Direct comparisons of adjuvant endocrine therapy, chemotherapy, and chemoendocrine therapy for operable breast cancer patients stratified by estrogen receptor and menopausal status

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Summary

Based on estrogen receptor (ER) and menopausal status, operable breast cancer (UICC stage I, II, III-a) patients were randomized for adjuvant endocrine therapy, chemotherapy, and chemoendocrine therapy, and the effects on the relapse-free survival (RFS) and overall survival (OS) were compared. Tamoxifen (TAM) 20 mg/day was administered orally for 2 years after mastectomy as an adjuvant endocrine therapy in postmenopausal patients. In premenopausal patients, oophorectomy (OVEX) was performed before TAM administration. In the chemotherapy arm (CHEM), patients were given 0.06 mg/kg of body weight of mitomycin C (MMC) intravenously, followed by an oral administration of cyclophosphamide (CPA) 100 mg/day in an administration of a 3-month period and a 3-month intermission. This 6-month schedule was repeated 4 times in 2 years. The chemoendocrine arm (CHEM + TAM) was composed of TAM with MMC + CPA chemotherapy. The patients were randomized according to ER and menopausal status. ER-positive patients were randomized to three arms: OVEX + TAM, CHEM, and CHEM + TAM. For ER-negative patients there were two arms: CHEM and CHEM + TAM. 1579 patients entered the trial between September 1978 and December 1991, with median follow-up of 8.2 years. In ER positive, premenopausal patients, there were no significant differences in RFS or OS among OVEX + TAM, MMC + CPA, TAM + MMC + CPA arms. On the contrary, in ER-positive, postmenopausal patients, the chemoendocrine therapy showed a significantly higher RFS (p = 0.0400) and OS (p = 0.0107) as compared with TAM to chemotherapy alone. There were no significant differences in RFS or OS by addition of TAM on the chemotherapy, in both pre- and post-menopausal ER-negative patients. It was concluded that in ER-positive premenopausal breast cancer, endocrine therapy alone may be equivalent in prolonging RFS and OS to chemotherapy or chemoendocrine therapy, and that ER-positive postmenopausal breast cancer may be better controlled with the combination of TAM and chemotherapy, as compared to TAM or chemotherapy alone. The importance of stratification of operable breast cancer by ER and menopausal status, as well as the direct comparisons of different treatments, were stressed.

Introduction

In the overview analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [1], ovarian ablation shows an absolute reduction in long-term risk of recurrence or mortality among

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women aged under 50 (most of whom were presumably premenopausal), even in the mixed population of ER (estrogen receptor)-positive and ER-negative patients. On the contrary, tamoxifen has been evaluated to be less effective in this patient group in reducing risk as compared indirectly with postmenopausal patients or with polychemotherapy. In premenopausal patients, recurrence and mortality were significantly reduced by polychemotherapy, while the treatment was shown to be less potent in postmenopausal women. This paradigm that polychemotherapy is recommended for premenopausal patients and tamoxifen for postmenopausal was essentially based partly upon indirect comparisons of the treatments [1]. There have been a few investigations which compare directly different kinds of treatment: chemotherapy versus endocrine therapy for pre- or post-menopausal patients, separately.

In premenopausal women with pathological stage II breast cancer, the Scottish trial group [2] has confirmed no significant overall difference in relapse rates, or in event-free or total survival, for ovarian ablation compared with CMF chemotherapy. In patients with ER-positive (> 20 femoles/mg protein), ovarian ablation was associated with improved survival, and CMF chemotherapy was more beneficial for patients with values less than the cut-off level. They concluded that ER status has a role in decisions about adjuvant treatment for primary breast cancer.

In the current report, we present a prospective randomized trial of adjuvant endocrine therapy, chemotherapy, and chemo-endocrine therapy for operable breast cancer stratified by ER and menopausal status of the patients, and suggest the importance of direct comparisons of different treatments in the adjuvant therapy. A preliminary report was previously published [3].

Patients and methods

In this one-institutional trial, we have randomized early breast cancer patients into treatment arms according to ER and menopausal status. The ER assay was performed in the primary breast cancer tumor using the dextran-coated charcoal method, as described in the previous reports [3, 4]. Tumors with a 3.0 fmol/mg of protein of the binding or more were designated to be positive for receptors. Progesterone receptors were simultaneously assayed in most cases, but were not related to the randomization of the patients.

Premenopausal status was defined when the menstruation was confirmed within 12 months before the operation day. When a patient younger than 51 had undergone hysterectomy with at least one ovary remained, we included the patient in the premenopausal group. Others were considered as postmenopausal. Randomization of operable breast cancer patients was done by means of the envelop method according to the ER status and the menopausal status of the patients, as indicated in Figure 1. Premenopausal patients with ER-positive cancers were randomized into 3 treatment arms: (1) endocrine therapy: oophorectomy (OVEX) performed within 2 weeks after mastectomy, followed by the oral administration of tamoxifen (TAM) 20 mg/day for 2 years (OVEX + TAM); (2) chemotherapy: mitomycin C (MMC), 0.06 mg/kg of body weight intravenously in 2 days (day 1 after operation, 0.04 mg/kg and day 2, 0.02 mg/kg), and thereafter oral administration of cyclophosphamide (CPA) 100 mg/day for 3 months with intermission of CPA in the next 3 months (i.e., 3 months administration and 3 months intermission). This 6-month intermittent schedule was repeated four times in 2 years (MMC + CPA); and (3) chemo-endocrine therapy with the same schedule as in the chemotherapy arm with MMC + CPA, in combination with TAM with the same schedule as in the endocrine therapy arm (MMC + CPA + TAM). However, OVEX was not performed in this group of the patients.

In postmenopausal patients with ER-positive cancers, the adjuvant therapy consisted of 3 treatment arms in the randomization: (1) endocrine therapy with TAM; (2) chemotherapy with MMC + CPA and (3) chemo-endocrine therapy with MMC + CPA + TAM. Pre- and post-menopausal patients with ER-negative tumors were randomized into two treatment arms, respectively; (1) MMC + CPA and (2) MMC + CPA + TAM. Pre- and post-menopausal patients with unknown ER status (mainly