Cisplatin & IV Etoposide combination in the treatment of advanced breast cancer pretreated with anthracyclines

Anmar A. Allami[1]

ABSTRACT

Background: Aims of this study was to determine the benefit of cisplatin and i.v etoposide combination in treatment of advanced breast cancer (ABC) patients who were pretreated with anthracyclines, as an alternative to the newer, more expensive, and unavailable anticancer drugs like Taxanes, carboplatin, and gemcitabine.

Patients and methods: The study was performed in the period from March 2010 to June 2016, 235 patients were given cisplatin 50mg/m^2 and etoposide 100mg /m^2 for 6 cycles. The patients were divided into 4 groups according to the site of metastasis (vertebral metastases, liver metastases, loco-regional metastases, and pleuro-pulmonary metastases).

Results: Evaluation of treatment was considered on two levels: Whole 235 patient level, and patient-group level. On whole patient level: Response to Treatment was 65.1%, which is higher than similar responses in many other studies. While on patient-group level: response to treatment was highest in patients with vertebral secondaries 75.3%. There was drug toxicity in all groups of patients. Some patients did not continue the treatment protocol because of bad performance status, toxicity and death.

Conclusion: In comparison with other regimes of chemotherapy cisplatin and i.v etoposide are still useful anticancer drugs in the management of advanced breast cancer.

Key words: advanced breast cancer, anthracyclines, taxanes, cisplatin, etoposide.

مزيج سيسبلاتين ورابع إيتوبوسيد في علاج سرطان الثدي المتقدم الذي يتم علاجه بالأنثراسكلينا

الخلفية: تهدف هذه الدراسة إلى تحديد فائدة مزيج سيسبلاتين وإيتوبوسيد الرابع في علاج مرضى سرطان الثدي المتقدم (ABC) الذين عولجوا بمضادات أنثراسيكلين كبديل للعقاقير المضادة للسرطان الأحدث والأكثر تكلفة وغير المتاحة مثل التاكسان، كاربوبلاتين، وجيمسيتابين.

المرضى والطرق: أجريت الدراسة في الفترة من مارس ٢٠١٠ إلى يونيو ٢٠١٦، وتم إعطاء ٢٣٥ مريضا سيسبلاتين 50mg/m2 و etoposide 100mg / m2 لمدة ٦ دورات. تم تقسيم المرضى إلى ٤ مجموعات وفقا لموقع ورم خبيث (الانبثاث العمود الفقري، الانبثاث الكبد، الانبثاث الموضعي ، والانبثاث الرئوي الرئوي).

النتائج: تم اعتبار تقييم العلاج على مستويين: مستوى المريض بالكامل ٢٣٥، ومستوى مجموعة المريض. على مستوى المريض ككل: كانت الاستجابة للعلاج ٦٥.١ ٪، وهو أعلى من الاستجابات المماثلة في العديد من الدراسات الأخرى. بينما على مستوى مجموعة المريض: كانت الاستجابة للعلاج أعلى في المرضى الذين يعانون من المرتبات الثانية للفقراء ٧٥.٣٪. كان هناك سمية الدواء في جميع مجموعات المرضى. بعض المرضى لم يواصلوا بروتوكول العلاج بسبب حالة الأداء السيئة والسمية والموت.

الخلاصة: بالمقارنة مع الأنظمة الأخرى للعلاج الكيميائي، فإن سيسبلاتين وإيتوبوسيد على سبيل المثال لا يزالان من الأدوية المضادة للسرطان مفيدة في علاج سرطان الثدي المتقدم.

الكلمات المفتاحية: سرطان الثدي المتقدم، أنثراسيكلين، تاكسان، سيسبلاتين، إيتوبوسيد

[1]Internist, Hematooncologist, Al-Sader Teaching Hospital, Basrah, Iraq.

INTRODUCTION

Survival in breast cancer is improving, mostly, due to early diagnosis, better ways of diagnosis, better ways of evaluation, and newer modalities of treatment. However about 40% of patients after curative surgery with or without adjuvant chemotherapy may have tumor recurrence. Hormonal therapy may be used for advanced breast cancer (ABC) but chemotherapy is used for patients with negative receptors and hormone refractory disease, and for patients with unknown receptors (like many of our patients). Chemotherapeutic regimes using anthracyclines were used to treat ABC for long time but since the nineties Taxanes became the standard treatment after these chemotherapeutic failures.[1-5] The discovery of Her 2/neu receptor which is a member of the human epidermal growth factor receptor (HER/EGFR/ERBB) family, was a great an advance in to breast cancer management. Amplification or over-expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer. In recent years the protein has become an important biomarker and target of therapy for approximately 30% of breast cancer patients.[6] Single agent docetaxel was superior to two combination regimes mitomycin + vinblastine (MV), and methotrexate + 5Fu (MF), but equivalent to 5FU + vinorelbine (FUN).[2] A higher response rate than that achieved with CMF was observed by giving etoposide + cisplatin as first-line treatment in small randomized trial.[3] Another study using continuous infusion etoposide plus cisplatin in advanced breast cancer as second-line treatment that resulted in moderate short-term, antitumor activity at the expense of marked toxicity.[4] Furthermore 42%-50% response rates were reported by prolonged administration of oral etoposide and cisplatin in two trials which were higher than paclitaxel results.[5] Another study held by the Turkish oncology group (TOG) showed 36% response rate that was higher than paclitaxel using cisplatin and oral etoposide in advanced breast cancer.[1]

Aim of this study was to determine the benefit of cisplatin and i.v etoposide combination in treatment of advanced breast cancer (ABC) patients who were pretreated with anthracyclines, as an alternative to the newer, more expensive, and unavailable anticancer drugs like Taxanes, carboplatin, and gemcitabine.

PATIENTS AND METHODS

This study was a prospective study of patients with advanced breast cancer who were pretreated with at least three cycles of chemotherapy protocol containing an anthracyclie (doxorubicine, epirubicine), relapsed after 6 months of anthracycline-based chemotherapy. They should have a histologically or cytologically confirmed, locally advanced or metastatic breast cancer. They should meet the following criteria: Age 20-60 years with a median of 40.33, with a performance status of 2,3 or 4 according to WHO criteria,[8] having a measurable or evaluable disease (metastasis to vertebrae, skin, pleura, lung and liver). They may have an unknown, positive, or negative hormonal status, and positive or negative Her2neu receptors, acceptable bone marrow reserve (Hb > 9 gm / 100ml, WBC > 4000/cmm, and Platelet count > 100000/cmm), acceptable liver (s.bilirubin, sGOT, sGPT and s. alkaline phosphotase) and renal (blood urea and s. creatinine) reserves. And none have ever radiotherapy. The following patients were excluded: Those with brain secondaries, because chemotherapy is useless and better treated with radiotherapy. Also those with a second primary tumor. Those with two or more breast metastases even if discovered after two or more cycles of chemotherapy. In this study, held at BCOH, 235 female patients with advanced breast cancer

were assigned to start 2nd line chemotherapy of i.v cisplatin 50 mg / m2 on day I + day II and i.v etoposide 100 mg / m2 on day I + II. The number of cycles were six, but the dose of cisplatin was reduced to 25 mg / m2 (70 patients) and the dose of etoposide was reduced again to 50 mg/m2 (38 patients) in cases of severe toxicity with the addition of G-CSF (Neupogen) to these patients' protocols. These patients were divided into 4 groups according to site of metastasis, but later some of them and because of bad performance status and deteriorating general condition, never completed their further cycles of chemotherapy. The number of patients who received an anthracycline-containing protocol as 1st line chemotherapy was 235 patients. And the number of patients who were given chemotherapy as 2nd line (this study) was 235 patients.

Two hundred and thirty five female patients were started on the chemotherapeutic protocol:

Group 1, vertebral and bone secondaries proved by MRI of 73 patients   spinal areas and bones.

Group 2, liver secondaries proved by ultrasonic study and CT 59 patients scan of abdomen and FNAC.

Group 3, wide local recurrence including axillary, supra-40 patients clavicular, and cervical lymph nodes, surgery being not applicable (extensive).

Group 4, pleuro-pulmonary metastases proved by CXR, CT 63 patients scan of chest, and pleural fluid aspiration.

Study Design

This is a prospective study carried out in Basrah Center for Oncology and Hematology (BCOH). The patients were given Cisplatin 50 mg/m^2 (reduced to 25 mg/m^2 in 70 patients due to toxicity) as iv infusion (4 hrs) on days 1 & 2, and Etoposide (VP-16) 100 mg/m^2 (reduced to

50mg/m^2 in 38 patients due toxicity) as iv infusion (2hrs) on days (1&2), and a hematopoietic growth factor (G-CSF)[7] (neupogen).

The patients' responses were evaluated by the physician according to WHO criteria:[8]

1. Response To Treatment measured by performance score.
2. Time To Progression (period from 1st day of giving chemotherapy to the date of disease progression).
3. Median Response Duration (period from the date of response to chemotherapy till the date of disease progression).
4. Overall Survival duration (from 1st day of chemotherapy to the date of death).

Performance status (Eastern Cooperative Oncology Group-ECOG):[8]

Stage 0, Fully active. No house work restrictions.

Stage 1, Restricted in strenuous activity. Ambulatory. Light house works.

Stage 2, Ambulatory. No house works. Up and about > 50% of waking hours.

Stage 3, Limited self-care. Cofined to bed or chair > 50% of Waking hours.

Stage 4, Bed-ridden. **_Completely_** disabled. No activity.

Stage 5, Dead.

Patients were selected with performance status of stage 2, 3 or 4. The **aim** was to transfer these patients to a **better** stage (**1** or **0**). **Complete** response to be achieved when stage **0** was reached, and **Partial** response when stage **1** was reached. While **No** response to treatment means being stationery at stage 2 or deteriorating.

Primary assessment and Investigations:

The patients were examined clinically and complete investigations were ordered: complete blood counts, blood urea, s. creatinine, s. total bilirubin, s.GOT, s.GPT, s.alkaline phosphatase, s. calcium, s. albumin, chest X-ray, ultrasonic

study of abdomen, computed tomography scans of chest and abdomen in patients with suspicious chest X-rays and abdominal ultrasonic studies. Magnetic resonance imaging of spine for suspicious areas, and s.CA 15-3.

Follow-up

Clinical examination and appropriate investigations were repeated as required before each cycle of chemotherapy: hematological and biochemical tests every visit, chest X-rays, ultrasound examination of abdomen every 2 months, Computed tomography scans of chest and abdomen every 3-4 months (difficult for our patients because of long waiting lists in public hospitals and being expensive in private clinics), magnetic resonance imaging every 3-4 months (also difficult, same reason), and s.CA 15-3 every 3 months

RESULTS

patients. On ***the whole-235 level*** the Response To Treatment was 153 patients (65.1%), and Time To Progression was 6.5 months, while Median Response Duration was 5.4 months. And the Median Overall Survival was 15.4 months. But on ***the patient-group level***, the patients with vertebral secondaries had the highest Response Rate 75.3% followed by the pleuro-pulmonary group 69.8%. While time to progression was longest in those with vertebral secondaries 10.3 months, then the pleuro-pulmonary and the wide local metastases groups 4.7 months. The Median overall survival was longest in vertebral secondaries group also 25 months. (Table-1,2,3).

Table 1. Patient characteristics

Median age (yrs) (range)	40.33 (20-60)
Performance status:	
Stage 2	82
Stage 3	85
Stage 4	68
Site of metastases:	
Vertebral secondaries	73
Liver secondaries	59
Wide local metastases	40
Pleuro-pulmonary metastases	63
Hormonal status:	
ER/PR+	13
ER/PR-	3
Unknown	219
HER2 neu status	
HER2 neu+/HER2 neu-	0
Unknown	235
Previous treatment:	
Surgery	235
Radiotherapy	None
Adjuvant CTX	235
Metastatic	235
Hormonal therapy	None

Table 2. performance status in different groups.

Performance status	Vertebral metastasis	Liver metastasis	Local metastasis	Pleuropulmonary metastasis	Total
2	17	17	23	25	82
3	21	28	11	25	85
4	35	14	6	13	68
Total	73	59	40	63	235

Table 3. Response rates according to site of metastasis.

Site of metastasis	Response rate No. (%)	Time to progression (months)	Median response duration (months)	Overall survival duration (months)
Vertebral metastasis 73	55 75.3	10.3	9.3	25
Liver metastasis 59	32 54.2	3.6	3.3	9.5
Local metastasis 40	22 55	4.7	3	9.7
Pleuropulmonary metastasis 63	44 69.8	4.7	3.3	10.7

Those patients whose conditions deteriorated, because of complications related to their disease and not to cytotoxic drugs, after starting cisplatin-etoposide protocol were 36 [vertebral metastasis 7, liver metastasis 12, wide local metastasis 8, pleuropulmonary metastasis 9] and treatment therefore was stopped. Five and 6 patients in vertebral metastasis category died after 1st and 2nd cession of chemotherapy respectively. In the liver metastasis group 7 and 8 patients never came back or died after 1st and 2nd cessions respectively. In locoregional metastasis 6 patients never came back after 1st chemotherapy cession, and 4 died after 2nd cession. While in pleuro-pulmonary metastasis group 3 and 7 died after 1st and 2nd cessions respectively. All these events were considered due to the disease itself again. The responses, in general, were complete and partial, the first comprising 33.3% while the second comprising 66.6% of responders.

Table 4. Response to treatment complete and partial.

No. of patients		No. of responders	Partial (stage I) No. (%)	Complete (stage 0) No. (%)
Vertebral metastasis	73	55	37 67.2	18 32.7
Liver metastasis	59	32	18 56.2	14 43.7
Locoregional metastasis	40	22	16 72.7	6 27.2
Pleuropulmonary metastasis	63	44	31 70.4	13 29.5
Total	**235**	153	102 66.6	51 33.3

Of those patients who received 2nd line chemotherapy for ABC in our study (235), only 86 patients (36.5%), survived beyond one year. And only 29 patients (12.3%) were alive at the end of 2nd year. By June 30 2016, 11 patients were alive.

Table 5. Comparison between 4 cisplatin - etoposide trials and our cisplatin - i.v etoposide study

Trial	No. of pt.	R.R No. (%)	TTP (months)	MRD (months)	OS (months)
Krook JE, et al[11]	260	70 (26.8)	-	-	-
Icli F, et al[5]	35	15 (42.8)	-	6	8
Fried G, et al[12]	26	13 (50)	-	7	-
TOG[1]	100	(36.3)	5.5	7	14
This study	235	153 (65.1)	6.5	5.4	15.4

Toxicity: The type of toxicity that occurred was hematological (increasing anemia 22 due to repeated vomiting, anorexia), infections due to leucopenia 9, and bleeding due thrombocytopenia 3) and treated accordingly by giving blood, heavy antibiotics and platelets. Gastro-intestinal (severe nausea 1, severe vomiting 1, anorexia 9, diarrhea 1, and abdominal pain 3), renal (acute renal failure due to dehydration 5, or precipitation of cisplatin in renal tubules 2), and dermatological (non-specific rash 5, allergy to drug 33, or skin swelling and ulceration due extravasation of drug in skin 16). In addition to deaths occurring from the disease we had 4 deaths because of severe leucopenia and septicemia in spite of heavy use of antibiotics, fresh blood, platelet concentrates, gcsf. Two deaths occurred due to renal failure. And one death due to severe gastroenteritis.

Table 6. Toxicity and deaths

No. of patients 235	Hematological No. (%)	Gastro-intestinal No. (%)	Renal No. (%)	Dermatological No. (%)
Toxicity	34 (14.4)	15 (6.3)	7 (3)	54 (22.9)
Deaths	4 (1.7)	1 (0.42)	2 (0.85)	0 (0)

DISCUSSION

Cisplatin has been used for long time in treatment of several tumors, like tumors of testis, urinary bladder, prostate, ovary, and squamous cell tumors of head, neck and lung…etc. Etoposide has also been used in treatment of many tumors like testicular tumors, small cell lung cancer, acute myeloid leukemia…etc. These two drugs have been used together for their synergistic action in many cancers like lung and germ cell tumors.[9] But since the 1980's they were started to be used in treatment of advanced breast cancer.[10] The efficacy of cisplatin and i.v etoposide was assessed in one multicenteric trial including 260 patients previously treated for advanced breast cancer total response rate of 26.8% was obtained by giving etoposide 100-130 mg m^{-2} i.v. for 3-5 days and cisplatin 60-100 mg m^{-2} i.v. every 3 weeks to these heavily pretreated patients (received 360 mg doxorubicin, or 450 mg epirubicin). The highest rate of leucopenia was 31% in one trial, and altogether four toxic deaths were reported in these trials.[11] Following the emergence of oral etoposide, the role of prolonged oral etoposide in the treatment of breast cancer was investigated in several studies.[5] Etoposide 50 mg BD p.o. daily for 7 days + cisplatin 70 mg/m^2 i.v. on day 1 with adequate i.v. hydration every 3 weeks. Out of 35 (42.8%) heavily pretreated patients, 15 responded. Median response duration and OS were 6 and 8

months, respectively. severe leucopenia was observed in 14.3% of the patients and only one patient had severe anemia. A lower dosage of cisplatin (50 mg/ m^2) and longer duration of oral etoposide (50 mg/ m^2 for 17 days) were utilized in the another study. In 26 patients previously exposed to anthracyclines, 50% response rate with 7 months of response duration has been reported.[12] Four patients (15%) required hospitalisation for neutropenic fever in this study. In a study held by the Turkish oncology group[1] (TOG), 201 patients were divided in two groups; cisplatin-oral etoposide group 100 patients and paclitaxel group 101 patients. The response rate in cisplatin-etopodide group was 36.3%, time to progression was 5.5 months, and median response duration was 7 months. While the overall survival was 14 months. The response rate in paclitaxel group was 22.2%.[1] In our study the cisplatin dose was 50mg/m^2 and etoposide dose 100mg/m^2 both for two successive days, the response rate was 65.1%, which is very high compared to other studies, and the time to progression was 6.5 months. While the median response duration was 5.4 months and the median overall survival was 15.4 months, severe anemia occurred in 22 patients, infections in 9 patients and bleeding in 3 patients. We think that the cause of better results of higher response rate and longer overall survival is decreasing the cisplatin dose, reducing the etoposide dose and period of giving it to make our therapy effective and less toxic. Also in our study we divided the patients in groups according to the site of metastasis, in order to know more about the disease behavior and drugs' effects: patients with vertebral secondaries had the highest response rate 75.3%, the longest time to progression 10.3 months, the longest median survival duration 9.3 months, and the overall survival was 25 months. A study by Kenneth D. Swenerton et al in 1979, declared that there was a trend, for patients with bone involvement to have a longer survival than did patients with metastasis to other organ sites.[13] In another study by Meng-

Ting Chen, et al in 2017, it was shown that patients with bone metastasis only had superior survival compared to other metastatic patients and those with brain only group and multiple sites metastasis group had the poorest prognosis.[14] The serious toxicities observed in our study were mostly hematological, due to bone marrow suppression (severe leucopenia, anemia and thrombocytopenia) was (14.4%) and deaths were 1.7%; secondly gastro-intestinal (6.3%) with 0.42% deaths; and thirdly renal complications (3%) with 0.85% deaths. Minor toxicities included mild nausea, lassitude, generalized weakness, and depression. These toxicities had no effect on any of the study assessment parameters that include response rate, time to progression, median response duration, and overall survival in the drugs' doses used in this study. While this has been the contrary in several trials using cisplatin-etoposide combination where the dose of cisplatin and etoposide have to be reduced in order to decrease the toxicities and continue treatment.[15,16] From our study we conclude that cisplatin + i.v etoposide combination is still a useful regime in the treatment of advanced breast disease. And more studies are needed with other doses / duration of same drugs to decrease toxicities and get better results.

REFERENCES

1. **F Icli, H Akbulut, SD Sak, et al. Cisplatin and oral etoposide versus paclitaxel in treatment of advanced breast cancer. British Journal of Cancer 2005; 92, 639-644.**
2. **Nabholtz JM, Senn HJ, Bezwoda WR, Melnychuk D, Deschenes L, Douma J, et al Prospective randomized trial of docetaxel vs mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline - containing chemotherapy. 304 Study group. J Clin Oncol 1999; 17: 1413-1424.**
3. **Cocconi G, Bisagnei G, Bacchi M, Boni C, Bartolucci R, Ceci G, et al. Cisplatin and etoposide as first line of chemotherapy of metastatic breast carcinoma: a prospective**

randomized trial of the Italian Oncology group of clinical research. J Clin Oncol 1991; 9:664-669.

4. Cox EB, Bruton GV, Olsen GA, Vugrin D cisplatin and etoposide: an effective treatment of refractory breast cancer. Am J Clin Oncol 1989; 12:53-56.

5. Icli F, Deminkrazik A Cisplatin and oral etoposide (PEO) in heavily pretreated patients with advanced breast cancer. Proc ASCO 1998; 17:256 (abstr).

6. Mitri Z, Constantine T, O'Regan R . "The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances Therapy". *Chemotherapy Research and Practice. 2012.*

7. Petit, I, et al. GCSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. *Nat. Immunol.* 2002. 3:687-694.

8. Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.

9. Burchenal JH, Kalaher K, Dew K, Lokys L Rationale Development of platinum analogs. Cancer Treat Rep,1979; 63: 1493-1498.

10. Sledge Jr GW, Roth BJ Cisplatin in the management of breast cancer. Semin Oncol, 1989; 16:110-115.

11. Krook JE, Loprinzi CL, Schaid DJ, Kardinal CG, Mailiard JA, Pfeifle DM, et al Evalution of continuous infusion of etoposide plus cisplatin in metastatic breast cancer. A colloborative North Central Caner Treatment Group Mayo Clinic phase II study. Cancer, 1990; 65:418- 421.

12. Fried G, Stien ME, Haime N, clinical activity of cisplatin and prolonged administration of etoposide in previously treated, anthracycline - resistant, metastatic breast cancer patients: a phase II study. Med Ped Oncol, 2000; 34: 10-13.

13. Kenneth D. Swenerton, Sewa S. Legha, Terry Smith, et al. Prognostic Factors in Metastatic Breast Cancer Treated with Combination Chemotherapy. Cancer Research May 1979; 39(5).

14. Meng-Ting Chen, He-Fen Sun, Yang Zhao, et al. Comparison of patterns and prognosis among distant metastatic breast cancer patients by age groups: a SEER population-based analysis. Scientific reports 7, Article number 9254 (2017).

15. Giaccone G, Donadio M. Ferrati P, Calciati A cisplatin and etoposide in chemotherapy-refractory advanced breast cancer. Tumori 1988; 74:191-193.

16. Ceci G, Besagni G, Cocconi G, Rodino B, Belsanti V, Bertusi M, et al Cisplatin and VP-16 in metastatic breast carcinoma as third line chemotherapy: a randomised study comparing low vs high dose of cisplatin. Tumori 1995; 81: 241-244.