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ORIGINAL ARTICLE

Toru Watanabe

Phase III randomized comparison of postoperative adjuvant chemotherapy with 2-year oral uracil/tegafur versus 6-cycle cyclophosphamide/methotrexate/5-fluorouracil in high-risk node-negative breast cancer patients

Abstract The value of cyclophosphamide/methotrexate/5-fluorouracil (CMF)-type regimens in surgical adjuvant therapy in certain subsets of patients with axillary lymph node-negative breast cancer has been evaluated in Europe and the USA. However, Japan has a distinctive standpoint regarding the indications for surgical adjuvant chemotherapy for breast cancer patients. In addition, oral fluoropyrimidines are widely used to treat breast cancer patients in both adjuvant and metastatic settings due to their low toxicity and convenience for long-term administration. Although the antitumor activity and the ability to prolong disease-free survival times of oral fluoropyrimidines have been evaluated in patients with breast cancer, available data are not sufficient to justify replacing CMF-type regimens with oral fluoropyrimidines in postoperative chemotherapy for breast cancer patients. To evaluate the utility of oral fluoropyrimidines in surgical adjuvant chemotherapy, the National Surgical Adjuvant Study Group (N-SAS) was founded in 1995 as a government-funded research group, and nationwide multiinstitutional trials were designed for breast cancer as well as colon and gastric cancers. For high-risk, node-negative breast cancer patients, a prospective randomized trial of surgical adjuvant chemotherapy comparing 6 cycles of CMF with 2 years of daily uracil/tegafur (UFT) started in October 1996. The endpoints of this study include disease-free and overall survival, adverse reactions, quality of life, and cost.

Key words Uracil · Tegafur · Cyclophosphamide · Methotrexate · 5-FU · Phase III

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T. Watanabe
Department of Medical Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104 Japan
Tel. +81 3 3542 2511; Fax +81 3 3542 3815

Introduction

Several international consensus meetings have established the indications for surgical adjuvant chemotherapy using regimens comprising a combination of cytotoxic drugs such as cyclophosphamide, methotrexate, and 5-fluorouracil (5-FU) (CMF) in certain subsets of patients with axillary lymph node-negative breast cancer. The recommendations of these meetings were based on data obtained from large-scale clinical trials and metaanalyses [1, 2].

Japan has long maintained a distinctive standpoint concerning this issue. Two widely held views are the basis for the lack of rigorous evaluation of postoperative combination chemotherapy for breast cancer patients. The first view is that breast cancer in Japanese women is biologically less aggressive than that in Caucasian women. Evidence to support this view includes the 5-year disease-free survival rate in Japanese node-negative breast cancer patients, which is approximately 90% and thus better than that observed in European or US women [3]. The prevailing opinion among Japanese surgeons is that cytotoxic chemotherapy using drugs of moderate or severe toxicity is not indicated in node-negative breast cancer patients. Secondly, oral fluoropyrimidine compounds such as uracil/tegafur (UFT) (Taiho Pharmaceutical Co., Tokyo, Japan) and doxifluridine (Japan Rosch Co. Ltd., Tokyo, Japan) are used widely to treat breast cancer patients in both adjuvant and metastatic settings due to their low toxicity and convenience for long-term administration.

UFT is a combination of tegafur (1-(2-tetrahydrofuranyl)-5-fluorouracil) and uracil at a molar ratio of 1:4. Tegafur is a prodrug which is slowly metabolized to 5-FU. Preclinical studies indicated that UFT produces significantly higher tumor:serum 5-FU ratios than were observed with tegafur alone [4]. UFT is administered orally and is active against gastric, colon, rectal, and breast cancers [5]. The major reported side effects are gastrointestinal toxicity such as nausea/vomiting and diarrhea, which occur in $<10\%$ of patients who receive oral UFT at a dose of 300–400 mg/day for 2 years [6]. Although oral

UFT has been evaluated for its antitumor activity in metastatic breast cancer [7] and prolongation of disease-free survival time in patients with stage II breast cancer [8], the data available are not sufficient to justify replacing CMF-type regimens with oral UFT as postoperative chemotherapy for breast cancer patients.

National Surgical Adjuvant Study Group of Breast Cancer

To assess the usefulness of antineoplastic agents already available on the market, a government-funded program for developing guidelines for the appropriate conduct of clinical trials of chemotherapeutic agents in the context of surgical adjuvant therapy was founded in 1995 with Kaoru Abe, president, National Cancer Center, Japan, as its chair. In accordance with the guideline draft, the National Surgical Adjuvant Study Group (N-SAS) was organized to conduct clinical trials of postoperative adjuvant chemotherapy for breast cancer (N-SAS-BC), colon cancer (N-SAS-CC), and gastric cancer (N-SAS-GC). Initially, UFT was selected as the trial drug and nationwide multi-institutional trials were designed for these 3 cancers supported by a trust fund from Taiho Pharmaceutical Co.

N-SAS-BC 01 protocol

Objectives

The objectives of N-SAS-BC 01 are to: 1) compare the disease-free survival and overall survival rates after 2-year treatment with oral UFT 300 mg/m^2 and 6 courses of CMF in women with high-risk, node-negative breast cancer; and 2) assess the adverse reactions, quality of life, and cost-effectiveness in patients treated using these regimens.

Selection of high-risk patients from among node-negative breast cancer patients

The presence or absence of metastatic involvement in the axillary lymph nodes is the most powerful prognostic factor for patients with primary breast cancer. In node-negative breast cancer patients, 5- and 10-year disease-free survival rates are 92% and 83%, respectively, according to the National Cancer Center database. To select node-negative breast cancer patients who were at higher risk for recurrence, determination of tumor size, estrogen receptor status, and pathological tumor grade were recommended [1]. Because a single reliable criterion for evaluating pathological grade has not been established, the N-SAS-BC Pathology Committee developed new grading criteria for this study. These criteria categorize node-negative breast cancer as grade 1 to grade 3 based on the nuclear grade, which in turn is based on nuclear atypia and mitotic counts. Five-year disease-free survival rates in patients with nuclear grade 2 or 3 was between 75% and 80%. By extrapolating the 5-year disease-free survival rate, the 10-year disease-free survival rate is expected to be 60–70%. Thus by choosing patients with grade 2 and 3 breast cancer according to the N-SAS-BC pathological grading criteria, patients with a higher risk of recurrence can be selected, increasing the proportion of such patients in study populations three-fold.

Statistical considerations

Tests of the equivalency concept were employed for this study to compare the potency of 2-year oral UFT versus 6-course CMF in terms of improvement of 5-year disease-free survival. The clinically acceptable range for UFT was first determined by surveying 78 N-SAS participating physicians using a questionnaire. The results of this questionnaire indicated that in a patient population where 5-year disease-free survival is 70% with no surgical adjuvant chemotherapy and 80% with CMF, the upper and lower acceptable limits for 5-year disease-free survival rate were 87.5% and 72.5%, respectively. This translates to a UFT:CMF hazard ratio for tumor recurrence of 0.77–1.30. With α error = 0.05 and β error = 0.20, the required sample size for each treatment arm was calculated to be 650 [9]. Follow-up duration was set at 5–10 years depending on the number of recurrences observed in the period. A total of 1300 patients from 42 participating institutions are scheduled to be accrued over 3 years.

Patient eligibility criteria

Patients with node-negative, histologically confirmed breast carcinoma (clinical stage I–IIIA) confined to a single breast are eligible for the study. Other eligibility criteria include no evidence of lymph node metastasis on pathological examination of level I and II lymph nodes, exclusion of distant metastasis using chest X-ray, bone X-ray, and liver ultrasound scan or computed tomography scan, breast-conserving surgical procedure with or without radiotherapy, total mastectomy or radical mastectomy $\leq$12 weeks prior to the initiation of chemotherapy, and high risk for recurrence as determined according to the N-SAS histopathological grading score. Patients must be aged $>$18–75 years, of Eastern Cooperative Oncology Group performance status 0–1, and have adequate organ function. Patients with inflammatory breast cancer are excluded. Written informed consent is mandatory.

Randomization procedure

Eligible patients are randomized to one of the 2 treatment regimens after registration at the N-SAS data center by telephone or facsimile. Stratification factors include participating institution, pathological tumor size ($<$3.0 cm vs $\geq$3.0 cm), age at registration ($\leq$49 years vs $>$50 years), hormone receptor status (both negative vs others), operation

mode (breast conservation vs mastectomy), and postoperative radiation.

Treatment regimens

Patients allocated to the UFT arm receive UFT 300 mg/m^2/day (as 100-mg capsules) po daily for 2 years. Patients in the CMF arm receive CPA 100 mg (as a 50 mg tablet) po on days 1 to 14, methotrexate 40 mg/m^2 i.v., and 5-FU 500 mg/m^2 i.v. on days 1 and 8. Treatment cycles are repeated every 28 days for 6 cycles. Tamoxifen 20 mg/day daily for 2 years is added to both regimens unless patients are both estrogen and progesterone receptor negative.

Conclusions

The majority of patients with breast cancer are not cured by chemotherapy once the disease has metastasized. Prevention of clinical recurrence is the aim of perisurgical adjuvant therapy, which is being intensively tested according to patients' prognostic and predictive factors.

Oral chemotherapeutic agents such as UFT may have several advantages such as lower toxicity, painless administration, and reduced number of hospital visits for patients who are proved to be disease free. Therefore each treating physician must recognize the inadequacy of the evidence indicating the routine use of oral fluoropyrimidines in adjuvant chemotherapy in patients with node-negative breast cancer and urge all eligible patients to participate in well-designed clinical trials. As CMF-type chemotherapy is one standard regimen, but not the best, the best approach for the patient is an experimental one designed to improve the total benefit of chemotherapy for patients. If a patient with high-risk, node-negative breast cancer is not eligible or does not wish to participate in a clinical trial, CMF, as inadequate as it is, remains the standard against which all other therapies must be compared.

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