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ORIGINAL ARTICLE

Cisplatin-ifosfamide combination chemotherapy in metastatic triple-negative, anthracycline- and taxane-pretreated breast cancer patients; a phase II study

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Summary

Purpose: *The purpose of this study was to prospectively evaluate the efficacy and toxicity of cisplatin and ifosfamide combination chemotherapy in metastatic triple negative breast cancer (TNBC) previously treated with anthracyclines and taxanes.*

Methods: *Patients were treated with cisplatin 20 mg/m^2 iv, days 1-5, over 30 min and ifosfamide 1200 mg/m^2 iv, days 1-5 over 2 h with mesna uroprotection. Therapy was repeated every 3 weeks. Responding patients received a maximum of 6 cycles of chemotherapy. Treatment was delayed in the event of grade 3 or higher hematologic or non hematologic toxicity until resolution to grade 2 or less. Treatment then proceeded as scheduled but with 20% dose reduction of both drugs.*

Results: *40 TNBC patients were enrolled. Median age was 43 years (range 37-49). Thirty (75%) patients had visceral involvement. Fourteen (35%) patients achieved objective response, disease stabilization occurred in 2 (5%) patients, while disease progression occurred in 24 (60%) patients. Grade 3/4 neutropenia occurred in 11 (27.5%) patients, while grade 3/4 thrombocytopenia was registered in 9 (22.5%) patients. Neurosensory toxicity was the commonest non hematologic acute severe toxicity (10%). With a median follow up of 14 months the median time to progression was 6 months and the median overall survival 12 months. Survival of responding patients was significantly better compared with non responders (p=0.000).*

Conclusion: *Our outpatient cisplatin / ifosfamide regimen displayed reasonable efficacy and toxicity in TNBC. However, the outcome did not differ from relevant studies in the literature. Further molecular studies and phase III trials are still needed to further improve treatment strategies in TNBC.*

Key words: breast cancer, chemotherapy, cisplatin, ifosfamide, metastatic, triple negative

Introduction

In our developing country screening programs for breast cancer are not well established. Consequently, we are confronted with many locally advanced and metastatic cases at oncology outpatient clinics.

The approach to breast cancer management nowadays is based not only on the TNM tumor stage and other classic clinicopathological information. Older and newer molecular markers play an ever increasing role in treatment decision of breast cancer.

TNBC is a breast cancer subtype that lacks expression of estrogen (ER), progesterone (PR), and HER-2 receptors. Treatment options for TNBC are thus limited [1].

Breast cancer must be considered as a heterogeneous group of diseases. Using microarray analysis, breast cancer had been classified into 5 subgroups of tumors: luminal A, luminal B, HER-2 positive, normal breast-like, and basal-like [2-4]. Up to 85% of TNBC correspond to basal-like breast cancer [5,6]. In view of the high level of genomic instability of TNBC and basal-like breast cancer due to deficiency of DNA repair mechanisms [7], the use of platinum derivatives and alkylating agents in these patients is currently under investigation [8].

We carried out this study to evaluate the efficacy and toxicity of an outpatient regimen based on cisplatin and one of the alkylating agents (ifosfamide) in metastatic TNBC patients previously treated with anthracyclines and taxanes.

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Methods

Eligibility criteria

Eligible patients were non pregnant females aged 18 years or above, having histologically confirmed TNBC, with clinically or radiologically measurable disease and having received prior treatment with anthracyclines and taxanes in the adjuvant or metastatic setting. Other eligibility criteria were ECOG performance status (PS) ≤2, life expectancy greater than 12 weeks, and adequate organ function (white blood cell count >3.5 × 10/ L, absolute neutrophil count ≥ 1.5 × 10/L, platelet count ≥ 100 × 10/L, hemoglobin > 9 g / dl, serum creatinine ≤ 1.4 mg, bilirubin ≤ 1.5 × upper limit of normal, ALT or AST ≤ 2.5 × upper limit of normal).

Hormone receptors estimation

For immunohistochemical detection of ER rabbit the monoclonal antibody, clone SP1, code 249R-18 (Cell Marque, Rocklin, CA 95677, USA), was used. For PR detection the mouse monoclonal antibody, clone PgR636 (code IS068 DAKO, Glostrup, Denmark) was used. ER and PR were scored according to Allred et al. [9].

HER-2 estimation

HER-2 was detected using the mouse monoclonal antibody, clone CB-11, code 237M-18 (Cell Marque, Rocklin, CA 95677, USA). HER-2 staining was scored according to the American Society of Clinical Oncology/College of American Pathologists guideline [10]. When the score by immunohistochemistry was 2, FISH was applied to determine negativity or positivity.

The study was approved by the local ethics committee and all subjects gave written informed consent.

Study regimen

Patients were treated with cisplatin 20 mg/m^2 iv, days 1-5, administered in 150 ml N/S over 30 min, preceded by 250 ml 5% D/W plus 250 ml Ringer's solution. Ifosfamide was administered at a dose of 1200 mg/m^2 iv, days 1-5, in 500 ml N/S over 2 h. Mesna uroprotection was by giving 20% of the ifosfamide dose at the time of administration of ifosfamide and then at 4 and 8 h. Cycles were repeated every 3 weeks. Responding patients received a maximum of 6 cycles of chemotherapy. Subsequent courses were at the discretion of the treating physician. All patients received standard antiemetic medication. Routine use of primary prophylactic granulocyte colony-stimulating factors (G-CSF) was not permitted, although secondary prophylaxis was allowed for patients who had absolute neutrophil count <0.5 × 10 / L or neutropenic fever. Treatment was delayed in the event of grade 3 or higher toxicity until resolution to grade 2 or less. Treatment then proceeded with 20% reduction of the drug doses.

Response and toxicity assessments

Detailed clinical evaluations, including toxicity assessments were performed before the start of every new cycle of chemotherapy. Toxicity was assessed using the NCI CTC version 3 [11]. Radiologic evaluations were performed every 6 weeks.

Standard WHO criteria were used to define response [12].

Statistical methods

The endpoints of this study included tumor response, treatment toxicity, progression-free and overall survival. Progression-free survival was measured from the date of the start of treatment until the date of progression or death. Overall survival was measured from the date of the start of treatment until the date of death. Post-treatment toxicities were coded as the worst grade observed after the start of treatment. Patient characteristics and adverse events were presented as percentages or median values with ranges.

The Kaplan-Meier method was used to estimate the median progression-free and overall survival rates and the Wilcoxon-Gehan test was used to define the significance of difference between the survival of responders and non responders. Statistical significance was set at $p<0.05$.

Results

From December 2006 to March 2009, 40 TNBC patients were enrolled. Patient characteristics are listed in Table 1. Median age was 43 years (range 37-49). Thirty (75%) patients had visceral involvement.

Four (10%) patients received the study regimen as their first-line therapy for metastatic disease, while 36 (90%) received it as second-line therapy.

Response

The overall response rate was 35% (14 patients). Disease stabilization occurred in 2 (5%) patients and disease progression in 24 (60%) patients. All 4 cases that received the protocol as a first-line therapy for metastatic disease were among the responding cases. Table 2 shows the different responses.

Toxicity

Patients received a median of 4 cycles (range 2-6). Generally, toxicity was manageable. Severe hematologic and non-hematologic toxicities are summarized in Table 3. The median duration of delay due to toxic-

Table 1. Patient characteristics

Characteristics	*Patients, N*	*%*
Median age, years (range)	43 (37-49)	
Previous adjuvant chemotherapy		
TAC	4	10
FAC	36	90
ECOG performance status		
0	3	7.5
1	34	85
2	3	7.5
Sites of metastasis		
Liver	14	35
Lung	16	40
Extensive bone disease	10	25

TAC: paclitaxel, adriamycin, cyclophosphamide; FAC: 5-fluorouracil, adriamycin, cyclophosphamide

Table 2. Treatment response

Response	*Patients, N*	*%*
Complete	2	5
Partial	12	30
Stable	2	5
Progression	24	60

All of the patients developed metastatic disease after receiving adjuvant chemotherapy, but the study regimen was administered as first-line for metastatic disease in only 4

ity was 8 days (range 6-15). Grade 3/4 neutropenia occurred in 11 (27.5%) patients, while grade 3/4 thrombocytopenia was registered in 9 (22.5%) patients. Neurosensory toxicity was the commonest non-hematologic severe toxicity (10%).

Survival

After a median follow up time of 14 months (range 4-21), median time to progression was 6 months (range 3-10), and median overall survival 12 months (range 5-22).

Figures 1 and 2 show the progression-free and overall survival curves of the studied patients. Figure 3 shows the overall survival curves of responders and non responders, with highly statistical better survival for responders (p=0.000).

Discussion

Breast cancer is the most frequent cancer among Egyptian females. It accounts for 35.7% of all newly diagnosed cancers in females [13]. It is worth studying TNBC in African countries like Egypt because clustering of such cases in women of African descent has been reported [14].

Table 3. Grade 3 and 4 toxicities

Toxicity	*Grade 3*		*Grade 4*	
	N	*%*	*N*	*%*
Hematologic				
Neutropenia	11	27.5	1	2.5
Thrombocytopenia	9	22.5	–	–
Anemia	3	7.5	1	2.5
Non hematologic				
Neurosensory toxicity	4	10	–	
Nausea and vomiting	3	7.5	–	
Fatigue	3	7.5	1	2.5
Alopecia	3	7.5	–	
AST	1	2.5		
ALT	1	2.5		
Bilirubin	–	–	–	–

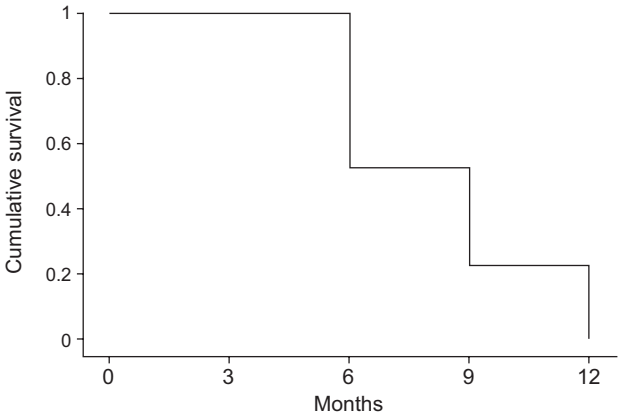

Figure 1. Progression-free survival of all patients.

Several studies on TNBC have provided data establishing that this type of breast cancer is associated with the poorest prognosis [6,15-17].

No treatment recommendations can be proposed at the present time due to absence of phase III data [8].

Approximately 70% of breast cancers in individuals carrying a germline BRCA1 mutation are triple neg-

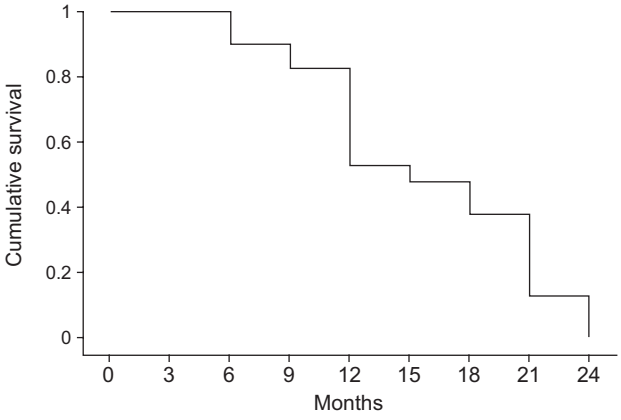

Figure 2. Overall survival of all patients.

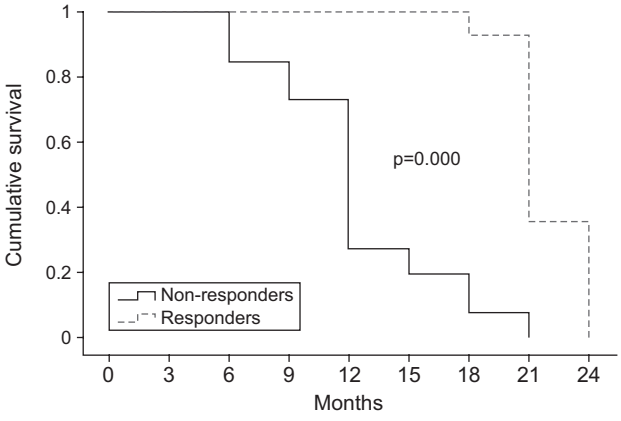

Figure 3. Overall survival of responders and non responders.

ative. Both BRCA1-associated and sporadic TNBCs share many histopathologic and molecular features. Both are typically basal-like. These tumors share a pattern of genomic instability. BRCA1-associated and at least a subset of sporadic TNBCs may be sharing defects in BRCA1-associated pathway related to DNA repair. BRCA1-deficient cells are particularly susceptible to interstrand cross-linking agents like cisplatin [18].

Single-agent cisplatin has been investigated as a neoadjuvant therapy in TNBC. Ten patients with breast cancer and BRCA1 mutation were treated with 4 cycles of neoadjuvant cisplatin. Pathologic complete response was observed in 9 patients (90%) [19]. In another study 28 TNBCs were treated with 4 cycles of cisplatin. Six (22%) achieved pathologic complete response including 2 cases with BRCA1-germline mutation. Eighteen patients (64%) achieved clinical response [20].

Many authors have used platinum-based chemotherapy (PBCT) as salvage therapy in anthracycline/taxane-resistant metastatic breast cancer [1,21-24]. However, few published studies investigated PBCT in metastatic TNBC [8].

Sirohi et al. [1] retrospectively studied the effect of PBCT in early and metastatic breast cancer. In the metastatic cases (155 patients), PBCT achieved significantly better progression-free survival in TNBC compared to non-TNBC.

Krockenberger et al. [25] treated a 52-year-old female with metastatic TNBC who had extensive liver metastases resistant to taxane and yttrium radiotherapy. Cisplatin /ifosfamide (12 cycles) induced regression of the liver metastases from over 30 cm to 6 cm as revealed by CT scan. Dose-limiting toxicity was impairment of renal function and pancytopenia.

Koshy et al. [26] retrospectively examined the clinical outcome of cisplatin and gemcitabine combination chemotherapy in 36 patients with metastatic breast cancer. The median progression-free survival for TNBC and non-TNBC were 5.3 and 1.7 months, respectively (p=0.058).

Maisano et al. [27] carried out a phase II study to evaluate the activity of carboplatin/gemcitabine combination in 31 pretreated metastatic TNBC. Overall survival rate was 32%. After a median follow up of 34 months, all patients progressed with a median time to progression of 5.5 months and median overall survival of 11 months. Dose reductions, delays, and omissions occurred in 60, 29 and 18% of the cycles. Grade 3/4 neutropenia occurred in 17/31 patients. Ten patients had grade 3/4 thrombocytopenia. Non hematologic toxicities were manageable. They concluded that carboplatin/gemcitabine combination could be a reasonable option for treating metastatic TNBC.

Staudacher et al. [8] retrospectively studied the difference of efficacy of PBCT in the treatment of TNBC and non-TNBC (total number of cases was 143). No difference in the outcome was observed despite the fact that TNBC is known to have a poorer survival. They hypothesized that PBCT could improve the poor prognosis of metastatic TNBC with acceptable toxicity.

In the present study the commonest hematologic and non hematologic grade 3/4 toxicities were neutropenia and peripheral neuropathy, respectively, which coincides with many literature reports concerning PBCT [21-24,27,28].

No patient refused continuation of chemotherapy and no treatment-related deaths occurred. Despite the fact that responders showed statistically better survival than non responders, the protocol did not achieve extraordinary response rates or survival figures.

Increasing understanding of the cellular aberrations inherent to cancer cells has allowed the development of therapies to target biologic pathways. The clinical development of poly(ADP-ribose)polymerase (PARP) inhibitors is an example of this strategy. PARP plays a key role in DNA repair mechanisms. Inhibition of PARP in a DNA repair defective tumor can lead to gross genomic instability and cell death [29]. Future phase III studies comparing different chemotherapy and target therapy combinations are warranted.

Conclusion

This outpatient cisplatin/ ifosfamide protocol showed reasonable efficacy and toxicity in TNBC, however survival figures did not exceed those of the relevant literature. Molecular studies and phase III trials are needed to further improve treatment strategies.

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