Docetaxel–cisplatin might be superior to docetaxel–capecitabine in the first-line treatment of metastatic triple-negative breast cancer†


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Background: Triple-negative breast cancer (TNBC) may be more sensitive to platinum. This study was to compare platinum-based regimen with nonplatinum regimen in the first-line treatment of advanced TNBC.

Patients and methods: Eligible metastatic TNBC (mTNBC) women without prior treatment for advanced disease were randomized (1 : 1) to receive either docetaxel–cisplatin (TP) or docetaxel–capecitabine (TX) q3w for up to 6 cycles, until disease progression or unacceptable toxicity. The primary end point was objective response rate (ORR) and the secondary end points included progression-free survival (PFS) and overall survival (OS). In total 53 patients were enrolled.

Results: The median follow-up was 24 months. ORR was higher in the TP group than in the TX group (63.0% versus 15.4%, P = 0.001). PFS was more than doubled (10.9 months versus 4.8 months, P < 0.001) and median OS was also greatly improved (32.8 months versus 21.5 months, P = 0.027). Toxic effects were not different except G3/4 vomiting and G2/3 hand-foot syndrome.

Conclusions: This study suggested that cisplatin-based chemotherapy was superior to capecitabine-based regimen in the first-line treatment of mTNBC, as measured by ORR, PFS and OS. Further large-scale study should be warranted. These results are not sufficient to change clinical practice.

Key words: capecitabine, cisplatin, mBC, triple-negative

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introduction

The so-called ‘triple-negative breast cancer’ (TNBC), defined as ER-/PgR-/HER2-, is a specific subtype of breast cancer accounting for 12%–20% of all breast cancer cases [1, 2]. TNBC appears to have an aggressive behavior with early visceral metastasis and consequently poorer outcomes [2, 3]. Numerous efforts are currently being undertaken to improve prognosis for patients with TNBC. It comprises both optimization in choice and scheduling of common cytotoxic agents or dose intensification strategies and introduction of novel target agents including anti-EGFR, antiangiogenesis, etc. Unfortunately, none of the target therapies has been proved to be beneficial, and some such as PARP inhibitors [4] have even turned out to be disappointing. Therefore, for the time being, chemotherapy remains to be the only possible therapeutic option in the adjuvant or metastatic setting in TNBC.

The histological similarity between BRCA1-related breast cancer and TNBC has shed some light on the choice of chemotherapy. The deficiency of BRCA1, which leads to defective DNA homologous recombination of double-strand break repair, confers hypersensitivity to the interstrand cross-linking agents such as platinum and mitomycin C [5, 6]. A few retrospective study or small-sample neoadjuvant trials have suggested that TNBC may be more sensitive to DNA-damaging agents such as CDDP [7, 8], but others have shown contrary results [9]. The use of platinum and alkylating agents in these patients is currently under investigation by many researchers [10, 11]. Several phase II or III clinical trials testing platinum drugs in metastatic TNBC (mTNBC) patients are ongoing [12, 13]. However, to our knowledge, no published data are yet available on this particular issue. This article presents the results of the very first prospective, randomized phase II clinical trial comparing different regimens in mTNBC.

patients and methods

study design

This was a prospective, open-label, randomized phase II clinical trial carried out in the Cancer Hospital, Chinese Academy of Medical Sciences. Eligible locally advanced or metastatic TNBC women without prior treatment for advanced disease were randomized (1:1) to receive either TP regimen (docetaxel 75 mg/m² plus cisplatin 75 mg/m² i.v. infusion day 1) or TX regimen (docetaxel 75 mg/m² i.v. infusion day 1 plus capecitabine 1000 mg/m² bid, 2 weeks on, 1 week off) every 3 weeks for up to six cycles, until disease progression, unacceptable toxicity or patient consent withdrawal (Figure 1). The primary end point was to compare the objective response rates (ORRs); the secondary end points were progression-free survival (PFS), overall survival (OS) and safety. Tumor response was evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) guidelines by computed tomography scanning (or magnetic resonance imaging if indicated) every two cycles during treatment and every 3 months after discontinuation of study treatment. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria for adverse events, version 3.0 [14]. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee, and informed consent was obtained from all the patients.

patient selection

The major inclusion criteria included patients aged ≥18 years with histologically confirmed ER-, PR-, and HER2- primary breast cancer (ER- and PR- were first defined as <10% positive tumor cells with nuclear staining in Immunohistochemistry [IHC] and then <1% after April 2010 according to new College of American Pathologists guidelines at that time. HER2- was defined as IHC scoring 0 or 1+ or FISH nonamplified according to the ASCO guidelines); patients must have at least one measurable lesion according to RECIST 1.0; No prior treatment of advanced disease; Anthracyclines should have been given in the neoadjuvant or adjuvant setting; An Eastern Cooperative Oncology Group (ECOG) score ≤1 was required. Patients must have adequate organ function. Previous paclitaxel was allowed. Patients were excluded if original primary tumor or subsequent relapse was known to be positive for any of ER, PR or HER2 or if they had been treated for advanced disease. Previous treatment with a platinum or docetaxel was not allowed.

statistics

PFS was defined as the time from the start of the treatment until disease progression or death. OS was calculated from the date of first administration of treatment to death by any cause or censored at the last date the patient was known to be alive. When the study was designed, the expected response rate of TP regimen was 50%. To detect a difference of 0.35 in response rate between groups with a power of 80% and two-sided significance level at 0.05, at least 26 patients were needed in each group. Patients’ characteristics were compared with chi-square test or Fisher exact test. Median TTP, OS were all estimated by the Kaplan–Meier method compared by log-rank test. Response rates of different regimens were compared by chi-squared testing.
results

patients characteristics
Totally 53 patients were randomized and evaluated. Patient demographics at baseline are summarized in Table 1. All the patients had received anthracyclines while 66.7% of patients in the TP arm and 57.7% of patients in the TX arm received paclitaxel in the adjuvant/neoadjuvant setting. The median ages were 48 (32–67) and 49 (27–71) years, respectively. Sixteen of 27 patients in the TP arm and 19 of 26 patients in the TX arm had visceral metastases. More liver metastases were detected in the TX arm, but no difference in visceral/ nonvisceral metastases was found between the two arms. Overall, the two arms were well balanced with regard to the baseline characteristics except grade 3 tumors, which was more dominant in the TP arm than in the TX arm \( P = 0.014 \).

response and survival
The ORR was 63.0% (3 CR, 14 PR) in the TP arm and 15.4% (4 PR) in the TX arm \( P = 0.001 \). The clinical benefit rate was numerically but not statistically higher in the TP arm than in the TX arm \( P = 0.797 \).

Table 1. Patient baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>TP arm ((n = 27))</th>
<th>TX arm ((n = 26))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years, range)</td>
<td>48 (32–67)</td>
<td>49 (27–71)</td>
<td>0.797</td>
</tr>
<tr>
<td>Menstrual status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre/Post-menopausal</td>
<td>16/11</td>
<td>16/10</td>
<td>0.865</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1</td>
<td>17/10</td>
<td>18/8</td>
<td>0.630</td>
</tr>
<tr>
<td>TNM staging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>12</td>
<td>0.392</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Pathological types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>27</td>
<td>23</td>
<td>0.111</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vascular or lymphatic invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes/no</td>
<td>5/22</td>
<td>8/18</td>
<td>0.300</td>
</tr>
<tr>
<td>Histological grade(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>10</td>
<td>0.014</td>
</tr>
<tr>
<td>III</td>
<td>13</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral/nonvisceral</td>
<td>16/11</td>
<td>19/7</td>
<td>0.184</td>
</tr>
<tr>
<td>Bone</td>
<td>8</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>15</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Chest wall/breast</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>13</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Liver(^b)</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Brain(^b)</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Previous paclitaxel</td>
<td>18 (66.7%)</td>
<td>15 (57.7%)</td>
<td>0.500</td>
</tr>
</tbody>
</table>

\(^a\)Some of histological grades from local hospital were missing.

\(^b\)Brain metastasis was allowed to enroll as long as the brain disease was well controlled and nonsymptomatic.

DFI, Disease-free interval defined as the time from operation to first relapse; ECOG, Eastern Cooperative Oncology Group. Bold letter indicates statistically significant.

The clinical benefit rate was statistically higher in the TP arm than in the TX arm \( P = 0.014 \) (Table 2, a). Responses according to disease sites in evaluable patients are reported in detail in Table 2, b. The response rates were unanimously higher in the TP arm than in the TX arm, no matter where the metastases were.

For the secondary end points, median PFS (Figure 2) was 10.9 months in the TP arm (95% CI 2.2–19.8 months) and 4.8 months in the TX arm (95% CI 3.0–6.7 months) \( HR 0.29, 95\% CI 0.14–0.57, P < 0.001 \). Median OS was also statistically longer in the test arm \( P = 0.027 \) as illustrated in Figure 3.

safety
Supplementary Table 3, available at Annals of Oncology online, summarizes major treatment-related toxic effects. Overall, both treatment regimens were well tolerated and quite manageable. There were no treatment-related deaths. The incidence of G1/2 leukopenia and that of neutropenia were statistically higher in the TP arm than in the TX arm but no difference in other G1/2 hematological toxic effects was found. G3/4 neutropenia was similar between both arms. No G3/4 thrombocytopenia and anemia were observed. As what had been expected, GI tract toxic effects, such as vomiting (74.1% versus 34.6%, \( P = 0.004 \)), were more common in the TP arm than those in the TX arm while no big differences were seen in other toxic effects, including diarrhea, fatigue, hepatic abnormalities, and neuropathy. Likewise, more instances of G2/3 hand–foot syndrome were reported in the capecitabine arm \( P = 0.023 \).

A total of 256 cycles were given with a median of 5 cycles (range 2–6) in the TP arm and 4.6 cycles (range 2–8 cycles) in the TX arm. The dose of docetaxel was decreased in 6 patients mostly for G2/3 hand–foot syndrome. A total of 256 cycles were given with a median of 5 cycles (range 2–6) in the TP arm and 4.6 cycles (range 2–8 cycles) in the TX arm. The dose of docetaxel was decreased in 6 patients mostly for G2/3 hand–foot syndrome.

Table 2. Responses

<table>
<thead>
<tr>
<th></th>
<th>Arm A (TP) ((N = 27))</th>
<th>Arm B (TX) ((N = 26))</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>CR</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>14</td>
<td>51.9</td>
</tr>
<tr>
<td>SD</td>
<td>5</td>
<td>18.5</td>
</tr>
<tr>
<td>PD</td>
<td>5</td>
<td>18.5</td>
</tr>
<tr>
<td>b. Overall response rates according to disease sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm A(TP) ((N = 27))</td>
<td>Arm B(TX) ((N = 26))</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>CR/PR</td>
<td>ORR (%)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Lung</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Liver</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

ITT, intent to treat; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; TP, docetaxel–cisplatin; TX, docetaxel–capecitabine.
However, cisplatin was reduced only in two patients and docetaxel in one patient in the TP arm. Administration delay occurred mainly in the TX arm for reason of hand-foot syndrome. Note that two patients continued with single-agent capecitabine at the discretion of physicians after completing the study.

**Figure 2.** Progression-free survival (PFS) curves for two arms: the median PFS was 10.9 months in the TP arm (95% CI 2.2–19.8 months) and 4.8 months in the TX arm (95% CI 3.0–6.7 months) (HR 0.29, 95% CI 0.14–0.57, P < 0.001).

**Figure 3.** Overall survival (OS) curves for two arms: the median OS was 32.8 months in the TP arm (95% CI 23.2–42.2 months) and 21.5 months in the TX arm (95% CI 8.0–35.0 months) (HR 0.41, 95% CI 0.18–0.92, P = 0.027).
discussion

Several preclinical studies in TNBC cell lines had provided data establishing that they were more sensitive to DNA-damaging agents [6, 15], highlighting the potential value of platinum in this phenotype. A possible explanation would be the substantial overlap between TNBC and BRCA1-related breast cancer. Although there is doubt that sporadic TNBC are not carriers of BRCA1 mutation, there is evidence of BRCA1 pathway dysfunction in these tumors such as by epigenetic mechanisms [16]. Recently, a molecular pathway by which cisplatin induces cell death selectively in TNBC has been discovered, which suggests that p53 family members p63/p73 may play an important role in mediating platinum sensitivity in TNBC [17].

This hypothesis seems to be supported in neoadjuvant treatment of TNBC patients. Garber first reported in 2006 SABCS meeting that cisplatin monotherapy can achieve an ORR of 50% and a 22% pCR in TNBC patients. Decreased BRCA1 expression may identify subsets of TNBCs that are CDDP sensitive [8]. This was followed by Byrski et al. [18], showing that in a neoadjuvant setting a rather high rate of pathological CR was observed after treatment with CDDP in 10 (83%) of 12 BRCA1 mutation carriers. Platinum agents have also been proved to be effective in combination with other agents, including paclitaxel and bevacizumab in the neoadjuvant setting [19, 20].

However, it was not the same in all cases in a metastatic setting. The study by Sirohi et al. [7] retrospectively reviewed 155 patients treated by platinum-based chemotherapy (PBCT) for MBC and then analyzed outcomes according to the TNBC status. There was a slight significant gain in median PFS for TNBC patients (6 versus 4 months, \( P = 0.05 \)), a nonsignificant trend toward improvement of ORR (41% for TNBC versus 31% for non-TNBC, \( P = 0.3 \)) and similar OS. The authors concluded that PBCT could slightly improve the poor prognosis of TNBC. Nevertheless, in a recent report of Staudacher [9], among 143 patients treated for metastatic breast cancer with PBCT, although ORR was higher (33.3% versus 22%, \( P = 0.1 \)) in the TNBC group than the non-TNBC group, no difference in OS or PFS was observed.

So the question that remains to be asked is: are platinum specific to TNBC? Docetaxel and capecitabine is one of the most common choices in first-line treatment of MBC. However, in the present study of mTNBC patients, cisplatin-based combination chemotherapy demonstrated not only higher response rate but also remarkable improvement in PFS and OS compared with the TX regimen, even though 12 of 26 patients from the TX group received platinum-based chemotherapy in the second-line treatment. Although it is not suitable to draw a conclusion on survival advantage from merely a phase II trial, it is without doubt that in this subtype, it is cisplatin that generated extra clinical benefit out of these agents. The absolute values of PFS and OS in this group of TNBC patients were almost equal to what we have seen in so-called 'better' Luminal type or HER2 positive MBC after treatment of trastuzumab-based regimen. To further elaborate on this question, let us look back at the literature on the efficacy of cisplatin in MBC. The response rate of cisplatin was reported to be 42%–54% as single agent [21, 22]. If combined with docetaxel, the response rate was in the range 40%–70% and PFS/TTP was in the range 5–11 months [23–25]. It seems that these results in general MBC patients were similar to what we have seen in mTNBC patients of our study. But the fact was that quite a few patients in the literature were anthracycline-naïve. Furthermore, none of them received paclitaxel previously while all the TNBC patients in our trial were anthracylines-pretreated and two-thirds were paclitaxel treated. As we all know, when given after other chemotherapy, the response rate of cisplatin fell to 0%–9% [26, 27]. So one can speculate that it is possible that TNBC is more sensitive to cisplatin than non-TNBC. Although this study cannot yet tell for sure whether cisplatin is more efficacious in TNBC than non-TNBC, cisplatin is without doubt very effective in mTNBC.

The role of capecitabine in TNBC is even more insufficiently discussed, no work addressing this particular issue is found in the literature. Clues can be found only from retrospective subgroup analyses. In the famous FinXX study comparing recurrence-free survival with XT → CEX versus T → CEF as adjuvant therapy in patients with early-stage BC, XT → CEX improved RFS only in women with triple-negative disease (HR, 0.48; \( P = 0.0177 \)) [28]. A similar trend was also observed in another capecitabine adjuvant study US01062 trial [29]. However, studies in MBC indicated that capecitabine may not be suggested in mTNBC. In the randomized phase III trial comparing capecitabine–ixabepilone with capecitabine monotherapy, 1712 patients were treated with prior anthracycline and taxanes therapy, and 857 patients received capecitabine alone, of which 208 patients were TNBC patients. The overall response rate and PFS in the capcitabine monotherapy arm were 25% and 4.2 months in the overall population, but only 15% and 1.7 months in the TNBC subgroup [30], respectively. Furthermore, a single-arm phase II study of capecitabine with bevacizumab found that the response rate was nearly double in ER+ patients compared with triple-negative patients (47% versus 27%) with a similar difference in time to progression (8.9 versus 4.0 months) and OS (>16.6 versus 7.5 months) [31].

However, based on Kotsori’s study, among 89 mTNBC patients receiving capecitabine monotherapy as first to third line treatment, the response rate was 21% and OS was 39 weeks. The investigator concluded that capecitabine was a feasible treatment choice in mTNBC [32]. But as a matter of fact, the median TTP was only 11 weeks even in first-line treatment, which was definitely far from satisfaction. Even combined with docetaxel, as in our study, the PFS was just 4.8 months, which was not much better than results mentioned above. So capecitabine seems to have limited potency in mTNBC. Of course, it is too early to say that capecitabine should be avoided, since all these results came from retrospective analyses or small-sample studies. After all, capecitabine is one of the mainstay chemotherapeutic agents after anthracyclines and taxanes failure. Besides, one of the shortcomings of this study was that capecitabine was stopped after 6 cycles of combination therapy and it is possible that capecitabine can play a role in maintenance treatment.
Since these two regimens had been previously well studied and reported, toxic effects were not the main focus of this study. It turned out that the toxicity profile in our study was just as expected: Gastrointestinal toxic effects were more common in the cisplatin group, while hand-foot syndrome was mostly in the capecitabine group. Both regimens were well manageable.

Of course, there are some limitations of this open-label, phase II study, including small sample size and potential investigator bias as a single-institution study and inconsistency of the hormone receptor positivity cutoff due to the modification of international guidelines during the trial. Another issue is that TNBC is heterogeneous and response to chemotherapy might be different between basal and nonbasal TNBC. There possibly were imbalances of TNBC subtypes on the study arms. Despite its limitations, this phase II study provides proof of concept that cisplatin is considerably effective in TNBC and if not contraindicated, cisplatin, rather than capecitabine, might be a better first-line treatment choice. Capecitabine is acceptable but may play a limited role in mTNBC patients. The results are not sufficient to change clinical practice and need to be further validated in a large cohort of patients.

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disclosure

The authors have declared no conflicts of interest.

references

Elevated levels of preoperative CA 15-3 and CEA serum levels have independently poor prognostic significance in breast cancer

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Background: To evaluate the prognostic value of preoperative tumor markers, cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA), in breast cancers.

Patients and methods: Preoperative CA 15-3 and CEA levels of 1681 patients were measured. The association of both tumor markers levels with clinicopathological parameters and outcomes was investigated by univariate and multivariate analyses.

Results: Among 1681 patients, elevated preoperative CA15-3 and CEA levels were identified in 176 and 131 patients, respectively. Higher preoperative CA 15-3 and CEA levels were significantly associated with a larger tumor size, axillary node metastases, and advanced stage. Patients with elevated CA 15-3 and CEA levels showed worse survival, even in stage-matched analysis. Patients with normal levels of both CA15-3 and CEA showed better survival than those with one or both markers levels elevated. In multivariate analysis, elevated preoperative CA 15-3 and CEA levels were independent prognostic factors. The statistical significance of elevated preoperative tumor markers levels on survival was solidified with longer follow-up and larger study population.

Conclusions: Elevated preoperative CA 15-3 and CEA levels are associated with tumor burden and showed independent prognostic significance. Therefore, new treatment strategies are necessary for patients with elevated preoperative CA 15-3 and CEA levels in clinical practice.

Key words: breast cancer, CA 15-3, CEA, prognostic factor, tumor marker

introduction

Breast cancer is the most frequently occurring cancer in women from western countries and continues to be the most common fatal cancer together with lung, bronchus and colorectum cancers [1]. It is also the second most common malignancy in Korean women [2]. Despite the rising incidence of breast cancer, the survival rates have improved in recent years due to earlier detection and an increasing use of more effective systemic treatments based on prognostic factors [3].

Therefore, identifying prognostic and predictive factors is important to assist in decision making about treatment and to improve survival.

Along with the traditional prognostic factors such as tumor size, tumor grade, and lymph node status [4], the prognostic value of serum tumor markers has been investigated in breast cancer [5–8]. Some studies suggested that elevated carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA 15-3) levels provided the significant prognostic information; however, others reported no independent value of serum tumor markers [5–7]. Recently, Maric et al. [8] reviewed the role of serum tumor markers in breast cancer and they pointed out conflicting results of its prognostic value and rather emphasized the necessity of more extensive investigations for improved and a more cost-effective management of breast