Efficacy and Toxicity of Vinorelbine with Doxorubicin/Cyclophosphamide Combination Chemotherapy in a Phase I-II Study for Advanced or Recurrent Breast Cancer Patients


*Department of Surgery, National Shikoku Cancer Center Hospital, Matsuyama, **Department of Surgery, National Sapporo Hospital, Sapporo, **Department of Endocrinology, Saitama Cancer Center, Saitama, **Department of Medical Oncology, National Cancer Center Hospital, Tokyo, **Department of Internal Medicine, Miyazaki Prefectural Hospital, Miyazaki, **Department of Surgery, National Osaka Hospital, Osaka, **Department of Surgery, Hamamatsu Medical Center, Hamamatsu, **Department of Breast Oncology, Saitama Medical School, Saitama, **Department of Surgery, National Hakodate Hospital, Hakodate, **First Department of Internal Medicine, School of Medical, Fukuoka University, Fukuoka, **Department of Surgery, Kansai Rosai Hospital, Hyogo, **Department of Surgery, Saitama Medical School, Saitama, **First Department of Internal Medicine, School of Medical, Fukuoka University, Fukuoka

Background: To evaluate the efficacy and toxicity of vinorelbine (VNB) with doxorubicin/cyclophosphamide (AC) combination chemotherapy, a phase I-II study was carried out in patients with advanced or recurrent breast cancer.

Methods: The phase I part of this study was carried out to determine the treatment schedule and acceptable dose of VNB for the phase II study. In phase I, VNB was initially given as a short infusion on days 1, 8 and 15, every 4 weeks. The initial dose of vinorelbine was 15 mg/m2. In the AC regimen, 20 mg/m2 of doxorubicin (ADM) was given intravenously (i.v.) on days 1 and 8, and 100 mg/body of cyclophosphamide (CPA) was administered orally from days 1 to 14. Subsequently, a phase II study was carried out at the maximum acceptable dose (MAD).

Results: Twenty-three patients were entered into this study. In patients receiving VNB at a dose of 15 mg/m2, neutropenia (≥grade 3) frequently occurred on day 15. The treatment schedule of this study was therefore changed to VNB given IV on days 1 and 8 with AC combination chemotherapy. In this treatment schedule, grade 4 neutropenia lasting for more than 4 days occurred in patients given VNB at a dose of 20 mg/m2 with AC more frequently than in those given 15 mg/m2 of VNB. Therefore, the MAD of VNB was determined to be 20 mg/m2 in this regimen. At this recommended dose, there were 1 complete (CR) and 8 partial responses (PRs) in 15 patients, with an overall response rate of 60.0%. No treatment-related death occurred.

Conclusions: These data indicate that VNB plus AC combination chemotherapy was effective and well tolerated for breast cancer patients. A randomized trial of VNB plus AC vs. AC combination chemotherapy may be required to ascertain the benefit of this regimen for advanced or recurrent breast cancer patients.


Key words: Vinorelbine, Doxorubicin, Cyclophosphamide, Advanced or metastatic breast cancer, Phase I-II trial

Introduction

Recently, breast cancer has become the most common malignancy in women, and in Japan 30,000 women develop breast cancer per year. For advanced or recurrent breast cancer, anthracycline-containing combination regimens such as FAC (F, 5-FU; A, doxorubicin; C, cyclophosphamide) and doxorubicin/cyclophosphamide (AC) are commonly used as first-line chemotherapy, since doxorubicin (ADM) and cyclophosphamide (CPA) are among the key agents for

Reprint requests to Toshiaki Saeki, Department of Breast Oncology, Saitama Medical School, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama, 350-0495, Japan

Received December 27, 2004, accepted January 11, 2006
Saeki T, et al

Study of Vinorelbine with ADM/CPA

breast cancer treatment\(^\text{[3]}\). In fact, for Japanese breast cancer patients, AC combination chemotherapy is highly effective and well tolerated\(^\text{[4]}\). Nevertheless, despite the progress achieved in providing either tumor reduction or improvement of quality of life, it has failed to prolong the survival of these patients. The main cause for the poor prognosis may be a low incidence of complete responses in the responding patients treated with conventional chemotherapy such as an AC combination regimen. To improve the poor prognosis of these patients, an intensive combination chemotherapy must be developed. At present, the most promising new anti-cancer agents are taxanes, but these agents have severe hematopoietic toxicity when used in combination with anthracycline. One promising cytotoxic drug for breast cancer is vinorelbine (VNB), which demonstrates a high response rate against breast cancer when used in combination with anthracycline\(^\text{[5]}\). VNB is a new vinca alkaloid that shows high antitumor activity in advanced breast cancer\(^\text{[6]}\). The main mechanism of VNB is an inhibitory effect on mitotic tubulin, like the classical vinca alkaloids. Alkylating agents exhibit a steep dose response effect, and some alkylating agents have demonstrated less cross-resistance and possess therapeutic synergy when used in combination with other alkylating agents. In this regard, a combination of VNB and CPA may potentially be superior to either alone. VNB and CPA may have the common toxicity of myelosuppression but differ in major non-myelosuppressive dose-limiting toxicity. VNB has mild neurotoxicity, while CPA can cause hemorrhagic myopericarditis and hemorrhagic cystitis. Therefore, a new combination chemotherapy regimen containing VNB and AC has been designed. To ascertain if vinorelbine + doxorubicin + cyclophosphamide might be a useful treatment for breast cancer patients, we analyzed the efficacy and toxicity in a multi-institutional phase I-II study.

Materials and Methods

Eligibility Criteria

Women with histologically diagnosed advanced or recurrent breast cancer, with a PS of 0 to 2, aged 20 to 75 years, and an estimated life expectancy greater than 4 months were eligible for this study. The patients had to have received prior treatment and had at least one evaluable lesion. Any previous chemotherapy as first- or second-line treatment was allowed except FU derivatives; however, patients who had received ADM (≥250 mg/m\(^2\)) were excluded. At least 4 weeks had to have passed after the last dose of previous chemotherapy or radiotherapy before the study start. Patients had to have had leukocyte counts ≥4,000/mm\(^3\); hemoglobin ≥9.0g/dl; thrombocyte counts ≥10,000/mm\(^3\); bilirubin ≤2.0mg/dl; SGOT, SGPT, and Al-P ≤2.5x the upper limit of normal at each institution; serum creatinine ≤1.5 mg/dl; PaO\(_2\) ≥ 70 mmHg; and ejection fraction ≥ 50%. Patients with clinically significant neuropathy, infection, or symptomatic brain metastases were excluded.

This protocol was accepted by the clinical trial reviews committee of each institution. Written informed consent was obtained from all patients.

Treatment Schedule

Phase I study

To determine the treatment schedule and a maximum acceptable dose (MAD) of VNB in combination with an AC regimen, a phase I study was carried out. Initially, a temporary protocol was designed: briefly, on days 1, 8 and 15, 15 mg/m\(^2\) of VNB (Navelbine; Kyowa Hakko Kogyo Co., Tokyo, Japan) was given as a short infusion, followed by 20 mg/m\(^2\) of ADM (Kyowa Hakko Kogyo Co, Tokyo, Japan) given intravenously (i.v.) on days 1 and 8. Those drugs were given every 4 weeks. In addition, CPA was given orally from days 1 to 14. The dose escalation was to be suspended when any of the following toxic events occurred; grade 4 neutropenia or grade 4 leukopenia with an infectious episode, grade 4 thrombocytopenia, hepatic/renal toxicity (≥grade 3), non-hematological toxicity (≥grade 3), and violation of treatment schedule due to these toxicities. The dose causing these events in more than 50% of the patients was regarded as the maximum tolerated dose (MTD), the preceding dose being considered as the MAD.

Phase II study

Based on the results of the phase I study, the MAD of VNB with AC combination chemotherapy was determined to be 20 mg/m\(^2\) with a treatment schedule of VNB on days 1 and 8. On days 1 and 8, 20 mg/m\(^2\) of ADM was given i.v. and 100 mg/body of CPA was orally administered from days 1 to 14. On day 1, when the white blood cell