Phase 1 Trial of Ifosfamide and Adriamycin in Metastatic Breast Cancer

Z. Aziz,S. Sana,M. Akram (Department of Oncology, Allama Iqbal Medical College, Lahore.)
N. Ilyas (INMOL Hospital, Lahore.)

Abstract

Objective: A Phase I trial was conducted in patients with estrogen negative receptors (ER) or hormone refractory metastatic breast cancer to determine the maximum tolerated dose (MTD) of ifosfamide with a fixed dose of doxorubicin. A secondary objective was to determine the efficacy of the combination in metastatic breast cancer.
Methods: Fifteen patients were entered in the study in cohorts of three patients at each dose level of ifosfamide. The dose of doxorubicin was fixed at 45mg/m2. Five different dose levels of ifosfamide were tested ranging from dose level I of 1.5gms/m2 day 1-3 to level V at 2.5 gms/m2 day 1-3.
Results: Dose escalation of ifosfamide was stopped at 2.5gms/m2 . The MID of ifosfamide was 2.25gmsIm2 day 1-3 in combination with doxorubicin. All patients in the study were assessable for toxicity. Neutropenia and thrombocytopenia were the major dose limiting toxicities. Other toxicities included anemia, confusion and hematuria. Objective responses were documented in 11 of 15 patients (73.3%). Median time to treatment failure (TTF) was 13 months. Median overall survival (OS) was 18 months.
Conclusion: The combination of ifosfamide and doxorubicin was a practical well tolerated regimen. There was substantial evidence of clinical activity in this phase I trial. This combination should be further evaluated, as an attractive alternative to taxanes for patients in developing countries where cost effectiveness is important (JPMA 51 :400, 2001).
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Introduction

Breast cancer is the second most common cause of cancer related deaths in women[1]. Standard adjuvant chemotherapy regimens for early breast cancer include CMF (cyclophosphamide/methotrexate/5-florouracil), AC (adriamycin/cyclophosphamide) and FAC (fluorouracil! cyclophosphamide/doxorubicine)[2-4]. Despite adjuvant chemotherapy, metastatic disease occurs in up to 50% of patients and becomes incurable.
Anthracycline based regimens remain standard first line treatment for advanced breast cancer with an objective tumor response rate of 50-60%[5]. Classical agents used in combination with doxorubicin include cyclophosphaniide, taxanes, ifosfam ide, 5-fluorouracil and cisplatin.
Cyclophosphamide is one of the most active and widely used drugs in adjuvant treatment of breast cancer. Ifosfamide is a non-cross resistant and structurally related alkylating agent with significant anti-tumor activity seen in testicular cancers, lymphornas and lung cancer[6-8]. In advanced breast cancer single agent activity of ifosfamide is approximately 30%[9]. Ifosfamide based combination with etoposide, mitoxantrone, epirubicin and doxorubicin have significant activity in advanced breast cancer[10-12].
Based on the activity of ifosfamide we conducted a phase 1 trial to determine the maximum tolerated dose of of ifosfamide in combination with a fixed dose of doxorubicin at 45mg/m^2. The patients who had received prior adjuvant chemotherapy with a non-anthracycline regimen were included. We elected

to start with a dose of 1.5gms/m^2 (day 1-3) of ifosfamide. A secondary objective was to determine objective response rates, time to treatment failure and overall survival.

Patients and Methods

Eligibility

Fifteen patients with hormone refractory or estrogen receptor negative metastatic breast cancer were enrolled. Eligibility criteria included metastatic breast cancer in patients who had not received doxorubicin either as part of adjuvant treatment or in metastatic disease. All patients 18 years or older, with ECOG performance status of 2 or less, with normal hematologic, hepatic and renal profile were eligible for the protocol. A complete history and physical examination was performed on all patients entering the trial. Metastatic workup included mammography, bone scan, abdominal and pelvic ultrasound and liver scan. CT scans were done when indicated. Echocardiography was performed on all patients and patients with ejection fraction of less than 50% were excluded. Patients who had central nervous system metastasis documented on MRI or CT scan were also excluded.

Treatment Plan

Doxorubicin and ifosfamide were given on an outpatient basis at three weeks interval. Doxorubicin 45mg/m^2 was given in one hour on day one only. Ifosfamide and mesna were mixed in 500m1 of normal saline and administered over 3 hours in outpatient setting for three days. Patients were encouraged to take oral fluids prior to and throughout therapy. In case they were unable to achieve adequate oral hydration intravenous fluids were given. Besides hydration patients received appropriate supportive care to ameliorate the symptoms of nausea and vomiting. Intravenous lorazepam Img, dexamethasone 20mg and topisetron were used as part of anti-emetic protocol prior to therapy. Prophylactic use of growth factors and antibiotics were not permitted.

Dose Escalation and definitions of MTD and Dose-Limiting Toxicity

Doxorubicin was given at fixed dose schedule of 45mg/m^1. Initial starting dose of ifosfamide was 1 . 5gms/m^2 day 1-3. Evaluation of further ifosfamide dose levels studied is indicated in Table 2.

Table 2. Dose Escalation Levels.

Studied Dose Level						
Level	Drug doses (mg/m^2) (Range/Patient)		G-CSF	No. of patients	No. of cycles	DLT[a]
	Ifosfamide	Doxorubicin				
1.	1500 (1.5g) -	45	No	3	15 (3-6)	
2.	1750 (1. 75g) -	45	No	3	15 (3-6)	
3.	2000 (2.0g) -	45	No	3	15 (3-6)	
4.	2250 (2. 25g)	45	No	3	12 (3-6)	
1[b,c]						
5.	2500 (2.5g)	45	Yes	3	12 (3-6)	
3[b,c,d]						

a Dose-limiting toxicity
b Febrile neutropenia
c Grade 3 thrombocytopenia
d Severe anemia

Mesna was used with ifosfamide at equivalent doses.

A modified Fibonacchi system was used. A minimum of three patients were entered at each dose level and maintained at that dose level throughout the treatment. If none of the three patients experienced dose-limiting toxicity (DLT; defined later), then the next three patients were enrolled at the next higher level. If one patient experienced DLT, then the treatment level was expanded to six patients. If no more than one of six patients experienced DLT, then the next cohort of patients was treated at the next higher dose level. If two or more patients at any dose level experienced DLT, then that level was considered to have. exceeded MTD and the level immediately preceding that level was designated as the MTD.

DLT was defined as any first course grade III or grade IV non-hematologic toxicity (except nausea and vomiting), grade IV leukopenia, neutropenia or thrombocytopenia, or neutropenic fever. DLT also considered to have been reached if the patient was unable to complete the first treatment cycle and having recovered from toxicity in time to begin the second cycle as scheduled (beginning week 4). Patients who required more than one week of dose delay in their first treatment cycle were thus considered to have experienced DLT. During a treatment cycle both doxorubicin and ifosfamide were withheld for one week, if on the day of planned treatment, ANC was <1000 and platelet count <100,000/mi, or if >2 nonhematologic toxicities were present. For initiation of the next chemotherapy cycle patients were required to achieve ANC >1500, platelet count >100,000 and full resolution of all non-hematologic toxicities.

Dose modifications and duration of treatment

No dose level changes were allowed on individual patient entering a dose level. Patients who experienced DLT were permitted to continue treatment if clinically indicated at the next lower dose level. Treatment cycles were continued till disease progression in responding patients.

Evaluation at Baseline and during treatment

Pre-treatment analysis included a complete history and physical examination. A complete blood count,

biochemical profile and urine analysis were obtained prior to each cycle. During each treatment cycle urine analysis was done daily for four days to check for microscopic hematuria. Hematologic profile was repeated on day 8 and 15 of every cycle. Patients were evaluated weekly for toxicities. Imaging studies were repeated after every two cycles. Echocardiogram was performed on all patients after cycle four and subsequently in patients who received maximum cumulative dose of 450mg/m^2 of doxorubicin.

Response time to treatment failure and survival Standard response criteria defining CR, PR, stable disease or no response was used. Objective response (CR, PR) had to have a minimum duration of thirty days. Time to treatment failure was defined as death or progressive disease and was calculated from day one of the first cycle of ifosfamide and doxorubicin. Survival was calculated from day one of the first cycle of ifosfamide and doxorubicin.

Results

Fifteen women with metastatic and hormone refractory or estrogen receptor breast cancer were entered in this Phase 1 trial. The age range was between 40 and 55 years with a median age of 45 years. Dominant disease sites included liver (8 patients), lung (7 parents), bone (4 patients) and soft tissue involvement (12 patients). Other organ involvement included bone marrow, lymph nodes and in one patient adrenal glands. Eight patients had received prior chemotherapy with cyclophosphamide, methotrexate and 5-florouracil while the remaining patients presented with stage IV disease.The median disease free survival of eight patients receiving prior adjuvant therapy was 19 months (range 4-42 months). General profile of the patients is listed in Table 1.

Table 1. General Patient Profile (n=15).

Age (Years)	40 -55
Median	45
Menopausal Status	
Pre-menopausal	6
Post-Menopausal	9
Performance Status (ECOG)	
I	7
II	8
Chemotherapy	
Prior	8
None	7
Organs	
Liver	8
Lung	7
Bone	4
Soft Tissue	12
Others	8
No. of Organs Involved	
>2	7
>3	8
Cycles Delivered	1-9 (69)
Median	6

All 15 patients received a total of 69 cycles (median 6 cycles).

Dose escalation and determination of MTDs and DLT

The First six patients treated at dose levels 1 and 11 with 1.5gms/m2 and 1.75gms/$m^2$of ifosfamide day 1-3 completed the first two cycles without any DLT. The next three patients at dose level III of

ifosfamide 2.0gms/m^2 day 1-3 also tolerated their first cycle without complications. However, one of three patients experienced grade III neutropenia after completing two cycles. This resolved within three days without any significant complications. Two patients at level IV had haemorrhagic cystitis in the second and third cycles, which resolved on hydration. One patient developed grade III neutropenia, septicemia and thrombocytopenia on cycle four. The sepsis resolved on intravenous antibiotics without any complications. Three patients were entered at level V. The first patient developed grade IV neutropenia (ANC <100), anemia and thrombocytopenia seven days after administration of first cycle. She was admitted with gram-negative sepsis and required platelets, packed cells and growth factors. She also became delirious and confused and subsequently expired. Patient two developed grade III hematuria, neutropenia and thrombocytopenia. She required two units of packed red cells. Patient three at level V also developed grade IV anemia, thrombocytopenia and neutropenia after cycle one requiring blood products, antibiotics and growth factor support. She also had grade III hematuria on third day of her chemotherapy. She recovered and was put on level IV that she tolerated well and continued to complete four cycles. Thus ifosfamide 2.5gms/m^2 day 1-3 exceeded the MTD and 2.25gms/m^2 day 1-3 was judged to be the MTD.

Toxicities during all cycles of chemotherapy

The most frequent non-dose limiting adverse events observed were hematologic toxicities as shown in

Table 3. Hematological toxicity grade according to SWOG Criteria of Ifosfamide and Doxorubicin.

Hematological	Leve I n=3	Level II n=3	Level III n=3	Level IV n=3	Level V n=3
Anemia					
Grade 1	-	-	-	-	-
Grade 2	-	-	-	-	-
Grade 3	-	-	1	2	1
Grade 4	-	-	-	-	2
Neutropenia					
Grade 1	-	-	-	-	-
Grade 2	-	-	-	-	-
Grade 3	-	-	2	2	1
Grade 4	-	-	-	1	2
Febrile Neutropenia	-	-	1	1	3
Thrombocytopenia					
Grade 1	-	-	-	-	-
Grade 2	-	-	-	-	-
Grade 3	-	-	-	1	1
Grade 4	-	-	-	1	2

Table 3, which included grade III leukopenia in six patients and thrombocytopenia in two patients. All these 3 patients had neutropenic fever. Grade 3 anemia was noted in four patients. Among non-hematologic grade 3 adverse events, stomatitis (five patients), nausea and vomiting (six patients),

microscopic hematuria (one patient) and asthenia (three patients) were encountered (Table 4).

Table 4. Non -Hematological toxicity grade according to SWOG Criteria of Ifosfamide and Doxorubicin.

Non-Hematological	Leve I n=3	Level II n=3	Level III n=3	Level IV n=3	Level V n=3
Hematuria	-	-	-	-	-
Grade 1	-	-	-	2	-
Grade 2	-	-	-	-	-
Grade 3	-	-	-	-	1
Grade 4	-	-	-	-	1
Neurological					
Grade 1	-	-	-	-	-
Grade 2	-	-	-	-	-
Grade 3	-	-	-	-	-
Grade 4	-	-	-	-	-
Nausea and vomiting					
Grade 1	-	-	-	-	-
Grade 2	-	-	-	-	-
Grade 3	-	-	-	-	-
Grade 4	-	-	1	2	3
Asthenia					
Grade 1	-	-	-	-	-
Grade 2	-	-	1	1	-
Grade 3	-	-	-	1	2
Grade 4	-	-	-	-	-
Stomatitis					
Grade 1	-	-	-	-	-
Grade 2	-	-	-	-	-
Grade 3	-	-	-	2	3
Grade 4	-	-	-	-	-

Grade IV alopecia was universal.

Overall Chemotherapy Administration

Overall a total of 69 cycles were administered on this trial. The median of cycles per patient was six, with a range of one to nine cycles. There was little evidence of cumulative toxicity during this trial. Treatment delays occurred in six patients due to hematologic toxicities.

Anti-tumour Activity

Response was not the primary end point in this Phase I study; however significant anti-tumor activity was observed. Objective responses were achieved in 11 patients (73.3%). Complete responses were seen in three patients and partial response in eight patients. One patient had stable disease and two patients had disease progression. One patient died before assessment for response could be made.

Present Status

Four patients have expired of which one death was due to treatment related mortality and three patients expired due to progressive disease. Median time to treatment failure was 13 months with a range of 3 to 27 months. Overall survival ranged from 6 to 39 months with a median of 17 months.

Discussion

Combination chemotherapy is considered more effective than monotherapy in metastatic breast cancer[13]. To date anthracyclines are perhaps the most widely used and may be the most active drugs in breast cancer[14,15] with single agent response rates of 40% to 50%.

Cyclophosphamide is an alkylating agent frequently' used in adjuvant setting in combination with anthracyclines or methotrexate. Ifosfamide is closely related to cyclophospharnide and is non-cross resistant. Ifosfamide is not part of standard adjuvant therapy for breast cancer.

Previous studies with ifosfamide and anthracyclines have shown high response rates with tolerable side effects[12,16,17]. Miliward et al[17] treated 31 patients with advanced breast cancer using ifosfamide at Sgms/m^2 and doxorubicin at 40mg/m^2 every 21 days. An objective response of 71% (22 of 31 patients) was seen with five patients achieving a CR. Grade 3 and 4 neutropenia was observed in 7% and a median survival of 44 weeks. In another study Perez et al used ifosfamide at 2grns/m^2 from day 1-3 in combination with mitoxantrone 12mg/m^2 every 21 days. Sixty one percent patients achieved an objective response with 12% achieving CR. Grade 3 and 4 neutropenia was observed in 39% patients. The broad spectrum of activity of ifosfamide and doxorubicin provided a strong rationale for the combination of these two drugs. The selection of doses for the combination was based on the fact that patients who had received prior chemotherapy were eligible for the study. We therefore started level I dose of itoslamide at 1 .5gms/m^2 day 1-3 with doxorubicin at a fixed dose of 45mg/m^2 . The dose of doxorubicin was chosen en the basis of the study by Jones et al[18] which allowed us the to increase the dose of ifosfamide without running into significant toxicities of doxorubicin.

We defined the MTD of ifosfamide at 2.25gms/m^2 day 1-3 with a total dose of 6.75gms/m^2. Increasing the dose to level V at 2.5gms/m^2 day 1-3 patients developed grade 4 neutropenia and thrombocytopenia and grade 3 hematuria. One patient expired due to febrile neutropenia.

CSF use may ameliorate neutropenia to permit an increase in dose intensity, evidence for substantial increases in dose intensity or'clearly improved chemotherapy activity based on CSF support is so far lacking[19]. The high cost of CSFs places a significant burden on health rare resources especially in developing countries where the entire cost of treatment is borne by the patient[19-21]. However G-CSF was used in two patients who developed febrile neutropenia at level V. The only grade III non-hernatologic toxicity at level IV was hematuria, which resolved on hydration and required additional dose of mesna in one patient.

Although efficacy was not the primary outcome measure, the anti neoplastic activity of this combination was significant. Objective responses were observed in eleven patients (73.3%) with complete responses in three patients (26.6%).This response is somewhat similar to that reported by Bitran et al[16]. Median time to treatment failure was 13 months (range 5-26 months). Overall survival ranged from 7 to 45 months (median 18 months). Definition of true activity level of ifosfamide-

doxorubicin level will have to be tested in a larger number of patients in a phase II trial. It is encouraging to note the activity of this regimen. This is important for patients in developing countries where economic constrains are a major impediment in the treatment of cancer patients and use of taxanes is limited. In conclusion ifosfamide at a dose of 2.25gms/m^2 day 1-3 with doxorubicin at 45mg/m^2 is a well-tolerated regimen with significant antineoplastic activity. Phase I/Il studies are ongoing with an amended dose of Doxorubicin to 60mg/m^2.

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