RESEARCH COMMUNICATION

Weekly TP Regimen as a Postoperative Adjuvant Chemotherapy for Completely Resected Breast Cancer in China: Final Result of a Phase II Trial

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Abstract

Objectives: To investigate the safety and long-term survival with weekly paclitaxel combined with cisplatin (wTP) as a postoperative adjuvant chemotherapy regimen for breast cancer. Methods: Patients with breast cancer were treated postoperatively with paclitaxel 40 mg/m^2 intravenously on days 1, 8 and 15, cisplatin 25 mg/m^2 also intravenously on days 1,8 and 15, repeated every 21-28 days as a cycle. Toxicity and survival rate were evaluated after chemotherapy. Results: Between September 1993 and August 2001, 20 patients were enrolled. Median age was 52 years (range, 35–71 years). According to the TNM stage system, all patients were staged II or III. Median number of chemotherapy cycles was 3 (range, 1–6), and 10 patients received 4 to 6 cycles of wTP. After a median follow-up of 83 months, 2 deaths and 6 relapses were documented. The five year overall survival rate was 90%. All patients could be evaluated with regard to toxicity. No treatment related deaths were recorded. Neutropenia occurred in 75% of patients during treatment, all recovering after G-CSF injection. Other symptoms included nausea/vomiting, elevation of transaminase, urea nitrogen/creatinine and alopecia. Conclusions: wTP is safe and effective at the doses tested. However, a randomized clinical trial is needed to compare wTP with other conventional adjuvant regimens of breast cancer postoperatively.

Keywords: Breast cancer - adjuvant chemotherapy - paclitaxel - cisplatin

Asian Pacific J Cancer Prev, **12**, 2797-2800

Introduction

The incidence and mortality rate of breast cancer increased significantly in China over the last several decades (Yu et al., 2007). It was estimated that 121,269 new cases of breast cancer were diagnosed in China in 2000 and 168,013 in 2005 (Yang et al., 2005). Despite advances in prevention, risk factor reduction, early diagnosis and treatment, breast cancer remains a main public health concern, with more than a million new cases diagnosed annually, resulting in >400,000 deaths worldwide (Ferlay et al., 2002; Huang et al., 2004).Of particular significance, postoperative adjuvant chemotherapy could substantially reduce the risk of recurrence and death for surgically treated patients (Mamounas et al., 2005). Regarding postoperative treatment in China, adjuvant chemotherapy which is in line with the NCCN guideline (www.nccn.org) has been an important component of medical management for breast cancer (Yan et al., 2010). Regimens administered in adjuvant setting include cyclophosphamide, methotrexate, and fluorouracil (CMF); doxorubicin and cyclophosphamide (CA); fluorouracil, doxorubicin, and cyclophosphamide (FAC), and fluorouracil, epirubicin, and cyclophosphamide (FEC), etc. However, treatment with CMF for six months results in permanent ovarian failure in 70% of women over 40 years of age and in 40% of younger women (Goodwin et al.,1999); and the majority of women with breast cancer who are treated with CMF gain weight. Weight gain may adversely affect the quality of life and has been associated with higher rates of recurrence (Camoriano et al.,1990). FEC regimen is associated with more adverse effects, especially increases risks of cardiotoxicity and secondary leukemia (Cardoso et al.,2002). Two studies in which patients received four cycles of paclitaxel every 3 weeks after receiving four cycles of doxorubicin and cyclophosphamide every 3 weeks (Henderson et al., 2003; Mamounas et al., 2005) established a new standard of care for operable breast cancer and led to regulatory approval of paclitaxel for axillary lymph node–positive breast cancer. However, taxanes, i.e. paclitaxel administered every 3 weeks compared with weekly use is reported to cause more neutropenia, myalgias, and arthralgias, and paclitaxel every 3 weeks concomitantly with epirubicin may exacerbate cardiotoxicity (Conte et al., 2004). Therefore, efforts have been made to find more effective

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regimes with acceptable toxicities as postoperative adjuvant chemotherapy for breast cancer patients.

Weekly paclitaxel as a single agent has been widely used in the treatment of metastatic breast cancer with an overall response rate of 56% (12% complete and 44% partial) (Holmes et al. 1991). The dose-limiting toxicities of this regimen are neutropenia, neuropathy and gastrointestinal reaction (Holmes et al. 1991). To improve the treatement effect, a combination of paclitaxel and cisplatin was tested in clinical trials to treat patients in this setting (Tolcher et al. 1995; Gelmon et al.1995). It showed that this combination could bring a response rate of more than 66% (Tolcher et al. 1995; Gelmon et al.1995). One mechanism underline these findings is that the combination of paclitaxel and cisplatin does not lead to cross drug resistance(Wasserheit et al. 1996).

To improve tolerability, Frasci et al. reported In 1998 that weekly instead of triweekly paclitaxel combined with cisplatin could achieve further higher therapeutic effect (response rate 81%, including 26% complete remission) with less toxicities in patients with advanced breast cancer (Frasci et al. 1998). But weekly paclitaxel combined with cisplatin (wTP) as a postoperative adjuvant chemotherapy has not been well investigated in breast cancer.

For the present study, we hypothesized that the safety and effectiveness of wTP would not be inferior to currently administered regimens for patients who need a postoperative adjuvant chemotherapy.

Materials and Methods

Patients

Patients eligible for this study should have histologically confirmed diagnosis of breast cancer (stage II, IIIA), no prior history of cytotoxic chemotherapy or hormonal therapy, with Karnofsky performance status (KPS) >=70, adequate haematological, hepatic and renal function. The study was approved by ethics committee of Jiangsu Cancer Hospital Institute, and all patients signed informed consent before chemotherapy.

Treatment

Patients who were eligible for the study received cisplatin at a dose of 25mg/m^2 on day1,8 and 15 in 500 mL normal saline intravenously over 60 minutes, and paclitaxel at a dose of 40 mg/ m^2 in 500 mL of normal saline intravenous infusion over 60–90minutes, on days 1, 8 and 15 of each cycle. For prophylaxis of acute and delayed emesis, antiemetic therapy with serotonin antagonist was given intravenously on day1 to day3 of each cycle.

The premedication of weekly paclitaxel was done as reported elsewhere (Zhou et al.,2009). Chemotherapy was repeated every 3 weeks. Complete blood counts were prepared weekly, and a full serum chemistry profile and ECG were obtained prior to each of the cycles of chemotherapy.

Toxicity

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

Overall Survival

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 et al., 1958).

Results

Patients

Between September 1993 and August 2001,20 patients were recruited into the study. Median age was 52 years (range, 35–71 years). According to TNM stage system, all patients staged II or III. Median number of cycle of chemotherapy was 3 (range, 1–6), and 10 patients received 4 to 6 cycles of wTP. Of our 20 patients, all (100%) had invasive ductal carcinoma.

Toxicity

All 20 patients were assessable for toxicity. No deaths were attributed to chemotherapy.

The main symptoms of toxicit included myelosuppression and nausea/vomiting. The incidence of leucopenia is 75% including 50% of grade III-IV, and thrombocytopenia of gradeI-IIand grade III-IVare both 10%,while the incidences of nausea and vomiting of gradeI-IIand grade III-IV were both 15% . Other toxicities include alopecia, elevation of transaminase, urea nitrogen and creatinine, etc (Table 1).

Table 1. Toxicities after Chemotherapy (n) (%)

	GradeI	GradeII	GradeIII	GradeIV
Neutropenia	1 (5)	4(20)	5 (25)	5 (25)
Thrombocytopenia	2 (10)	0 (0)	0 (0)	1 (10)
Nausea/vomiting	0 (0)	3 (15)	3(15)	0 (0)
Diarrhea	0 (0)	1 (5)	1 (5)	0 (0)
Constipation	2 (10)	0 (0)	0 (0)	0 (0)
Stomatitis	2 (10)	0 (0)	0 (0)	0 (0)
Alopecia	1 (5)	1 (0)	2 (10)	0 (0)
Elevation of alanine aminotransferase	2 (10)	1 (5)	0 (0)	0 (0)
Elevation of aspartate aminotransferase	2 (10)	1 (5)	0 (0)	0 (0)
Elevation of creatinine	2 (10)	0(0)	0 (0)	0 (0)

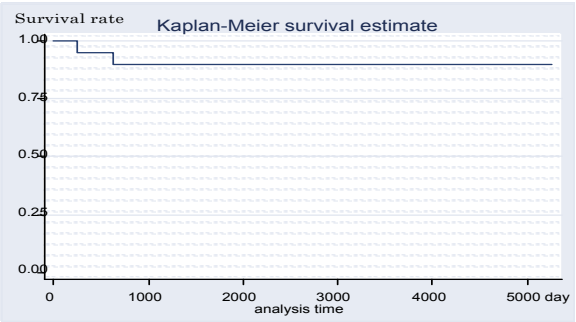

Figure 1. Five-year Survival Curves for the Groups that Received wTP (Paclitaxel-Cisplatin).

Overall Survival

After a median follow-up of 83 months, 2 patients had died and 6 cases of relapse had been documented. The five year overall survival rate was 90% (Figure 1). All recorded causes of death were breast cancer.

Discussion

Because of severe toxicities caused by paclitaxel-cisplatin combination(TP), few literatures document TP as a postoperative adjuvant regimen for breast cancer. On this background, we conducted current study to evaluate wTP in this setting. The rationale to combine cisplatin and paclitaxel is primarily based on their toxicity profile and documented activity and synergism. Paclitaxel is generally applied in the treatment of breast cancer during the last two decades, it performs anticancer activity by acting on G2 and M phase of cell cycle, promoting tubulin polymerization and preventing its depolymerization to form extremely stable microtuble, inhibiting the formation of splindle apparatus and finally tumor cell proliferation (Schiff et al., 1979).

In early 1990s, a phase I trial with 25 patients conducted in the United States reported that single paclitaxol administrated at a dose of 250 mg/m^2 by 24 hour infusion could produce good objective response rate, and also surprising myelosuppression (Holmes et al. 1991). Latter, a modification by combining paclitaxel with cisplatin, indicating that paclitaxel 170 mg/m^2 and cisplatin 75 mg/m^2 could be well tolerated (Rowinsky et al. 1991) and achieve a response rate of more than 50% (Wasserheit et al. 1996). In 1997, Frasci suggested in a phase II trial that weekly paclitaxel-cisplatin (wTP) was more tolerable than every three week administration (Frasci et al, 1997), and the objective effective rate was as high as 81% (26% complete and 55% partial) (Frasci et al, 1998).

Our study suggests that wTP as a postoperative adjuvant chemotherapy for breast cancer is safe, with satisfactory long-term survival rate. The main toxicities of wTP include myelosuppression and gastrointestinal reaction, but generally mild. So, wTP could be considered for elderly patients and those with poor performance status. For patients who demonstrate grade III or IV neutropenia, we recommend G-CSF be given preventively at a dose of 150~200μg/d for 3 consecutive days after chemotherapy.

In conclusion , wTP regimen is safe and effective at the doses tested. However, randomized clinical trial is needed to compare wTP with other conventional adjuvant chemotherapy for postoperative breast cancer patients.

Acknowledgements

Dr. Xin-En Huang is supported in part by a grant from Kang Lai Te, and in part from a special research fund of Jiangsu Cancer Hospital & Research Institute (ZK200805).

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