Salvage Chemotherapy with Cisplatin and 5-Fluorouracil in Metastatic Breast Cancer. Particular Activity against Liver Metastases

LAZAROS LEKAKIS, DIMITRIOS TRYFONOPOULOS, NIKOLAOS PISTAMATZIAN, CHRISTOS PANOPOULOS, GEORGE KOUMAKIS, STAMATINA DEMIRI and ANNA EFREMIDIS

Agios Savvas Cancer Hospital, Second Medical Oncology Department, Athens, Greece

Abstract. *Background: The prognosis of patients with metastatic breast cancer who have failed to respond to at least two different chemotherapy regimens is poor. Such patients with metastatic disease to the liver have even worse prognosis. Cisplatin and 5-fluorouracil (5-FU) can be given in patients with impaired hepatic function but their combination has not been extensively studied in this setting. Patients and Methods: We retrospectively collected data from our registry on patients with advanced metastatic breast cancer who received combination of cisplatin/5-FU. We sought to determine the toxicity, the response rate, the disease control rate and the survival of this combination. Results: We identified 25 heavily pre-treated patients, out of which 19 (76%) had liver metastases. They had been treated before with a median of three lines of cytotoxic chemotherapy. The majority of patients had also received hormonal manipulation or trastuzumab. The median number of cisplatin/5-FU administered cycles, without toxic deaths or unexpected toxicities was four. The partial response (PR) rate was 32% and the disease control rate (DCR) was 68%. The time to progression was five months and the median survival after starting on cisplatin/5-FU was six months. Conclusion: The combination of cisplatin/5-FU is active and safe in heavily pre-treated patients with metastatic breast cancer even in the presence of liver metastases and jaundice.*

The use of taxanes and of dose-dense regimens, as well as the use of aromatase inhibitors and trastuzumab in the adjuvant setting has reduced the rate of breast cancer relapse. The establishment of predictive and prognostic models including the Gail model, mRNA tests (OncotypeDx and Mammaprint) and the recognition of molecular profiles [luminal A and B, HER2+ and triple-negative (TN)] will further optimize adjuvant therapies.

In the metastatic breast cancer (MBC) setting, especially in cases of hormone-unresponsive or hormone-refractory disease, the options are limited, and the patients' responses become progressively shorter. This is particularly true for patients who have recently been exposed to adjuvant cytotoxic therapy. The introduction of capecitabine, vinorelbine, gemcitabine, eribulin, ixabepilone, lapatinib and bevacizumab has provided benefits but only limited prolongation of overall survival (OS). Since many cytotoxics are metabolized by or are toxic to the liver, the management of patients with impaired hepatic function is challenging. Cisplatin and 5-fluorouracil (5-FU) can be given with relative safety in the setting of liver dysfunction. In this report we announce our single center experience on the use of cisplatin and 5-FU in the advanced MBC setting. We have used this regimen mostly for patients with liver metastasis or liver dysfunction or as salvage therapy in the very advanced setting.

Patients and Methods

This is a retrospective analysis which was carried out at Agios Savvas Cancer Hospital, Athens, Greece. We reviewed the charts of 1137 patients who have been registered at the breast cancer data bank of the hospital for the last 5 years (2007-2011). We sought to identify those who received cisplatin/5-FU and to describe the pathological characteristics, the extent of the disease and the previous treatments that they had received. We determined the time to disease progression (TTP) and the survival from initiation of the cisplatin/5-FU combination. We documented the responses and we searched for toxic deaths. Patients received cisplatin at 75 mg/m^2 on day 1, and 5-FU at 1000 mg/m^2/day by continuous infusion on days 1-5. Standard hydration and anti-emetic prophylaxis was prescribed. The regimen was given in an inpatient setting and the use of myeloid growth factors was optional. No antimicrobial prophylaxis was given. The regimen was repeated every month for up to six cycles unless disease progression or

Correspondence to: Lazaros Lekakis, MD, Agios Savvas Cancer Hospital, Second Medical Oncology Department, 171 Alexandras Ave, 11522, Athens, Greece. E-mail: ljleka2@gmail.com

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Table I. *Patients' characteristics, response to treatment, survival and time to progression (TTP).*

No.	Age, years	Histology/ molecular subtype (possible)	Initial stage	Metastatic sites (before cisplatin /5-FU)	Previous endocrine or targeted agents	Previous cytotoxics (adjuvant, metastatic settings)	Time from diagnosis	No. of cycles	Best response	TTP (months)	Survival (months)
1	48	Lobular/Lum A $ER^+PR^+HER2^-$	T1N0M0 stage I	Bone, liver, adrenal, LN, peritoneum	TMX, Bev letrozole, anastrozole, fulvestrant, ibandronate	CMF, Dox-TXT, Xel, Taxol, Cb-CTX, GMZ	168	5	SD after 4 cycles	6	6
2	52	Ductal/LumB $ER^+PR^+HER2^-$	T4dN2M0 stage IIIb	Local, CNS	Goserelin, TMX	FEC, Cb-VNR,	7	2	SD after 2 cycles	6	12
3	42	Ductal/LumB ER^-PR^+ $HER2^-$	T1bN1M0 stage IIa	Liver, bone, pleura, LN	Exemestane Bev	CMF, FAC, Taxol, Xel	101	6	mR after 3 cycles (liver, local)	5	13
4	49	Ductal/$HER2^+$ $ER^-PR^+HER2^+$	T1aN0M0 stage I	Liver, lung, bone, brain	TMX, herceptin	FEC	28	4	PR	5	10
5	66	Ductal/$HER2^+$ $ER^+PR^+HER2^+$	T2N3M0 stage IIIc	Liver, LN	Bev, herceptin, letrozole, lapatinib	TAC, Xel, taxol, Cb-CTX, TXT	50	4	mR after 3 cycles (liver+ local relapse)	4	6
6	35	Ductal/$HER2^+$ ER^+PR^+ $HER2^+$	T4bN1M1 stage IV	Local, liver, bone	Herceptin, TMX, goserelin, exemestane	CDDP-NVL Epirubicin, taxol, Xel, TXT	75	6	mR after 4 cycles (liver+ tumor markers)	5	6
7	40	Ductal/TN ER^-PR^- $HER2^-$	T1bN3M0 stage IIIc	Liver, lung, brain	_	Epirubicin Taxol, Cb-TXT, Cb-CTX	14	2	mR (liver) after 2 cycles but grade IV thrombocy-topenia	2	4
8	58	Lobular/Lum B $ER^+PR^+HER2^-$	T4bN2M1 stage IIIb	Peritoneum, lung	Herceptin (along with CDDP-5FU)	Cb-Dox , Taxol	8	2	PD (peritoneal)	3	4
9	43	Ductal/Lum B ER^+PR^+ $HER2^-$	T1cN1M0 stage IIb	Bone, liver, lung	TMX, ibandronate triptorelin, exemestane, letrozole	FEC, Cb-CTX	45	2	PD (peritoneal): 5-FU stopped on the 1st cycle: coronary spasm	2	3
10	45	Ductal/$HER2^+$ ER^+PR^+ $HER2^+$	T2NxM1 stage IV	Liver, bone lung	-	CDDP-VNR	2	3	PR (CR in liver mets)	19	30+
11	54	Lobular/Lum A ER^+PR^+ $HER2^-$	T1cN2M0 stage IIIA	Bone, peritoneal, adrenal, LN	TMX, letrozole, zolendronic acid, fulvestrant	Cb-TXT, Xel-VNR	126	1 + Cb-5FUx3	PD	4	5?
12	54	Mixed lobular-ductal/ Lum A ER^+PR^- HER2 unknown	T4N2M0 stage IIIB	Liver	Anastrozole, Bev, TMX	FEC, Taxol Cb-CTX Xel	100	6	SD but improvement on tumor markers	6+	6+
13	57	Lobular/TN $ER^-PR^-HER2^-$	T2N2M0 stage IIIA	Liver	Bev	FEC, Cb-Tax Xel-VNR, CTX	84	2+	SD	5	5

Table I. *contined*

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14	47	Ductal/Lum A $ER^+PR^+HER2^-$	T2N2M0 stage IIIA	Bone, LNs, skin, BM, liver, ovary.	Goserelin, TMX, zoledronate, Bev	FAC, Tax, TXT	25	1	PD (skin nodules + pleural effusion)	1	5
15	35	Ductal/ $HER2^+$ ER^+PR^+ $HER2^+$	T1cN3M0 stage IIIc	Ovary, local, LNs,	TMX, letrozole, fulvestrant, herceptin	FEC, Cb-TXT	133	6	PR (local>LNs)	7	35+
16	60	Ductal/$HER2^+$ $ER^-PR^-HER2^+$	T1cN3M1 stage IV	LNs, bone, liver, peritoneal	Zolendronate, herceptin	Cb-CTX	3	6 (with herceptin)	PR (liver+local)	12	13
17	46	Lobular/ TN $ER^-PR^-HER2^-$	T4bN3M1 stage IV	Bone, BM, LNs, skin, peritoneal, intestinal, pleural	TMX	AC, Xel Cb-TXT Cb-CTX	37	4	PR after 3 cycles (ascites, skin)	5	9+
18	39	Ductal/ TN $ER^-PR^-HER2^-$	T1cN1M1 stage IV	Lung, bone, LN, liver	TMX, Bev, fulvestrant	FEC, CMF CDDP-VNR, Xel, Taxol, EC, Gemzar, TXT	204	4+	PD	5	5+
19	46	Ductal/$HER2^+$ $ER^+PR^+HER2^+$	T2N1M0 stage IIB	Liver, lung	Anastrozole, letrozole, herceptin, exemestane, zolendronate, lapatinib	FEC, VNR, Taxol, Caelyx, Cb-TXT, Xel	100	6 (with herceptin)	PR	5+	5+
20	42	Ductal/ Lum B $ER^-PR^+HER2^-$	T4dN0M1 stage IV	Bone	-	-	0	6	PR	6+	6+?
21	33	Ductal/Lum A $ER^+PR^+HER2^-$	T1bN0M0 stage I	Bone, local, pleura, liver	TMX, zolendronic, Bev	FEC, Cb-CTX, Taxol	122	2	PD	2	3
22	37	Ductal/$HER2^+$ $ER^-PR^-HER2^+$	T4dN1M1 stage IV	Liver, lung, bone, brain	Herceptin, Bev, lapatinib	Cb-TXT, Dox, Xel, CDDP-VNR, Taxol, GMZ	24	3 (with herceptin)	PD(brain)	2	3+
23	49	Ductal/$HER2^+$ $ER^-PR^-HER2^+$	T2N1M0 stage IIB	Liver	Herceptin	Cb-TXT	22	3	Too early	2	2+
24	44	Ductal/LumB $ER^+PR^-HER2^-$	T2N1M0 stage IIB	Breast, LN, liver, lung, bone, pancreas, stomach	TMX, letrozole, exemestane, fulvestrant, Bev	AC, Taxol, Cb-TXT, Xel	94	3	Too early	3+	3+
25	62	Ductal/TN ER^-PR^- $HER2^-$	T1cN2M0 stage IIB	Liver, lung, Med LNs		FAC	108	1	Too early	1+	1+

Lum: Luminal; LN: lymph node; BM: bone marrow; CNS: central nervous system; ER: estrogen receptor; PR: progesterone receptor; TN: triple negative; TMX: tamoxifen; Bev: bevacizumab; AC: doxorubicin+cyclophosphamide; Cb: carboplatin; CDDP: cisplatin; EC: epirubicin+cyclophosphamide; Taxol: paclitaxel; TXT: docetaxel; Xel: capacitabine; FAC: cyclophosphamide+doxorubicin+fluorouracil; 5-FU: 5-fluorouracil; TTP: time to progression; Herceptin: trastuzumab; FEC: cyclophosphamide+epirubicin+5-fluorouracil; Dox: doxorubicin; VNR: vinorelbine; Gemzar: gemcitabine; CMF: cyclophosphamide+methotrexate+5-fluorouracil; Caelyx: liposomal doxorubicin; SD: stable disease; PD: progressive disease; PR: partial response; CR: complete remission; mR: minor response.

prohibitive toxicity ensued. We analyzed the responses by using the standard RECIST criteria. We determined the toxicities with the NCI CTCAE v3.0. Descriptive statistics were used to analyze the results.

Results

We identified 25 patients who had received cisplatin/5-FU. One patient received it as an adjuvant treatment. She had a T4dN1M0, stage IIIB inflammatory TN breast cancer and underwent a modified radical mastectomy (MRM) followed by six cycles of adjuvant cisplatin/5-FU. The patient was alive and free of disease at the time of the last follow-up , 56 months after the operation. Table I depicts the data of the remaining 25 patients with metastatic disease.

Most patients were heavily pre-treated. Twenty out of 25 patients (80%) had been treated with anthracyclines and 18 out of 25 patients (72%) had received at least one taxane. Sixteen out of 25 patients (64%) were both anthracycline- and taxane-experienced. Eighty percent of patients had been exposed to a platinum agent (20/25) and 76% to a fluoropyrimidine. Fourteen patients had been exposed to taxanes, platinum analogs and anthracyclines (56%), while 12/25 patients (48%) had been exposed to a taxane, a fluoropyrimidine, a platinum compound and to anthracyclines (all four classes). The median number of different cytotoxic lines of treatment before cisplatin/5-FU was 3 (range=0-8) and the median number of previous cytotoxics was 5 (range=0-10). Sixteen patients (64%) had been exposed to hormonal manipulations: twelve of them (48% of total) had received at least two different hormonal drugs. Ten patients (40%) had received bevacizumab; nine patients (36%) had received trastuzumab (three of them along with cisplatin/5-FU) and three lapatinib.

The cisplatin/5-FU regimen was reasonably well tolerated with optimal supportive care and neither toxic deaths nor grade IV non-hematological toxicities were observed. Cytopenia, mucositis, diarrhea, asthenia, hand-foot syndrome, reversible renal dysfunction not requiring renal replacement therapy (RRT) and fever with neutropenia were observed as expected.

At this time, it is too early to evaluate three patients. The median number of delivered cycles of cisplatin/5-FU was four. From the 22 evaluable patients, seven have attained PR and four have responded (minor responses, mR) but do not meet the criteria for PR. Four patients achieved stabilization of disease (SD) and seven progressed (PD) through treatment. The PR rate is 32%, the mR rate is 18% and the SD rate is also 18%, for a disease control rate (DCR) (PR+mR+SD) of 68%. The median TTP is 5 months and the median OS after starting cisplatin/5-FU is 6 months. Seven out of 22 evaluable patients are still alive, three of them >9 months after the first cycle of cisplatin/5-FU.

Reasons for not completing at least four cycles of treatment with cisplatin/5-FU were among others: local infection of ulcerated local disease, coronary spasm due to 5-FU, renal dysfunction, grade IV thrombocytopenia, patient preference to continue with less aggressive regimen, and progressive disease (peritoneal, pleural and cerebral metastasis). Carboplatin was in some cases substituted with cisplatin due to renal dysfunction (defined for that purpose in our institution as creatinine clearance <60 ml/min calculated after urine collection of at least 12 hours, not correctable with intravenous fluids). However, in such cases, carboplatin did not seem to have the same good effects as cisplatin, although a formal comparison was not made due to the small number of patients.

Nineteen patients with liver metastasis received cisplatin/5-FU. These patients not only tolerated the regimen well but also had very good control of their metastatic disease in the liver and showed improvement in their liver function tests. Among the sixteen evaluable patients with liver metastasis, one achieved a CR in the liver lesions, three had a PR, four had mR and three had SD for an overall liver metastasis control rate of 69%. Another subgroup of patients who attained benefit from cisplatin/5-FU treatment were the HER2+ patients since 7/8 of them had either a mR or a PR. Pleural and peritoneal disease did not respond as well as liver disease. The regimen does not seem to work well for brain metastasis since few patients had a relapse, progression or new appearance of cerebral lesions.

Discussion

In this article, we described a series of heavily pretreated patients with advanced poor-prognosis MBC treated with salvage cisplatin/5-FU. Many of these patients had liver impairment and were unable to receive other aggressive regimens due to the fact that the liver plays an important role in the metabolism of cytotoxic chemotherapeutics, especially those that interfere with the mitotic spindle. Cross-linking agents such as cisplatin and antimetabolites such as 5-FU can be safer if administered under this setting. Although a few groups have treated liver metastatic disease with agents metabolized by the liver, we have opted in this setting not to use such agents because if they did not work, liver function could further deteriorate and death could actually be accelerated. This possibility is not trivial due to the cross-resistance of breast cancer to multi-drug resistance efflux pump-1 (MDR-1) substrates.

There is a relative underutilization of cisplatin for patients with MBC due to the need for vigorous hydration and potential nephrotoxicity, as well as due to the availability of many other active drugs. When other drug

combinations have been exhausted, patients may not have a good enough performance status to receive a cisplatin-based combination. However multiple reports confirm on excellent activity of cisplatin-based combinations. Vassilomanolakis *et al*. (1, 2) described a 49% overall response rate (ORR) to cisplatin-vinorelbine in 53 anthracycline-experienced patients with MBC and a 47% ORR in patients pretreated with both anthracyclines and docetaxel, results that were confirmed in a different study by Mustacchi *et al*. (3). The addition of continuous low dose infusional 5-FU to cisplatin/vinorelbine conferred a 55% ORR in a cohort of 100 patients (65% were anthracycline pre-treated and 35% were taxane-pre-treated) (4). The combination of cisplatin-gemcitabine achieves an ORR up to 80% as a first line treatment of MBC and 43% ORR in heavily pretreated patients (5). The combination of mitomycin-C, vinblastine and cisplatin gave a remarkable 32% ORR in a heavily pretreated MBC population with the use of lower cisplatin doses (6). Cisplatin and docetaxel offered a 68% ORR in the first line treatment of MBC (7) and the cisplatin-doxorubicin-cyclophosphamide combination was active in 63% of patients with MBC (8). Continuous simultaneous infusion of cisplatin and 5-FU for 120 hours offered a 52% RR to a cohort of 36 patients as first or second line treatment (9). Addition of leucovorin makes the regimen more toxic (10). The protracted continuous infusion of 5-FU (200 mg/m^2/d for 6 months) *via* an ambulatory pump along with epirubicin and cisplatin, both given every 3 weeks, gave an impressive 84% ORR (including a CR rate of 24%) in 43 patients with early inoperable breast cancer (11). A 34% ORR was obtained with 3 days' infusional 5-FU (1000 mg/m^2/d) along with small doses of cisplatin daily (for 3 days) for a total dose of 90 mg/m^2/cycle (12).

In our analysis there was a significant activity of cisplatin/5-FU in a difficult group of patients and liver disease improved, at least temporarily, in many of them. Concominant brain metastatic disease should be controlled by other means since the regimen did not show good activity for brain metastases. Consolidation strategies should be employed because the duration of the disease control was limited after stopping the chemotherapy. There is no doubt that this is an intensive regimen requiring hospitalization or pump infusion of 5-FU. Even in this advanced setting, the regimen was well tolerated, with optimal supportive care, making it a candidate chemotherapy for earlier use in the sequence of treatments for MBC especially for patients with liver dysfunction whether due to metastasis or not. In this last group of patients, cisplatin/5-FU treatment may have an impact on their OS. Whether or not HER2+ patients are more sensitive to this treatment needs to be confirmed.

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