RESEARCH COMMUNICATION

Clinical Comparison on the Safety and Efficacy of Fluorouracil/ Pirarubicin/Cyclophosphamide (FPC) with Fluorouracil/ Epirubicin/Cyclophosphamide (FEC) as Postoperative Adjuvant Chemotherapy in Breast Cancer

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Abstract

Objective: To compare the safety and efficacy of a combination of 5-Fu, pirarubicin and CTX (FPC) with FEC as a postoperative adjuvant chemotherapy for breast cancer. Methods: A total of 655 breast cancer patients were treated postoperatively in Jiangsu Cancer Hospital and Research Institute from 1995-2005, 292 were treated with FPC (5-Fu 500mg/m^2 iv gtt on day 1, pirarubicin 40mg/m2 iv on day 1, CTX 500mg/m^2 iv on day 1 and a cycle repeated every 21-28 days for totally 4-6 cycles); 363 with FEC (5-Fu 500mg/m^2 iv gtt on day 1, epirubicin 50mg/m2 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 FPC and FEC groups were leukopenia and gastrointestinal toxicity, with a 5 year survival rate 88.7% in FPC and 85.7% in FEC group. Conclusions: FPC regimen is safe with superior long-term survival rate when compared with FEC, thus could be recommended as a postoperative chemotherapy regimen for Chinese patients with breast cancer.

Keywords: Pirarubicin - epirubicin - breast cancer - adjuvant chemotherapy - China

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Introduction

The derivatives of Adriamycin, 4'-O-tetrahydropyranyl adriamycin (pirarubicin), was firstly reported by Umezawa et al in 1979 (Umezawa et al., 1979). Then, preclinical experiments suggested that pirarubicin was rapidly taken up by LI210 leukemia cells, accumulated in the cell nuclei, and inhibited DNA synthesis by inhibiting DNA polymerases (Tanaka et al., 1983). This could be the mechanism that pirarubicin had improved activity against tumor with less acute cardiotoxicity as compared with Adriamycin (Miniinole et al., 1983). Further experiments disclosed the uptake of pirarubicin by leukemia was markely faster than for Adriamycin and epiadriamycin (Tapiero et al., 1984), which may explain less cardiotoxicity and alopecia after the administration of pirarubicin (Dantchev et al., 1979).

Clinical trials have clarified that single-agent pirarubicin had a response rate of 23.2% in advanced breast cancer (Abe et al., 1986), which was simiar to that of epiadriamycin (Tominaga et al., 1984). Fluorouracil/ Pirarubicin/Cyclophosphamide (FPC) regimen showed higher response rate in the treatment of advanced breast cancer with safety profile not inferior to Fluorouracil/ Epirubicin/Cyclophosphamide (FEC) regimen (35.1% vs. 29.6%)(Abe et al., 1986). Thus we hypothesize that FPC regimen could be a proper choice as an adjuvant 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 hematological (white blood cell count > 3.0×10^9 and platelet count > 150×10^9), liver (bilirubin and transaminases < 1.5 times the upper normal limit) and renal function (creatinine leval < 1.5 times the upper normal limit); and no evidence of metastatic disease; 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.

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Treatment

All patients provided written informed consent and were placed central venous catheter prior to chemotherapy. Patients were treated by either FPC or FEC regimen as follows: FPC —fluorouracil 500mg/m2 by bolus intravenous infusion on day 1, pirarubicin 40 mg/m2 by intravenous injection on day 1 , cyclophosphamide 500 mg/m^2 by intravenous injection on day 1 every 21 – 28 days for totally four to six cycles; 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 21 - 28 days for totally 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 routinely performed every week during or after chemotherapy.

Assessment of toxicity

Toxicity was graded according to World Health Organization (WHO) criteria (Miller et al., 1981).

Follow-up

The primary end point of the study was overall survival, defined as time from the date of initial pathological diagnosis after surgery to the date of last contact or death. Survival data were obtained from the hospital follow-up team. The vital status of patients failing to attend a clinical examination was confirmed by local Ministry of Public Security. The last following was conducted in Feb 2008.

Statistical analysis

All the data were input by professionals unrelated to this study and survival data were analyzed by STATA 8.0 software. Survival curves were created using the Kaplan-Meier method.

Results

Six hundred and fifty-five 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. Two hundred and ninety-two patients received FPC and 363 patients received FEC regimen. Patient characteristics are presented in Table 1.

Toxicity

All the patients underwent toxicity assessment. Chemotherapy-related adverse events are shown in Table 2. Main side effects in both FPC and FEC groups were leukopenia and gastrointestinal toxicity. Leukopenia was observed in 129 patients (44.2%) with FPC versus 190 (52.3%) with FEC , whereas grade 3-4 leukopenia was reported in 66 (22.6%) versus 111 (30.6%) patients respectively. No patient developed infection. Fourty-five (15.4%) patients experienced grade 1-2, and 5 (below 2%) grade 3-4 thrombocytopenia with FPC versus 48 (13.2%) grade 1-2 and 15 (4.1%) grade 3-4 thrombocytopenia with FEC. Gastrolntestinal toxicity mainly manifested as nausea and vomiting. Grade I-II gastrolntestinal toxicity occurred

Table 1. Characteristics of 655 Breast Cancer Patients treated with Fluorouracil/Pirarubicin/ Cyclophosphamide (FPC) or Fluorouracil/Epirubicin/ Cyclophosphamide (FEC) as Postoperative Adjuvant Chemotherapy

All Patients	FPC N(%)	FEC N(%)
Age Median (Range)	48 (26-77)	48 (25-65)
Menopausal status:		
Pre	178 (61)	232 (64)
Post	114 (39)	131 (36)
Pathology:		
Infiltrating ductal	228 (78)	265 (73)
Infiltrating lobular	64 (22)	98 (27)
Grade:		
I	5 (2)	11 (3)
II	149 (51)	163 (45)
III	138 (47)	189 (52)
Vascular invasion:		
Positive	232 (79)	309 (85)
Negative	60 (21)	54 (15)
Pathological size (cm):	2.5 (0.5-6.0)	3.0 (0.5-7.0)
Nodal status:		
Positive	182 (62)	192(53)
Negative	110 (38)	171(47)

FPC, Fluorouracil/Pirarubicin/Cyclophosphamide; FEC, Fluorouracil/Epirubicin/Cyclophosphamide

Table 2. Toxicity of 655 Breast Cancer Patients treated with Fluorouracil/Pirarubicin/Cyclophosphamide (FPC) or Fluorouracil/Epirubicin/Cyclophosphamide (FEC) as Postoperative Adjuvant Chemotherapy

Toxicity	FPC Grade /Number (Rate)				FEC Grade /Number (Rate)			
	I	II	III	IV	I	II	III	IV
Leukopenia	26 (8.9%)	37 (12.7%)	48 (16.4%)	18 (6.2%)	24 (6.6%)	55 (15.2%)	75 (20.7%)	36 (9.9%)
Thrombocytopenia	40 (13.7%)	5 (1.7%)	4 (1.4%)	1 (0.3%)	42 (11.6%)	6 (1.7%)	14 (3.9%)	1 (0.3%)
Nausea, vomiting	24 (8.2%)	19 (6.5%)	23 (7.9%)	5 (1.7%)	28 (7.7%)	42 (11.6%)	67 (18.5%)	13 (3.6%)
Diarrhea	27 (9.2%)	3 (1.0%)	14 (4.8%)	1 (0.3%)	32 (8.8%)	14 (3.9%)	9 (2.5%)	1 (0.3%)
Constipation	35 (12.0%)	1 (0.3%)	0 (0%)	0 (0%)	33 (9.1%)	1 (0.3%)	0 (0%)	0 (0%)
Oral ulcer	33 (11..3%)	2 (0.7%)	2 (0.7%)	0 (0%)	31 (8.5%)	2 (0.6%)	2 (0.6%)	0 (0%)
Alopecia	34 (11.6%)	1 (0.3%)	1 (0.3%)	0 (0%)	31 (8.5%	8 (2.2%)	8 (2.2%)	7 (1.9%)
Elevated ALT	33 (11.3%)	9 (3.1%)	3 (1.0%)	1 (0.3%)	38 (10.5%)	11 (3.0%)	5 (1.4%)	0 (0%)
Elevated AST	33 (11.3%)	7 (2.4%)	4 (1.4%)	0 (0%)	38 (10.5%)	10 (2.8%)	3 (0.8%)	0 (0%)
Elevated BUN	37 (12.7%)	7 (2.4%)	0 (0%)	0 (0%)	39 (10.7%)	10 (2.8%)	1 (0.3%)	1 (0.3%)
Elevated Cr	37 (12.7%)	9 (3.1%)	0 (0%)	0 (0%)	36 (9.9%)	29 (8.0%)	1 (0.3%)	1 (0.3%)

FPC, Fluorouracil/Pirarubicin/Cyclophosphamide; FEC, Fluorouracil/Epirubicin/Cyclophosphamide; ALT- alanine aminotransferase AST- aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine

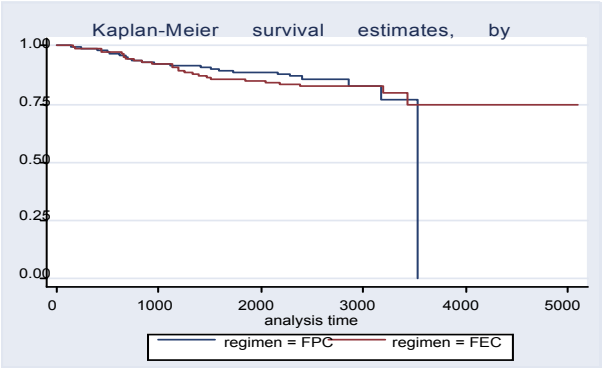

Figure 1. Survival. A total of 655 breast cancer patients were treated with Fluorouracil / Pirarubicin/ Cyclophosphamide(FPC) or Fluorouracil/Epirubicin/Cyclophosphamide (FEC) as Postoperative adjuvant chemotherapy (Department of Chemotherapy, Jiangsu Cancer Hospital and Research Institute: 1995-2005); Analyzed by Log-rank test, p = 0.6148.

in less than 20% patients with FPC versus 19.3% with FEC, and grade III-IV gastrolntestinal toxicity occurred in less than 10% patients with FPC versus 22.1% with FEC. Other side effects in both groups included alopecia, elevated aminotransferases, urea and creatinine elevation. Chemotherapy related side effects were reversible, and there was no termination of chemotherapy or death due to chemotherapy-related toxicity. No chemotherapy-related death occurred.

Survival

After a median follow-up of 71 months (range 4–167 months), 30 patients died in FPC group and 34 in FEC group. The cause of death was disease progression in all patients. 5-year survival rate was 88.7% for FPC group and 85.7% for FEC group. For survival-related endpoints, treatment groups were compared by use of the log-rank test, and p value is 0.6148 (Figure 1).

Discussion

Adjuvant chemotherapy reduces the risk of recurrence in patients with early-stage breast cancer (EBCTCG, 2005). From the era of cyclophosphamide-methotrexate-fluorouracil (CMF) to the anthracycline-containing regimens, women treated in the adjuvant setting had statistically significant lower risk for relapse and disease-related death than those who did not receive chemotherapy. The St.Gallen International Conference consensus (Goldhirsch et al., 2005) and a comprehensive meta-analysis by the Early Breast Cancer Trialists'Collaborative Group (EBCTCG, 1998; EBCTCG, 2005; Fumoleau et al., 1993; Garcia-Conde et al., 1994; Miguel et al., 2008; Mark et al., 2005) has demonstrated that CMF regimen administered after surgery is able to reduce the annual odds of recurrence and death among operable breast cancer patients by 24% and 14%, respectively. In the late 1970s, anthracycline-containing combination regimens were tested in adjuvant setting in prospectively randomized trials and appeared to be statistically more effective in preventing breast cancer relapse and death than CMF regimen (EBCTCG, 1998). The results of the MA5 trial published in 1998 demonstrated the superiority of FEC compared with classical CMF (Miguel et al., 2008). The 5-year disease-free survival for FEC was 63% compared with 53% for CMF. The 5-year overall survival for FEC and CMF were 77% and 70%, respectively. Based on this result, FEC is established as one of the standard adjuvant chemotherapy regimens for postoperative breast cancer patients, and regarded as a reference when being compared with other regimens (Miguel et al., 2008; Mark et al., 2005; Pierre et al., 2003; Yan et al., 2010). Comparison between anthracycline-containing regimens for breast cancer shows that epirubicin and pirarubicin were apparently less cardiotoxic than doxorubicin without compromising antitumor efficacy, so in China FEC or FPC regimen is more commonly used than FAC regimen (Goldhirsch et al., 2005). At present, standard chemotherapy regimens for postoperative breast cancer patients include CMF, FAC, FEC and TAC, but not include FPC regimen. In 1995, Dhingra et al conducted a phase II study of FPC regimen as front-line chemotherapy in women with metastatic breast cancer (Dhingra et al., 1995). In this study, the response rate was 62% , and the median survival was 16 months. Grade III/IV myelosuppression occurred in 81% of the course. They concluded that the efficacy as well as toxicity (with the exception of alopecia) appeared to be comparable to similar combinations containing doxorubicin. In contrast, in our study, the main side effects in both FPC and FEC groups were leukopenia and gastrointestinal toxicity. Chemotherapy related side effects were reversible, and there were no chemotherapy related death. Our result suggests the superiority of FPC compared with FEC regimen: five-year survival rate for FPC is 88.7% compared with 85.7% for FEC. Meanwhile, FPC brings no increasing side effects. As a conclusion, FPC regimen could be a reasonable option for breast cancer patients who will receive postoperative adjuvant chemotherapy, and our results deserve to be further investigated by randomized clinical studies.

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