IBCSG – International Breast Cancer Study Group IBCSG-Trial 11-93 Design: N+, ER+ or PgR+, Premenopausal Breast Cancer

Patient Population

Premenopausal patients with histologically proven breast cancer who have had either a total mastectomy with axillary clearance or a lesser procedure (quadrantectomy or lumpectomy) with axillary lymph node dissection and who are classified as T1a, b, c T2 or T3, pN1, M0 (UICC 1987) and are judged suitable for treatment with endocrine therapy alone. As a minimum, patients must have either estrogen or progesterone receptor-positive tumors (ER ≥ 10 fmol/mg or PgR ≥ 10 fmol/mg cytosol protein or positive by immunocytochemical assay).

Entry

Patients are randomized within 6 weeks after primary breast cancer surgery.

Stratification Factors

- Institution
- Type of primary therapy (mastectomy vs. local excision with radiation therapy planned vs. local excision without radiation therapy)
- Intended method of ovarian ablation (see below)

Randomization

Radiotherapy

For patients having breast conservation surgery, radiation therapy to the conserved breast is optional and to be carried out according to the prospectively defined guidelines of each participating institution.

Ovarian Ablation

Any of the following methods may be used:

- Bilateral surgical oophorectomy via laparotomy or laparoscopy *or*,
- bilateral ovarian radiation *or*,
- GnRH analogue e.g. goserelin every 28 days continued for 2 years or until the patient is 55 years old, whichever is the longer course.

Note – ovarian ablation initiated with GnRH analogue may be continued by oophorectomy or radiation therapy.

AC

A = doxorubicin 60 mg/m² *or* epirubicin 90 mg/m² i.v. day 1 every 21 days.

C = cyclophosphamide 600 mg/m² i.v. day 1 every 21 days.

Doxorubicin or epirubicin should be administered intravenously using all precautions to avoid extravasation.

AC should start immediately after the ovarian ablation procedure or at day 1 of GnRH analogue administration within 6 weeks of primary surgery.

Tamoxifen

20 mg daily to start for arm A immediately after the ovarian ablation procedure or at day 1 of GnRH analogue administration, or for arm B immediately after cycle 4 of AC (or immediately after any earlier discontinuation of AC) and continue for 5 years from randomization or until relapse.

Commentaries

1) Overview analysis of randomized trial data [1, 2] showed that several forms of adjuvant therapy were effective in prolonging overall and relapse-free survival in premenopausal patients with node-positive breast cancer. Prolonged multi-agent chemotherapy (and especially CMF), ovarian ablation, and tamoxifen (given alone without concurrent cytotoxic therapy) each showed highly significant efficacy.

Perhaps the most striking result of the 1990 overview was the rehabilitation of ovarian ablation as an effective adjuvant therapy capable of prolonging overall survival in early breast cancer. The 15 years update in 1995 confirmed the efficacy of ovarian ablation as an adjuvant treatment [3]. The trials on which this finding was based were in general performed before the availability of estrogen receptor measurement. Although some later trials considered the addition of ovarian ablation to cytotoxic therapy, trials to date give little evidence about the relative efficacy of ovarian ablation alone and ablation combined with cytotoxic therapy.

2) This trial compares a 'maximal' endocrine therapy with ovarian ablation and tamoxifen maintenance to the same treatment with the addition of a short chemotherapy preceding the tamoxifen maintenance as adjuvant therapy of patients with operable breast cancer and involved axillary lymph nodes. Because data are not available to allow definition of the group for which endocrine therapy alone is an acceptable option, the selection of patients for entry to this study will be at the discretion of the participating investigators, provided that the patient's tumor has at least one receptor (ER or PgR) positivity. This restriction is based largely on the trend in our own trial II, in which the additional benefit of ablation seems confined to ER receptor-positive patients.

3) To ensure adequate patient accrual given varying practices of ovarian ablation in different centers, a variety of optional

methods of ovarian ablation – surgical oophorectomy, radiotherapy or GnRH analogue – are acceptable. Surgical or radiation ovarian ablation should be completed before any other adjuvant systemic therapy.

4) The design of this trial is also influenced by emerging results from trial II, which used CMF for 12 cycles with or without surgical oophorectomy in premenopausal patients with 4 or more involved axillary lymph nodes [4, 5]. A benefit in disease-free and overall survival favoring CMF plus oophorectomy over CMF alone, and confined to the ER-positive subset, is emerging with prolonged follow-up. No arm involving cytotoxic therapy alone is therefore included in this study.

5) Experience from the National Cancer Institute in Milan (INT) [6] and the National Surgical Adjuvant Breast Project (NSABP) [7] has suggested the value of initial therapy with an anthracycline (doxorubicin) given alone (INT) or with cyclophosphamide (NSABP) before CMF chemotherapy. There is also interest concerning the studies of NSABP and the Cancer and Acute Leukemia Group B (CALGB) trials in the concept of increased dose intensity [8]. It has proved difficult to deliver increased dose intensity with CMF-based regimens, while treatments with anthracyclines and alkylating agents can be escalated significantly. Thus, in a trial aimed at investigating optimal chemotherapy, we have chosen to incorporate an anthracycline regimen, while leaving the choice of doxorubicin or epirubicin to the participating institutions.

Information

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References

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