RESEARCH COMMUNICATION

Clinical Comparison of Safety and Efficacy of Vinorelbine/ Epirubicin (NE) with Fluorouracil/Epirubicin/ Cyclophosphamide (FEC)

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Abstract

Objective: To compare the safety and efficacy of a combination of vinorelbine and epirubicin (NE) with fluorouracil/epirubicin/cyclophosphamide (FEC) as a postoperative adjuvant chemotherapy for breast cancer. Methods: Breast cancer patients were treated postoperatively in Jiangsu Cancer Hospital and Research Institute from 1997 to 2006 with either the NE regimen (vinorelbine 40mg/m^2 iv on day 1 and day 8, epirubicin 50mg/m^2 iv on day 1 and day 2, and a cycle repeated every 21-28 days for totally 4-6 cycles) or the FEC regimen (5-Fu 500mg/m2 iv gtt on day 1, epirubicin 50mg/m^2 iv on day 1 and day 2, CTX 500mg/m^2 iv on day 1 and a cycle repeated every 21-28 days for totally 4-6 cycles). Toxicity was evaluated after each cycle of chemotherapy. Results: Main side effects in both NE and FEC groups were neutropenia and gastrointestinal syndrome, with a 5 year survival rate of 87.9% in the NE and 85.2% in the FEC group. Conclusions: NE regimen is safe with good long-term survival rate, and thus could be recommended as a postoperative chemotherapy regimen for breast cancer.

Keywords: Vinorelbine - epirubicin - FEC - breast cancer - adjuvant chemotherapy

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Introduction

The St.Gallen International Conference consensus and a meta-analysis result of The Adjuvant Breast Cancer Trials Collaborative Group showed cyclophosphamide, methotrexate and fluorouracil (CMF) as a postoperative adjuvant chemotherapy could reduce the risk of recurrence and death rate of breast cancer to 24% and 14% (Early Breast Cancer Trialists' Collaborative Group, 1998; 2005; Goldhirsch et al., 2005). In late 1970's, anthracycline was approved in adjuvant chemotherapy for breast cancer, based on the result that response rate of anthracycline was higher than that of CMF regimen (Goldhirsch et al., 2005). Comparison between anthracycline-based regimens for breast cancer shows apparently less cardio toxicity of epirubicin than that of doxorubicin, without reduction in response rate (Early Breast Cancer Trialists' Collaborative Group,1998) ,so in China FEC is more commonly used than FAC regimen (Goldhirsch et al., 2005).

In recent years, several combinations have shown effective outcomes (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2005), but the combination of vinorelbine and epirubicin (NE regimen) is not included in standard adjuvant chemotherapy regimens for breast cancer yet. It is reported that, vinorelbine, a semi-synthetic vinca-alkaloid, is an active a and well-tolerated agent in the treatment of advanced breast cancer with reported response rates of 35%-50% as first-line single agent therapy (Fumoleau et al., 1993), with good subjective tolerability (Fumoleau et al., 1993; Garcia-Conde et al., 1994; Romero et al., 1994; Twelves et al., 1994). In this trial,the main toxicity of vinorelbine was neutropenia. Need to be mentioned is that, vinorelbine combined with epirubicin produced low cross-resistance (Fumoleau et al., 1993; Garcia-Conde et al, 1994; Romero et al., 1994; Twelves et al., 1994; Bruno et al., 1995; Weber et al., 1995; Terenziani et al., 1996; Vogel et al., 1999), which was well demonstrated since the mid-1990s (Blomqvist et al., 1995). Abundant clinical evidence further suggests that response rates of NE to treat metastatic breast cancer could be 50% to 70% (Baldini et al., 1998; Vici et al., 2002; Ejlertsen et al., 2004), and phase II studies show NE regimen as postoperative adjuvant chemotherapy for breast cancer is safe and feasible (Levine et al., 1998; Elling et al., 2003; Pierre, 2003; Mark, 2005; Nisticò et al., 2005; Miguel, 2008).

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But whether NE is superior to standard postoperative adjuvant chemotherapy regimens for breast cancer, FEC for instance, is still unknown. Therefore we carried out a research comparing safety and survival of NE and FEC regimen as postoperative chemotherapy for breast cancer .

Patients and Methods

Patients

Patients were required to be pathologically diagnosed as breast cancer postoperatively, with karnofsky performance status ≥ 70. Other eligibility criteria included: adequate bone marrow (white blood cell count $>3.0x10^9$and platelet count $>150x10^9$), liver function (bilirubin and transaminases <1.5 times the upper limit of normal and renal function (creatinine <1.5 upper limit of normal); and no evidence of metastatic disease; age <70 years, signed an informed consent before chemotherapy.

Patients were excluded from the study if they had active cardiac disease (LVEF <50%), significant arrhythmia, any serious medical or psychiatric condition, other malignancy (excluding carcinoma in situ of the cervix and basal cell carcinoma of the skin) and previous breast cancer. Pregnant or lactating women were excluded from the study.

Treatment

Patients were treated by either vinorelbine/epirubicin (NE) or fluorouracil/epirubicin/cyclophosphamide (FEC) regimen as follows: NE-vinorelbine 40mg into normal salineby 100ml intravenous bolus infusion in 20min - 30min on days 1 and 8 and epirubicin 50 mg/m2 by bolus intravenous infusion on day 1 and 2, every 3-4 weeks for four to six cycles. (To reduce vessel damage, dexamethasone 5mg by intravenous injection before vinorelbine and normal salineby 250ml flushing after vinorelbine); FEC-fluorouracil 500mg/m^2 by bolus intravenous infusion on day 1, epirubicin 50 mg/m2 by intravenous injection on day 1 and 2, cyclophosphamide 500 mg/m^2 by intravenous injection on day 1 every 3-4 weeks for four to six cycles.

Antiemetic treatment was granisetron 3mg by intravenous bolus infusion prior to chemotherapy. Routine blood test, blood biochemistry and tumor markers were reviewed during and after chemotherapy weekly.

Assessment of toxicity

Patients were assessed and graded for toxicity according to WHO criteria (Miller et al., 1991).

Follow-up

Our end point was overall survival from the data documenting pathological diagnosis after surgery to Feb 2008. Survival data were obtained from the hospital follow-up team. Records with no reply were followed by local Ministry of Public Security.

Statistical analysis

The study data were analyzed through the STATA 8.0 software. The Kaplan–Meier method was used for plotting survival curves.

Results

Four hundred and fifty-four female patients were enrolled in the study. All patients were diagnosed as breast cancer and received operation between 1995 and 2005. All pathologic type were invasive ductal carcinoma or lobular carcinoma. Sixty-one patients received NE and 393 patients received FEC regimen. Patient characteristics are presented in Table 1.

Toxicity

All patients underwent toxicity assessment. Treatment related side effects were reversible, and there was no termination of chemotherapy or death caused by adverse events. Sixty-one patients treated by NE regimen most commonly experienced myelosuppression and gastrolntestinal toxicity. Leukopenia rate was 63% , 38% of them with grade III-IV and none with infection. There were 28% patients with grade I-II thrombocytopenia and 1.6% with grade IV thrombocytopenia. Grade I-II gastrolntestinal toxicity rate was 20-30%, and grade III-IV below 10%. Other side effects included alopecia, elevated aminotransferases, urea and creatimine elevation. Three hundred and ninety-three patients treated by FEC regimen also most commonly experienced myelosuppression and gastrolntestinal toxicity. Leukopenia rate was 56.2%, 34.6% of them with grade III-IV and none with infection. There were 12.7% patients with grade I-II thrombocytopenia and 0.1% ones with grade IV thrombocytopenia. Grade I-II gastrolntestinal toxicity rate was 16.6%, and grade III-IV gastrolntestinal toxicity rate was 23.7%, both mainly manifested as nausea and vomiting. Other side effects also included alopecia,

Table 1. Characteristics of 454 Breast Cancer Patients Treated with Vinorelbine/Epirubicin or Fluorouracil Epirubicin/Cyclophosphamidas Postoperative Adjuvant Chemotherapy (Department of Chemotherapy, Jiangsu Cancer Hospital and Research Institute: 1995-2005)

All Patients	NE	FEC
	N(%)	N(%)
Age Median (Range)	48(30-64)	48(25-65)
Menopausal status:		
Pre	46 (75)	248 (63)
Post	15 (25)	145 (37)
Pathology:		
Infiltrating ductal	54 (89)	287 (73)
Infiltrating lobular	7 (11)	106 (27)
Grade:		
I	0	11 (3)
II	26 (43)	180 (46)
III	35 (57)	202 (51)
Vascular invasion:		
Positive	49 (80)	338 (86)
Negative	12 (20)	61 (14)
Pathological size (cm):	2.5(1.0-5.0)	3.0(0.5-7.0)
Nodal status:		
Positive	41 (68)	193 (49)
Negative	20 (32)	200 (51)

NE- Vinorelbine/Epirubicin FEC- Fluorouracil/Epirubicin/Cyclophosphamide

Table 2. Toxicity by 454 Breast Cancer Patients Treated with Vinorelbine/Epirubicin or Fluorouracil/Epirubicin/ Cyclophosphamide as Postopera tive adju vant Chemotherapy (Department of Chemotherapy, Jiangsu Cancer Hospital and Research Institute: 1995-2005)

Toxicity	NE				FEC			
Grade /Number (Rate)	I	II	III	IV	I	II	II	IV
Leukopenia	9(14%)	7 (11%)	11 (18%)	13 (20%)	24 (6.1%)	61(15.5%)	88(22.4%)	48(12.2%)
Thrombocytopenia	14(23%)	3(4.9%)	3(4.9%)	1(1.6%)	44(11.2%)	6 (1.5%)	15 (3.8%)	2 (0.1%)
Nausea, vomiting	9(14%)	6(9.8%)	1(1.6%)	1(1.6%)	28 (7.1%)	45(11.5%)	75(19.1%)	18 (4.6%)
Diarrhea	10(16%)	1(1.6%)	4(6.5%)	0 (0%)	32 (8.1%)	15(3.8%)	13 (3.3%)	2 (0.1%)
Constipation	14(23%)	1(1.6%)	0 (0%)	0 (%)	36 (9.2%)	0 (0%)	1 (0.1%)	0 (0%)
Oral ulcer								
Alopecia	14(23%)	0 (0%)	0 (0%)	0 (0%)	34 (8.7%)	2(0.1%)	2 (0.1%)	0 (0%)
Elevated ALT	13(20%)	0 (0%)	7(1.8%)	11(2.8%)	41(10.4%)	1(1.6%)	0 (0%)	0 (0%)
Elevated AST	14(23%)	1(1.6%)	0 (0%)	0 (0%)	41(10.4%)	10(2.5%)	5 (1.3%)	0 (0%)
Elevated BUN	15(24%)	0 (0%)	0 (0%)	0 (0%)	42(10.7%)	10(2.5%)	1 (0.1%)	1 (0.1%)
Elevated Cr	15(24%)	1(1.6%)	0 (0%)	0 (0%)	39 (10%)	32(8.1%)	1 (0.1%)	1 (0.1%)

NE- Vinorelbine/Epirubicin FEC- Fluorouracil/Epirubicin/Cyclophosphamide ALT- alanine aminotransferase AST- aspartate aminotransferase BUN- blood urea nitrogen Cr- creatinine

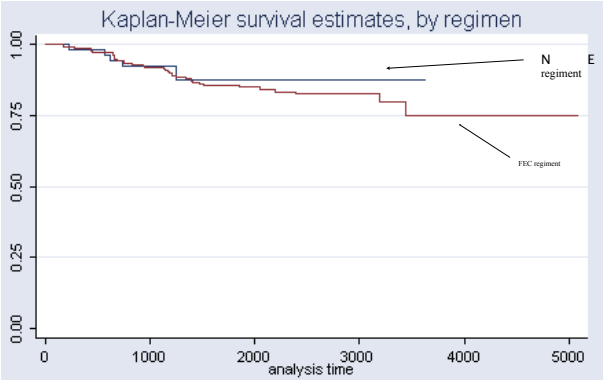

Figure 1. Survival by 454 Breast Cancer Patients Treated with Vinorelbine/Epirubicin (NE) or Fluorouracil/Epirubicin/Cyclophosphamide (FEC) as Postoperative Adjuvant Chemotherapy (Department of Chemotherapy, Jiangsu Cancer Hospital and Research Institute: 1995-2005) Analyzed by Log-rank test, p = 0.8657

elevated aminotransferases, urea and creatimine elevation, and no treatment-related death occurred. Treatment-related adverse events are shown in Table 2.

Survival

After median 35 months (3.4-121 months) follow-up, 13 recurrence and 5 breast cancer related death in NE group with 5-year survival at 87.9%; 34 breast cancer related death in FEC group with 5-year survival at 85.2%. Difference of survival curves in two groups was checked by Log-rank test, and p value is 0.8657 (Figure 1).

Discussion

The MA5 trial (Miguel, 2008) showed that breast cancer patients treated with FEC regimen as adjuvant therapy had better 5-year DFS and OS than those treated with CMF, another extensively prescribed postoperative adjuvant regimen in this setting (63% vs 53%, 77% vs 70%). Based on this result, FEC is established as one of the standard adjuvant chemotherapy regimens for postoperative breast cancer patients (Pierre et al., 2003; Mark et al., 2005; Miguel, 2008), and regarded as a reference when being compared with other regimens.

However, the side effects of different regimens needs to be considered before chemotherapy. For instance, we should consider hyperpigmentation as one of the side effects of 5-fluorouracil (Fumoleau et al., 1993) so that CMF regimen must be used cautiously to treat young patients; taxanes require high dose glucocorticoid as premediation, therefore DAC regimen should not be administered to patients with diabetes, gastritis or gastric ulcers (Romero et al., 1994). On this background, it is necessary for us to design clinical research and continuously explore new adjuvant chemotherapeutic combinations for breast cancer patients with special clinical conditions.

Vinorelbine, a semi-synthetic vinca-alkaloid, can inhibit tubulin polymerization to form microtubules and induce microtubule depolymerization, which is the mechanism that the proliferation of tumor cell division could be stopped at the metaphase (Nisticò et al., 2005). The combination of vinorelbine and epirubicin (NE) have been extensively tested in treating breast cancer patients since the 1990. Blomqvist et al. first reported vinorelbine 20mg/m^2 by intravenous injection on days 1 and 8 and epirubicin 60mg/m^2 for metastatic breast cancer patients and the response rate was 60% (Blomqvist et al., 1995). Later, this result was proved by another study, in which NE was used to treat 48 breast cancer patients with stage IIIa or IIIb disease and the objective response rate was 87.5%, with pathological complete remission rate 4.2%, 3-year disease-free survival 68% and overall survival 81% (Nisticò et al., 2005). These results are in line with other reports that NE regimen as first-lined therapy could achieve a response rate between 60% and 80% with nice tolerance and leucopenia as most common side effect(Fumoleau et al., 1993; Garcia-Conde et al., 1994; Romero et al., 1994; Twelves et al., 1994). In 2003, Elling from Germany first reported NE regimen in a phase II study as a postoperative adjuvant chemotherapy for breast cancer patients with good safety and efficacy (Elling et al., 2003). In 2009, a clinical observations on NE as a preoperative neoadjuvant chemotherapy, to treat 119

Chinese breast cancer patients (Huang et al., 2009). In this report, clinical complete remission rate was 22.7%, partial remission rate was 65.5%, and postoperative pathological response rate was 18.5%, five-year disease-free survival rate and overall survival rate was 58.7% and 71.3%,respectively (Huang et al., 2009). Based on these results, we designed our study. Our result suggests that five-year survival rate of NE regimen is superior to that of FEC (87.9% vs 85.2%). Meanwhile, NE brings no increasing side effects. As a conclusion, NE regimen could be a reasonable option for breast cancer patients who will receive postoperative adjuvant chemotherapy, and this conclusion deserves to be further investigated by randomized clinical studies.

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