<td>Steroidogenesis and</td>
</tr>
<tr>
<td>slower proliferation of follicular cells, less follicular recruitment and accelerated follicular atresia</td>
<td>GnRH receptor expression on immature follicles</td>
</tr>
<tr>
<td>Induce low estrogen state →</td>
<td>Anti-apoptotic effect</td>
</tr>
<tr>
<td>↓ ovarian blood flow →</td>
<td></td>
</tr>
<tr>
<td>↓ exposure of follicles to gonadotoxic effects of chemotherapy and ↓ chemotherapy-induced ovarian fibrosis</td>
<td></td>
</tr>
<tr>
<td>Interact with ovarian primordial germ cells</td>
<td></td>
</tr>
</tbody>
</table>

Preclinical Evidence

- Majority of data from mice/rats; limited data from primates
- Findings mixed, but majority of data suggests that temporary suppression with GnRH analogs during chemotherapy has protective effect on ovarian function
  - Differing findings may be attributable to methodological issues e.g. different experimental models, duration of GnRH analog, chemotherapy type/dose

Bird's Eye View of Clinical Evidence – Breast Cancer

- 14 randomized trials evaluating temporary ovarian suppression with GnRH analog during chemotherapy
  - 10 showed protective effect
- Key considerations:
  - Small N for many
  - Most used premature ovarian insufficiency as the endpoint
    - Varying/inadequate definitions of premature ovarian insufficiency, most relied on menstrual history (resumption of menses ≠ ovarian recovery, not all used hormone levels)
  - Timing for assessment of ovarian function varied (6 mo - 5 years after chemo), follow-up short for many studies
  - Limited information about pregnancy after chemo, often not adjusted for intent and attempt
  - Median age close to 40 for many
  - Different chemo regimens (AC for most)

SWOG POEMS Trial

- N=218
- Hormone receptor-negative early stage breast cancer
- Cyclophosphamide-based adjuvant chemotherapy
- Composite endpoint: amenorrhea and FSH levels
- Planned secondary endpoint: pregnancy

|                     | Goserelin | No Goserelin | OR 95% CI | P Value
|---------------------|-----------|--------------|-----------|----------
| Ovarian failure     | 8%        | 22%          | 0.3       |          |
|                     |           |              |           |          |
| Pregnancy within 5  | 21%       | 11%          | 2.23      |          |
| years               |           |              |           |          |
| 4-year DFS          | 92%       | 82%          | 0.43      |          |

- Caveat: Data for ovarian failure only available for 135 patients
- Significance of DFS findings unclear, but demonstrate safety of goserelin
German PROMISE-GIM6 Trial

- N=281
- Hormone receptor-negative or hormone receptor positive I-III breast cancer, subsequent endocrine therapy with ovarian suppression allowed
- Chemotherapy versus Chemotherapy + Triptorelin

<table>
<thead>
<tr>
<th></th>
<th>Triptorelin</th>
<th>No Triptorelin</th>
<th>OR 0.28 (p=0.05)</th>
<th>OR 1.28 (p=0.07)</th>
<th>HR 2.56 (p=0.14)</th>
<th>HR 1.17 (p=0.52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early menopause (amenorrhea AND FSH + estradiol in post menopausal range at 1 year after chemo)</td>
<td>8.9%</td>
<td>25.9%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years cumulative incidence estimate of resumption of menstrual function</td>
<td>72.6%</td>
<td>64%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-year cumulative incidence of pregnancy</td>
<td>2.1%</td>
<td>1.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 year DFS*</td>
<td>80.5%</td>
<td>83.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Association between study arm and did not differ by hormone receptor status (p for interaction not sig).

Anglo Celtic OPTION Trial

- N=221, hormone receptor-negative or hormone receptor-positive (no ovarian suppression allowed for endocrine therapy), stage I-III breast cancer
- Cyclophosphamide and/or anthracycline containing chemotherapy with or without Goserelin

<table>
<thead>
<tr>
<th></th>
<th>Goserelin</th>
<th>No Goserelin</th>
<th>P=0.015</th>
<th>P=0.048</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea (between 12 and 24 months after chemo)*</td>
<td>22%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature ovarian insufficiency (amenorrhea between 12 and 24 months after chemo with FSH &gt; 25)*</td>
<td>18.5%</td>
<td>34.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancies</td>
<td>9</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>9</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*When stratified by age, protective effect of goserelin on amenorrhea and premature ovarian insufficiency limited to women ≤ 40

Issues Related to Use of GnRH Analog for Ovarian Protection in ER-positive Breast Cancer

- Historical concern that concurrent endocrine therapy and chemotherapy may be associated with inferior outcomes:
  - Possible antagonism between tamoxifen and chemotherapy (preclinical)
  - Inferior DFS with concurrent versus sequential chemotherapy and endocrine therapy (SWOG 8814)
- Concern about losing the beneficial effect of chemotherapy-induced amenorrhea
- Difficulty in assessing ovarian function during adjuvant endocrine therapy

→ Some trials limited evaluation of GnRH analogs for ovarian protection to ER-negative disease for these reasons
Is Ovarian Protection with GnRH Analog an Option for ER+ Disease?

• Probably yes... Supporting data:
  – PROMISE-GIM6 Trial:
    • No difference in DFS according to ER status (p for interaction 0.19)
  – Extrapolate from SOFT/TEXT data:
    • No difference in breast cancer free interval (landmark analysis) with concurrent versus sequential ovarian suppression (supports safety of concurrent chemotherapy + ovarian suppression)

Bird’s Eye View of Clinical Evidence – Other Cancers

• 5 randomized trials (4 in lymphoma, 1 in ovarian cancer)
  – Only one (ovarian cancer) showed a protective effect
• Key considerations:
  – Young population (median age ~ 25)
  – Chemo regimens had variable gonadotoxicity
  – Small N for many
  – Varying definitions of premature ovarian insufficiency (based on either menstrual history or post-menopausal hormone levels; no composite endpoints)
  – Timing for assessment of ovarian function varied (6 mo - >5 years after chemo)
  – Limited information about pregnancy after chemo

Meta-Analyses

• 20 meta-analyses
  – 18 demonstrated protection against chemotherapy-induced premature ovarian insufficiency with temporary suppression with GnRH analog
  – 5 demonstrated more pregnancies with GnRH analog
  – Benefit larger in meta-analyses limited to breast cancer
**Lambertini Meta-analysis**

- Individual patient data meta-analysis of 5 randomized trials evaluating GnRH analogs for ovarian protection (PROMISE-GIM6, POEMS/SWOG S0230, Anglo Celtic Group OPTION, GBG-37 ZORO, and a Moffitt trial).
  - Included both ER+ and ER-
- 436 received chemo+GnRH analog
- 437 received chemo alone

<table>
<thead>
<tr>
<th></th>
<th>GnRHα</th>
<th>No GnRHα</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature ovarian insufficiency</td>
<td>14.1%</td>
<td>30.9%</td>
</tr>
<tr>
<td>1-year amenorrhea</td>
<td>36.8%</td>
<td>40.4%</td>
</tr>
<tr>
<td>2-year amenorrhea</td>
<td>18.2%</td>
<td>30%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>37 (10.3%)</td>
<td>20 (5.5%)</td>
</tr>
</tbody>
</table>

- No difference DFS (HR 1.01, 95% CI 0.72-1.42) or OS (HR 0.67, 95% CI 0.42-1.06)

**Why Are Findings Different for Breast Cancer and Lymphoma?**

- Lymphoma trials may be under-powered
- Younger age in lymphoma trials (less likely to develop ovarian failure)
- Variety of chemo regimens used for lymphoma (some highly gonadotoxic, others not); breast cancer typically treated with regimens with intermediate gonadotoxicity
- Follow-up short for lymphoma trials
- Disease characteristics: lymphoma may be associated with reduced ovarian reserve
- Varying definitions of premature ovarian failure

**Uptake of Temporary Ovarian Suppression with GnRH Analogs**

- Uptake unknown but likely low
- Overall, only ~ 10% of breast cancer patients pursue fertility preservation strategies (3% GnRH analogs)
- JH QI intervention to improve fertility care for pre-menopausal breast cancer patients:
  - 112 patients (1 year period)
  - 3 pursued temporary ovarian suppression, 7 pursued ovarian stimulation → oocyte harvesting, 2 pursued both strategies
Timing of GnRH use for Ovarian Protection

- Start at least 1 week prior to chemotherapy initiation
- Continue until after last chemotherapy cycle

What Does ASCO Say?

- "There is conflicting evidence to recommend GnRHa and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods"

What Does NCCN Say?

- "Randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy induced amenorrhea"
- "Smaller historical experiences in patients with ER-positive disease have reported conflicting results with regard to the protective effect of GnRH agonist therapy on fertility"
Conclusions

- Chemotherapy can cause premature ovarian insufficiency, leading to infertility and to other signs/symptoms of menopause
- Multiple randomized trials have evaluated temporary ovarian suppression with GnRH analogs for ovarian protection during chemotherapy
  - Majority of data in breast cancer patients supports protective effect against premature ovarian insufficiency
  - Limited data regarding effect on fertility preservation
- Mechanism of action uncertain
- Should not replace assisted reproductive techniques for fertility preservation, but may be considered in appropriate pre-menopausal breast cancer patients

Thank you