RESEARCH COMMUNICATION

A Cisplatin and Vinorelbine (NP) Regimen as a Postoperative Adjuvant Chemotherapy for Completely Resected Breast Cancers in China: Final Results of a Phase II Clinical Trial

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Abstract

Objective: To evaluate the efficacy and toxicity of cisplatin and vinorelbine (NP) for postoperative adjuvant chemotherapy of completely resected breast cancers. Methods: Between September 1994 and April 2005, 91 Chinese breast cancer patients, with pathologically-confirmed adenocarcinoma in Jiangsu Cancer Hospital and Research Institute, were enrolled. They received postoperative vinorelbine at 25mg/m^2 on days 1 and 8, and cisplatin 25mg/m^2 on days 1 to 3, this regimen being repeated every 3 weeks. Results: Median age was 49 years (range, 25-69 years). A ccording to the TNM stage system, stage I, II, IIIA patients accounted for 7.7%, 58.2% and 34.1%, respectively. The median number of chemotherapy cycles was 4.5 (range, 1-8), over half of the patients receiving 4 to 6 NP cycles. After a median follow-up of 48 months, 11 deaths and 29 relapses were documented. Median disease-free survival was 45 months, with disease-free and overall survival at 5 years being 76% and 88.7%, respectively. All patients could be evaluated with regard to toxicity, 17 (18.7%) developing grade III neutropenia during treatment, but all recovering after recombinant human granulocyte colony stimulating factor (G-CSF) injection, 3 suffering thrombocytopenia (3.3%), 5 anemia (5.5%) and 5 nausea/vomiting (5.5%). No treatment related deaths occurred. Conclusions: NP is an effective and feasible treatment for completely resected breast cancer cases at the doses tested. A randomized clinical trial is now needed to compare NP with other conventional regimens.

Keywords: Breast cancer - adjuvant chemotherapy - vinorelbine - cisplatin

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Introduction

Despite advances in early diagnosis and treatment, breast cancer remains a significant public health concern, with more than a million new cases diagnosed annually, resulting in >400,000 deaths worldwide (Ferlay et al., 2004). Of particular significance, the incidence and mortality rate of breast cancer increased sharply in China over the last couple of decades (Yu et al., 2007). It has been estimated that 121,269 new cases of breast cancer were diagnosed in China in 2000 and 168,013 in 2005 (Yang et al., 2005). Postoperative adjuvant chemotherapy can substantially reduce the risk of recurrence and death among surgically treated patients (Mamounas et al., 2005) and in China regimens in line with the NCCN (National Comprehensive Cancer Network) guidelines are established important components of medical management for breast cancer. In the adjuvant setting these include: cyclophosphamide in combination with methotrexate and fluorouracil (CMF); doxorubicin and cyclophosphamide (CA); fluorouracil, doxorubicin, and cyclophosphamide (FAC); and fluorouracil, epirubicin, and cyclophosphamide (FEC). However, CMF treatment with for six months results in permanent ovarian failure in 70 percent of women over 40 years of age and in 40 percent of younger women (Goodwin et al., 1999), the majority of women gaining weight and suffering from associated adverse effects like hypertension (Camoriano et al., 1990). The FEC regimen is also associated with adverse influences, especially increased risk of cardiotoxicity and secondary leukemia (Cardoso et al., 2002). Taxanes such as paclitaxel and docetaxel are reported to cause hypersensitivity reactions, peripheral neuropathy, myalgias, and arthralgias, and paclitaxel may exacerbate doxorubicin-related cardiotoxicity (Nabholtz et al., 2001; Nabholtz et al., 2003). In addition, docetaxel may cause fluid accumulation (Camoriano et al., 1990). Therefore, efforts have been made to find alternative effective regimes with acceptable toxicity as postoperative adjuvant chemotherapy for breast cancer patients.

Vinorelbine has been widely used for metastatic breast cancer (MBC). Used as a single agent, response rates are 41%-50% (Fumoleau et al., 1993; Garcia-Conde et al., 1994; Bruno et al., 1995; Weber et al., 1995), while in combination therapy, reported overall response rates are 52.9%-77% with docetaxel (Fumoleau et al., 1997),

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paclitaxel (Romero et al., 1999), doxorubicin (Martin et al., 2004), and/or trastuzumab (Burstein et al., 2001). At present, there is only very limited literature on vinorelbine-cisplatin (NP) as a postoperative adjuvant regimen for breast cancer, but the results appear promising (Shamseddine et al., 2005). Therefore we designed the present phase II study to investigate its efficacy focusing on a group of patients with completely resected lesions. A secondary objective was to estimate disease-free and overall survival rates.

Materials and Methods

Patients

Patients eligible for this study had a histologically confirmed diagnosis of breast cancer (stages I, II, IIIA), no prior history of cytotoxic chemotherapy or hormonal therapy, a Karnofsky performance status (KPS) >=70, and adequate haematological, hepatic and renal functions. The study was approved by the ethics committee of Jiangsu Cancer Hospital Institute, and all patients gave informed consent.

Treatment

Patients who were eligible for the study received cisplatin at a dose of 25mg/m^2 on days1 to 3 in 500 mL normal saline intravenously over 1 hour, and vinorelbine at a dose of 25 mg/m^2 in 50 mL of normal saline by intravenous infusion over 7-10minutes on days 1 and 8 of each cycle. For prophylaxis of acute and delayed emesis, antiemetic therapy with a serotonin antagonist was also given intravenously on days1 to 3 of each cycle. In addition, all patients received 5mg of dexamethasone intravenously after vinorelbine to alleviate irritation to blood vessels. Chemotherapy cycles were repeated every 3 weeks. Complete blood counts were obtained weekly, and a full serum chemistry profile and ECG were obtained prior to each new cycle of chemotherapy.

Toxicity

Clinical items including toxicity scores and vital signs, performance status (KPS), blood counts, and chemistry profile were recorded on special forms at regular intervals during follow-up visits. All symptoms of toxicity were evaluated according to the National Cancer Institute criteria (version 3.0).

Relapse-free and Overall Survival

Disease-free survival was calculated from the date of surgery to the date of first relapse, or to the date of death. Overall survival was calculated from the date of surgery to the date of death or to the date of data censoring (for women who remained alive). Survival curves were constructed with the use of Kaplan-Meier methods (Kaplan, 1958).

Results

Patient details

Ninety-one patients were recruited to the study from September 1994 until April 2005. All were assessable for toxicity, and disease-free as well as overall survival. The median age was 49 years (range 25-69). Out of the total of 91, 84 (92.3%) had infiltrating ductal carcinomas, 4 (4.4%) had infiltrating lobular carcinomas, and 3 (3.3%) had other pathological types. General patient characteristics are summarized in Table 1.

Table 1. Patient Characteristics

	n (%)
Age	
≤50yr	56 (61.5)
>50yr	35 (38.5)
Estrogen receptor	
Positive	36 (39.5)
Negative	35 (38.5)
Unknown	20 (22.0)
Progesterone receptor	
Positive	34 (37.4)
Negative	38 (41.7)
Unknown	19 (20.9)
Her-2 receptor	
Positive	30 (33.0)
Negative	37 (40.6)
Unknown	24 (26.4)
Stage	
I	7 (7.7)
IIa	24 (26.4)
IIb	29 (31.9)
IIIa	31 (34.0)

Table 2. Symptoms of Toxicity and Grades

	Grade I	Grade II	Grade III	Grade IV	%
Neutropenia	18	10	17	0	49.5
Thrombocytopenia	35	12	3	0	54.9
Anemia	30	17	5	0	57.1
Neurotoxicity	6	0	0	0	6.6
Nephrotoxicity	1	0	0	0	1.1
Nausea/vomiting	36	9	5	0	54.9
Alopecia	3	0	0	0	3.3
Stomatitis	5	0	0	0	5.5
Phlebitis	23	6	0	0	31.9

Table 3. Sites of Metastasis During Follow-up

Site	Number of Patients	Percentage(%)
Bone	10	34.5
Liver	1	3.4
Lung	6	20.7
Brain	2	6.9
Distant lymph nodes	7	24.1
Skin/chest wall	8	27.6

Toxicity

Hematological and non-hematological symptoms of toxicity by worst grade for all patients are listed in Table 2. During treatment with NP, 59.3% patients had grade II and 33% had grade III toxic effects, grade IV not being observed. Anemia was generally mild. Grade III neutropenia was encountered in 18.7% of the patients. Only 3 patients (3.3%) had grade III thrombocytopenia. There was no evidence of any cumulative hematological toxicity, grade III/IVphlebitis or sensory neuropathy. However, vinroelbine-related low grade phlebitis was frequent, occurring in 29 patients (31.9%). Nausea/

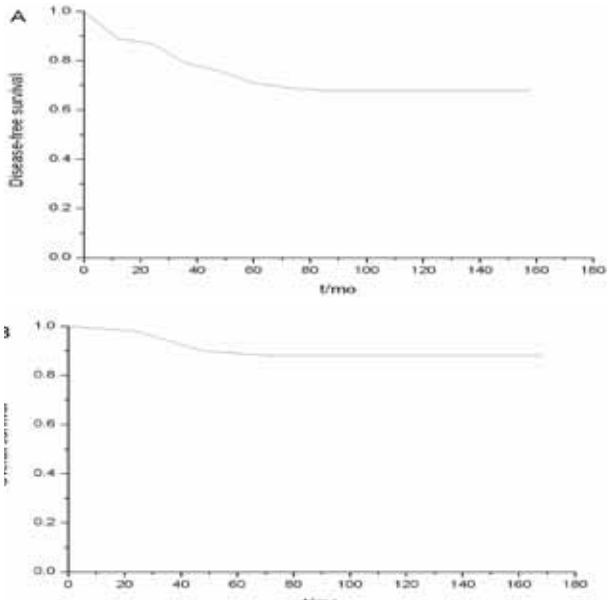

Figure 1. 10-yr Survival Curves for the Groups Receiving NP (Vinorelbine-cisplatin). A: Disease-free; B: Overall

vomiting was the most frequent non-hematological symptom toxicity, grade III nausea/vomiting being noted in 5 (5.5%). Three patients experienced alopecia (3.3%). There were no deaths attributed to chemotherapy treatment.

Disease-free and Overall Survival

After a median follow-up of 48 months, 11 women had died. The median time to progression was 45 months (range 1-160) and to death was 40 months (range 2-133). All recorded causes of death were breast cancer. Visceral metastasis (lung, liver) occurred in 7 patients (29.0%), while nonvisceral metastasis (bone, brain, lymph nodes, and skin metastasis) occurred in 25 (80.6%) (Table 3).

The estimated rates of disease-free survival at 5 and 10 years were 77% and 70% , and for overall survival were 89.9% and 85.7%, respectively (Figure 1A and B).

Discussion

In this study, at a median follow-up of 48 months, the estimated rate of disease-free and overall survival at 5 years were 77% and 89.9%, respectively in the NP group. This response rate is somewhat similar to that reported earlier for vinorelbine in combination with doxorubicin (Martin et al, 2004) trial, indicating equivalent efficacy to other regimens. The profiled of hematological and nonhematological toxicity in our trial were also moderate and manageable, neurotoxicity and nephrotoxicity being infrequent as found in pervious studies of the same agents after anthracyclin therapy of breast cancer (Ray-Coquard et al., 1998) or as a salvage regimen Gunel et al., 2000). In our view, these data further consolidate the applicability of NP chemotherapy as an option in the management of postoperative breast cancer.

In general treatment-related side effects are the major problem limiting the application of chemotherapy. For example clinical utility of anthracyclines is reduced in both early and advanced breast cancer, leading to cardiotoxicity (Jensen, 2006), leading to therapy discontinuation, hospitalization and clinically significant congestive heart failure (CHF) (Jensen, 2006). It is therefore reassuring to note that most of our patients (63.7%) completed 4 to 6 treatment cycles. The vinorelbine-cisplatin regimen was well tolerated and the main symptom of toxicity was myelosuppression, particularly neutropenia. Fortunately, with the support of prophylactic G-CSF, all the patients could complete their treatment cycles. Neurotoxicity and nephrotoxicity were also infrequent.

The rationale to combine cisplatin and vinorelbine in this study is primarily based on their toxicity profile and documented activity and synergism in other models. Vinorelbine is a myelotoxic drug, while cisplatin has only weak myelotoxic effects. The combination of both drugs has shown synergistic antitumor activity in animal models (Cros et al., 1989) and favorable results in clinical studies of lung cancer with (Klastersky et al., 1989). In metastatic breast cancer, this combination has emerged as a potential therapeutic option (Shamseddine et al., 2005). In conclusion, we consider that NP is a safe and active regimen in completely resected breast cancer as postoperative adjuvant chemotherapy. However, further randomized clinical trials with a larger sample size should be conducted to verify if this regimen is superior to other conventional chemotherapy regarding disease-free and overall survival.

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