JADPRO Clinical Case Series

Managing Fertility and Treatment-Related Side Effects in Premenopausal Patients with Breast Cancer

SUPPORTED BY

TerSera therapeutics

PRESENTER

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Program Agenda

- Examine suppression of ovarian function (SOF) for risk reduction in premenopausal women with early-stage breast cancer
- Recognize successful strategies for managing side effects associated with SOF
- Explore principles of fertility preservation for women with early-stage breast cancer undergoing chemotherapy

Introduction

- One-third of newly diagnosed invasive breast cancers occur in women < age 50
- Effective treatment strategies have improved prognosis
- Inferior long-term outcomes in those < age 40
- Inferior outcomes driven by suboptimal endocrine therapy
- SOF improves outcomes
- SOF characterized by a well-recognized side-effect profile
- Management of side effects improves quality of life

Gray RG, et al. *J Clin Oncol.* 2023;Suppl16:Abstr 503. Sella T, et al. *JCO Oncol Pract.* 2021;18:211-216. Siegel RL, et al. *CA Cancer J Clin*. 2023;73:17. Singhal M, et al. *South Asian J Cancer.* 2018;7:151-155.

Regarding the care of premenopausal patients with early-stage breast cancer who are receiving suppression of ovarian function (SOF) with or after chemotherapy, how confident are you about your knowledge regarding optimal management of side effects?

a. Extremely confident
b. Somewhat confident
c. Not confident at all

Goserelin injection has been associated with which of the following adverse events?

a. Bone pain
b. Hot flushes
c. Depressed mood
d. All of the above

Regarding the care of premenopausal patients with early-stage breast cancer who are receiving suppression of ovarian function (SOF) with or after chemotherapy, how confident are you about your knowledge regarding options for and resources about fertility preservation?

a. Extremely confident
b. Somewhat confident
c. Not confident at all

Polling Question: Case 1

How does your practice typically handle transition off of suppression of ovarian function (SOF)?

a. Treat for 5 years, then check menopause labs to determine next steps **77%**
b. Treat for 2-3 years then continue tamoxifen alone **0%**
c. Patients typically proceed to oophorectomies before completion of 5 years **17%**
d. Always stop endocrine at the recommended 5 years **7%**

Overview of SOFT/TEXT Trials

SOFT

- 3,066 premenopausal women
- Tamoxifen + SOF
- Exemestane + SOF
- Tamoxifen alone
- Triptorelin, oophorectomy, irradiation

TEXT

- 2,672 premenopausal women
- Triptorelin + exemestane
- Triptorelin + tamoxifen
- Oophorectomy or irradiation after 6 months was allowed

Francis PA, et al. *N Engl J Med.* 2018;379:122-137. Pagani O, et al. *N Engl J Med.* 2014;371:107-118.

Overview of SOFT/TEXT Trials *(cont.)*

SOFT (67 months)

- Adding SOF to tamoxifen did not provide a significant benefit
- Sufficient risk for recurrence warranting adjuvant chemotherapy in women who remained premenopausal, the addition of SOF improved disease outcomes.
- Improvement was seen with the use of exemestane plus SOF

TEXT

- 8-year rate of distant recurrence lower for women on exemestane + SOF vs. tamoxifen + SOF by 5 percentage points
- SOFT 8-year significant reduction in recurrence and improved overall survival with adjuvant tamoxifen plus OFS vs. tamoxifen alone

Francis PA, et al. *N Engl J Med.* 2018;379:122-137.

Long-Term Follow-Up Combined TEXT/SOFT

- Median follow-up of 9 years, exemestane + OFS significantly improved disease-free survival (DFS) and distant recurrence-free interval (DRFI), but not overall survival (OS), compared with tamoxifen + SOF

	12-year DFS	Statistics	12-year DRFI	Statistics	OS	Statistics
Exemestane + SOF	80.5%	4.6% absolute improvement; HR, 0.79; 95% CI: 0.70–0.90; $p < 0.001$	88.4%	1.8% absolute improvement; HR, 0.83; 95% CI: 0.70–0.98; $p = 0.03$	90.1%	HR, 0.93; 95% CI: 0.78–1.11; $p = 0.43$
Tamoxifen + SOF	75.9%		86.6%		89.1%	

Pagani O, et al. *J Clin Oncol.* 2023;41(7):1376-1382.

Long-Term Follow-Up Combined TEXT/SOFT

- Among patients with human EGFR2-negative tumors (86.0% of the ITT population), the absolute improvement in 12-year overall survival with exemestane + SOF was:
  - 2.0% (HR, 0.85; 95% CI: 0.70 to 1.04) for those who did not receive chemotherapy
  - 3.3% for those who received chemotherapy (45.9% of the ITT population)
- Overall survival benefit was clinically significant in high-risk patients:
  - Women aged < 35 years (4.0%)
  - Those with > 2 cm (4.5%)
  - Those with grade-3 tumors (5.5%)
- Sustained reductions of the risk of recurrence with adjuvant exemestane + SOF, compared with tamoxifen + SOF, provide guidance for selecting patients for whom exemestane should be preferred over tamoxifen in the setting of SOF

Pagani O, et al. *J Clin Oncol.* 2023;41(7):1376-1382.

STEPP Analysis: Composite Risk Application in SOFT/TEXT Trials

STEPP Methodology

- Subpopulations
- Age
- Number + nodes
- Tumor size
- Tumor grade
- ER expression
- PR expression
- Ki-67 expression

8-Year Freedom from Disease Recurrence

- 10%-15% absolute improvement
- Exemestane + SOF versus tamoxifen + SOF or tamoxifen alone
- Minimal in low those with low recurrence risk

ER, estrogen receptor; PR, progesterone receptor. Pagani O, et al. *J Clin Oncol*. 2019;38(12):1293-1300.

Confirmatory Evidence

2021 SABCS

- 12 (SOFT) and 13 years (TEXT)
- Reduced risk of breast cancer recurrence was observed when combining SOF with tamoxifen or exemestane for 5 years
- Greatest benefit among those receiving exemestane

Meta Analysis ABCSG-12, HOBOE, SOFT and TEXT

- Compared AIs vs. +SOF
- Reduced risk of recurrence for women treated with an AI vs. tamoxifen
- Greatest advantage observed in the first 4 years, when the type of ET received was different

AI, aromatase inhibitor; ET, endocrine therapy. Bradley R, et al. *Lancet Oncol*. 2022;23:382-392.

Extending Suppression of Ovarian Function

- High-risk vs. low-risk standards
- Proven benefits from extending adjuvant endocrine therapy
- ATLAS aTTom
- Extension with SOF still a gray area
- APPs roles in extended endocrine therapy

Buono G, et al. *Front Oncol.* 2022;12:1032166.

Gonadotropin-releasing Hormone Agonist

- Results in suppression of LH and release of FSH from the pituitary; reduction in ovarian estrogen production
- Two LHRH agonists in the United States
  - Goserelin: approved for the treatment of breast cancer
  - Leuprolide: off-label use
- Triptorelin: approved in European Union
- Concerning side effects: wide range but mood changes and vaginal dryness are among the most important

FSH, follicle stimulating hormone; LH, luteinizing hormone; LHRH, luteinizing hormone releasing hormone.

Polling Question: Case 2

How would you manage depression symptoms in a newly diagnosed patient receiving goserelin injection for Suppression of ovarian function (SOF)?

a. Prescribe an antidepressant **42%**

b. Refer to psychology for counseling **13%**

c. Provide emotional support, recognizing the emotional reaction that can come with this diagnosis and the potential side effect of the goserelin and continue to monitor **42%**

d. Help her tap into resources such as support groups **3%**

Management of Mood Alterations

- Begins with multidisciplinary approach
- Interpersonal psychotherapy, problem solving therapy, and brief supportive psychotherapy
- Cognitive-behavioral and psycho-educational therapy
- SSRIs/SNRIs can be used to treat depression (venlafaxine common)
- Avoid use or use with caution in patients on tamoxifen
- Exercise; mindfulness-based stress reduction, acupuncture

Blanco C, et al. *Breast Cancer Res Treat.* 2019;173(2):353-364. Grassi L, et al. *Annals of Oncology.* 2018;29:101-111. Guarino A, et al. *J of Clin Med.* 2020;9:209. Taylor C, et al. *Breast Cancer:Targets and Therapy.* 2013;5:79-85. Wang F, et al. *Front Oncol.* 2022;12:1036634.

Management of Vaginal Dryness

- Dyspareunia, irritation, soreness, UTIs
- Mainstay of therapy is nonhormone-based products
- Vaginal moisturizers/vaginal lubricants
- Hyaluronic acid vaginal cream; CO_2 laser therapy
- Estrogen, DHEA, testosterone
- Specialty consultation

CO2, carbon dioxide; DHEA, dehydroepiandrosterone; UTI, urinary tract infection. Sussman TA, et al. *J Oncol Pract.* 2019;15(7):363-371.

Hot Topic: Estrogen Replacement

Systemic or vaginal hormone therapy after early breast cancer: A Danish observational cohort study in the *Journal of the National Cancer Institute*—Cold S, et al.

> "In postmenopausal women treated for early-stage estrogen receptor-positive BC, neither vaginal estrogen therapy nor menopausal hormone therapy was associated with increased risk of recurrence or mortality. A subgroup analysis revealed an increased risk of recurrence, but not mortality, in patients receiving vaginal estrogen therapy with adjuvant aromatase inhibitors."

How do you counsel premenopausal patients on goserelin about birth control?

a. I recommend against hormone-based methods of birth control and suggest barrier methods, a copper IUD, or surgical intervention (i.e., oophorectomy or vasectomy for partner)

b. If they are on goserelin, I do not recommend additional birth control methods

c. It depends on their hormone receptor status

d. This is a conversation that is had during treatment planning with the physician, and I do not have ongoing discussions about this

IUD, intrauterine device.

Which of the following is NOT an established method of fertility preservation?

a. Embryo conservation

b. Ovarian tissue cryopreservation

c. Mature oocyte cryopreservation

d. Ovarian function suppression during chemotherapy

Polling Question: Case 3

What, if any, are the barriers to onco-fertility services in your practice? (Select all that apply)

a. No barriers—the process is easy and used for every patient that desires fertility preservation **14%**

b. Timing—getting scheduled for evaluation or initiating procedures promptly prior to planned chemotherapy start **45%**

c. Financial—out-of-pocket costs are too high for patients **27%**

d. Inadequate staff knowledge or resources **14%**

Monitoring Hormone Levels During SOF

- Complete ovarian suppression on GnRH agonist NOT 100%
- Persistent ovarian escape (OE) in as many as 1 in 4 women
- Young age may be a factor contributing to OE
- Monitor serial LH, FSH, estradiol to ensure postmenopausal
- Inform women of risk of pregnancy
- Advise on use of nonhormone-based birth control

FSH, follicle stimulating hormone; GnRH, gonadotropin hormone-releasing hormone; LH, Burns E, et al. *The Oncologist.* 2021;26:e936-942.

Fertility Preservation in Patients with Early-Stage Breast Cancer

- Discuss preservation earlier rather than later
- Patient-centered approach
- Cryopreservation (embryos, eggs, ovarian tissue)
- GnRH agonist prior to chemotherapy
- Referral to psychotherapy if necessary
- The Oncofertility Consortium (save.myfertility.com)

GnRH, gonadotropin hormone-releasing hormone. Oktay K, et al. *Clin J Oncol.* 2018;36(19):1994-2002.

Barriers in Fertility Preservation

Patient

- Decision urgency
- Lack of comprehension
- Moral conflict
- Financial barriers
- Patient age

Provider

- Limited knowledge
- Provider discomfort
- Financial concerns
- Desire to limit distress
- Outcome concerns

Dorfman CS, et al. *J Oncol Navig Surviv.* 2021;12(10): 332-348.

Reproductive Outcomes With or Without Fertility Preservation

- Pregnancy after breast cancer is acceptable
- APPs support in fertility preservation a must
- Fertility preservation associated with higher fertility success rate
- All-cause survival positive following fertility preservation

Marklund A, Lundberg FE, Eloranta S, et al. *JAMA Oncol.* 2021;7(1):1-6.

Clinical Pearls

- The SOFT and TEXT trials provide a roadmap for lowering 5-year rates of recurrence of breast cancer for premenopausal women using an aromatase inhibitor plus ovarian function suppression.
- Use of clinically approved screenings for distress and conversations with partners or caregivers can provide a more holistic view of a patient's emotional health compared with just a direct one-on-one conversation.
- Conversations regarding fertility preservation should be initiated as early as possible, as use of ovarian function suppression during chemotherapy has been shown to be successful for premenopausal women.

Q & A

Please type your questions for Kelley Mayden into the **question box** in the control panel.

Thank You