

Tailored Treatment Investigations for Premenopausal Women with Endocrine Responsive (ER+ and/or PgR+) Breast Cancer: The Open Questions

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Abstract

Chemotherapy (CT), tamoxifen (Tam) and ovarian ablation were demonstrated to be effective adjuvant therapies for patients who are younger than 50 year old. Most of these women are premenopausal at diagnosis and approximately 50% have tumors expressing some hormone receptors (classified as ER+). Among premenopausal women treated with CT alone, those who are < 35 years old with ER+ disease do poorly compared with others. In trials of patients with ER+ disease, CT and ovarian function suppression (OFS) with GnRH analog yielded similar outcome. The incidence of CT-induced amenorrhea is regimen – and patient age-dependent; it was associated with improved outcome in some studies, but not in others. Aromatase inhibitors (AI) provide some additional benefit compared with Tam for postmenopausal women with ER+ tumors, but they are ineffective in the presence of premenopausal estradiol levels. Open questions concerning adjuvant treatment for premenopausal patients with endocrine responsive disease include: 1) What is the role of OFS? (some regard this question answered based on indirect evidence from trials in the adjuvant and advanced disease setting); 2) What is the role of AI? (requires ovarian ablation/suppression concurrent with AI); 3) What is the role of CT in addition to "optimal/maximal" endocrine therapy? (some would avoid the question especially if higher metastatic potential); 4) What is the optimal duration of GnRH analog ovarian suppression when combined with SERMs? (not feasible to study duration with aromatase inhibitor). Data are sparse because, in addition to breast cancer in younger women being a rare disease, positive results for CT in the 1970s (mainly for women in their forties) and misleading overview reports on Tam in the 1980s and 1990s inhibited evaluation of endocrine therapies for younger women. Thus, the adjuvant treatment of choice for individual premenopausal women with endocrine responsive disease is largely a matter of physician prejudice based on assessment of risk of relapse and relative role of endocrine versus cytotoxic approaches. To offer a randomized clinical trial as the treatment of choice for the largest number of premenopausal women with endocrine responsive disease, 3 tailored treatment investigations are being conducted globally by the BIG and the North American Breast Intergroup with the IBCSG serving as the coordinating group. The specific designs are the subject of another St. Gallen Conference abstract.

Background

- Premenopausal women represent 25% of breast cancer patients in Western countries.
- 50% of premenopausal women with breast cancer have estrogen-receptor positive (ER+) disease.
- Among premenopausal women treated with chemotherapy alone, those under 35 years of age with (ER+) tumors have the worst prognosis (Goldhirsch et al. *JNCI Monographs*. 2001;30:44-51).
- In some studies, adjuvant chemotherapy-induced amenorrhea was associated with reduced relapses and improved survival; < 50% of women under age 40 develop amenorrhea with CMF (Pagani et al. *Eur J Cancer*. 1998;34:632-540).

This group of very young women with ER (+) disease may potentially benefit from "maximal" adjuvant endocrine therapy with or without chemotherapy.

Current Treatment Options

- Chemotherapy, tamoxifen, and ovarian suppression (OFS) (pharmacologically or by surgery or radiation) are individually effective adjuvant treatments (Adjuvant Therapy for Breast Cancer. NIH Consensus Statement 2000 November 1-3; 17(4):1-35)

Adjuvant Therapy Options for Operable Hormone-Sensitive Breast Cancer in Premenopausal Women (from the International Breast Cancer Consensus Panel. Goldhirsch et al. *J Clin Oncol*. 2001;19:3817-3827)

Nodal Status	Risk Group	Treatment
Node-negative	Minimal/Low	Tamoxifen or none
Node-negative	Average/High	Ovarian ablation (or GnRH analog) + Tam (± CT) or CT + Tam (± ovarian ablation or GnRH analog) or Tam or Ovarian ablation (or GnRH analog)
Node-positive		CT + Tam (± Ovarian ablation or GnRH analog) or Ovarian ablation (or GnRH analog) + Tam (± CT)

Abbreviations: CT = chemotherapy; GnRH = gonadotropin-releasing hormone, Tam = tamoxifen.

- Gonadotropin releasing hormone (GnRH) analogs
 - Estrogen deprivation can be achieved by suppression of estrogen synthesis by GnRH analogs in premenopausal women (Adjuvant Therapy for Breast Cancer. *NIH Consensus Statement* 2000 November 1-3; 17(4):1-35)
 - Chemotherapy and OFS with GnRH analogs yield similar outcomes (Adjuvant Therapy for Breast Cancer. *NIH Consensus Statement* 2000 November 1-3; 17(4):1-35)
 - There is accumulating evidence that the addition of tamoxifen to OFS plus chemotherapy is superior to OFS plus chemotherapy without tamoxifen (Pritchard. *Cancer* 2000;88:3065-3072)

Results of GnRH Analog Adjuvant Therapy Trials

Study	Treatment	Disease Characteristics	DFS
ZEBRA (N=1640)	Zol vs CMF	Node(+) 74% ER(+)	Zol = CMF in ER(+)
AC05 (N=1088)	Zol+Tam vs CMF	Node(+)/(-) ER/PgR (+)	Zol + CMF better
GROCTA (N=244)	Tam+OFS vs CMF	Node(+)/(-) ER(+)	Tam+OFS = CMF
INT-0101 (N=1504)	CAF vs CAF+Zol vs CAF+Zol+ Tam	Node (+) ER/PgR (+)	CAF+Zol+Tam >CAF+Zol CAF+Zol > CAF (Trend, NS)
ZIPP (N=2710)	Zol added to standard therapy vs. standard therapy alone*	Node (+)/(-) 70% ER(+)	Zol + standard therapy > standard therapy
IBCSG VIII (N=1109)	Zol vs CMF vs CMF+Zol	Node(-) 68% ER(+)	Zol = CMF in ER(+) CMF+Zol better (Trend, NS)

*Standard therapy defined as ± radiotherapy ± chemotherapy ± tamoxifen
Abbreviations: CMF = cyclophosphamide, methotrexate, fluorouracil; CAF = cyclophosphamide, doxorubicin, fluorouracil; DFS = disease-free survival; NS = difference not statistically significant; OFS = ovarian function suppression; Zol. Zoladex 3.6 mg (a Gonadotropin-releasing hormone analog)

- Research shows strong and consistent improvements in disease free and overall survival with adjuvant tamoxifen (EBCTCG *Lancet*. 1998;351:1451-1467)
- Anti-aromatase agents (AIs)
 - Administration of an AI plus a GnRH analog provides significantly greater inhibition of circulating estrogens than treatment with a GnRH analog alone (Celio et al. *Anticancer Res* 1999;19:2261-2268)
 - Adjuvant AIs provide superior benefit compared with tamoxifen in postmenopausal women with ER+ tumors (The ATAC [Arimidex or Tamoxifen Alone or in Combination] Trialists' Group. *Lancet*. 2002;359:2131-2139)

Open Questions Related to Adjuvant Treatment of Premenopausal Women with Endocrine-Responsive Early Breast Cancer

1. What is the role of ovarian suppression (OFS)?

- Feasible for study in patients whose ovarian function is maintained because:
 - Chemotherapy was not given and ovarian function is unchanged
 - Chemotherapy was given and ovarian function is either unchanged or resumed
- Feasible for study in patients whose physicians are convinced that the most appropriate endocrine treatment is tamoxifen alone

2. What is the role of anti-aromatase agents in premenopausal women? (ovarian ablation required in combination with AI)

- Feasible exclusively for patients whose ovarian function was suppressed AFTER demonstration of efficient endocrine activity of the ovaries
- Feasible for investigators who are convinced that this approach does not require use of a SERM-alone control.
- Especially suitable for very young women
- Feasible for patients whose physicians are convinced that ovarian suppression is required in all women

3. What is the role of chemotherapy in combination with optimal or maximal endocrine therapy?

- Feasible exclusively for women whose physicians think that chemotherapy may be superfluous if "optimal" endocrine therapy is given
- Trials may be conducted using a GnRH analog in combination with either an anti-aromatase agent or a SERM

4. What is the optimal duration of GnRH analog ovarian suppression when combined with SERMs?

- Several studies in this population used tamoxifen for 5 years, but GnRH analogs were used for various durations (ie, 2, 3, or 5 years)
- Patient acceptance of OFS is a major limitation and it is not clear that GnRH should last for more than 2 years
- Feasible only for patients who receive a concurrent SERM; this approach cannot be used with anti-aromatase agents

Conclusions

Three tailored treatment investigations are being conducted globally in premenopausal endocrine responsive patients with breast cancer to address these questions. The trials are being conducted by the BIG and the North American Breast Intergroup, with the IBCSG serving as the coordinating group.

- For patients who remain premenopausal within 6 months after chemotherapy or those for whom tamoxifen alone is considered adequate:

- SOFT (Suppression of Ovarian Function Trial)

Tamoxifen vs

OFS + Tamoxifen vs

OFS + Exemestane

- For patients who should receive ovarian function suppression from the start of adjuvant therapy:

- TEXT (Tamoxifen and Exemestane Trial)

OFS ± Chemotherapy + Tamoxifen vs

OFS ± Chemotherapy + Exemestane

- PERCHE (Premenopausal Endocrine-Responsive Chemotherapy Trial)

OFS + Tamoxifen or Exemestane vs

OFS + Chemotherapy + Tamoxifen or Exemestane