|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
Index Copernicus Value 2019: 79.34
Original Research Article
Volume 5, Issue 2; February: 2021; Page No. 90-95

RANDOMIZED PHASE III TRIAL COMPARING EPIRUBICIN/ DOXORUBICIN PLUS DOCETAXEL AND EPIRUBICIN/ DOXORUBICIN PLUS PACLITAXEL AS FIRST LINE TREATMENT IN WOMEN WITH ADVANCED BREAST CANCER

Seema Devi[1]*, Yogesh Kumar Sharma[2], Dilip Shah[3]
*[1] M.Pharma Student, Department of Pharmacology, Jaipur College of Pharmacy
[2] Department of Pharmacology, Jaipur College of Pharmacy
[3] Department of Oncology, Lions Hospital

Article Info: Received 04 January 2021; Accepted 12 February 2021
DOI: https://doi.org/10.32553/ijmbs.v5i2.1746
Corresponding author: Seema Devi
Conflict of interest: No conflict of interest.

Abstract
Background: The purpose of this study was to compare Epirubicin/ doxorubicin plus docetaxel and Epirubicin/ doxorubicin plus paclitaxel as first line treatment in women with advanced breast cancer.
Patients and methods: previously untreated patients with advanced breast cancer randomly assigned to recieve Epirubicin 75mg/m^2 and docetaxel 75 mg/m^2 (ED) 1-hour intravenous (IV) infusion every 21 days, Epirubicin 75 mg/m^2 and paclitaxel 175 mg/m^2 (EP) 3-hour IV infusion every 21 days, Intravenous bolus injections of doxorubicin 50 mg/m^2 and docetaxel 75 mg/m^2 (DD) administered as a 1-hour intravenous infusion every 21 days and doxorubicin 50 mg/m^2 and paclitaxel 175 mg/m^2 (DP) administered as a 1-hour intravenous infusion every 21 days. Previous anthracycline-based neo-adjuvant chemotherapy was allowed if completed > 1 year before entering the study.
Results: Ten women patients were treated on arm ED &EP and median TTP was 10 versus 11 months, 50 women patients were trated on DD & DP cand median TTP was 8.5 versus 9 months respectively. Severe toxicity include grade 3-4 leukopenia (4% versus 2%), neutropenia (20% versus 22%) , anemia (38% versus 34%), thrombocytopenia (18% versus 24%), neurotoxicity (2% versus 6%) with DD and DP, respectively.
Conclusion: The DD and DP regimens have similar efficacy but different toxicity. Either regimen can be used as front- line treatment of ABC. But in case of ED and EP regimen was difficult to compare the result due to very small sample size.
Keywords: Epirubicin, doxorubicin, docetaxel, paclitaxel, advanced breast cancer, chemotherapy, neurotoxicity.

Introduction

If cancerous cells remains localized to specific organ of body, it termed as benign tumor however when these tumor cells start migrating towards other organs then it becomes malignant. [1] Uncontrolled proliferation of cells which starts in breast cells and attains malignancy is called breast cancer.[2] Breast cancer is the most frequent malignancy in women and is a heterogeneous disease on the molecular level. Over the past 10–15 years, treatment concepts have evolved to take this heterogeneity into account, with emphasis being placed on more biologically- directed therapies and treatment de- escalation to reduce the adverse effects of treatment.[3]

Taxane (docetaxel and paclitaxel) based regimens are among the most effective and commonly used systemic therapies for breast cancer, particularly in the adjuvant chemotherapy [4]**.** Both paclitaxel and docetaxel were approved for use in patients with metastatic breast cancer (MBC)[5].

In early clinical studies, docetaxel ((isolated from extract from pacific yew trees *Taxus brevifolia*) demonstrated linear pharmacokinetics and less schedule dependence than paclitaxel (derived from extracts from the needles of the European yew tree *Taxus baccata*). The dose-limiting toxicity for both drugs is neutropenia, but differences in nonhematologic toxicities (toxicity worse with docetaxel)[6]. Docetaxel demonstrated superior efficacy compared with paclitaxel, Hypersensitivity reactions and neurotoxicity are described more commonly with paclitaxel, whereas fluid retention and fatigue are seen with docetaxel administration[7].

Anthracyclines (Doxorubicin and Epirubicin), broad spectrum anticancer drugs, still represent the most active and widely used cytotoxic drugs in the management of breast cancer: their introduction in the adjuvant chemotherapy provided a modest, but significant, improvement in survival and their use in first-line therapy for advanced disease significantly improved response rate and palliation[8].

The inclusion of epirubicin in combination regimens, such as fluorouracil/epirubicin/cyclophosphamide (FEC), has been shown to be safe and active as first-line treatment for advanced breast cancer. One important aspect of treating elderly BC patients is the increased risk of anthracycline-induced cardiotoxicity . According to a retrospective review of data from 630 patients involved in three phase III studies (two in BC), exposure to a cumulative dose of 550 mg/m2 doxorubicin was associated with a cumulative 26% risk of drug-related congestive heart failure (CHF) [9].

Until this time, only indirect clinical comparisons of the two taxanes and anthracyclines have been performed and they have been imprecise because of differences in patient populations. Therefore, a head-to-head comparison was necessary to compare more accurately the safety and efficacy of the two taxanes and anthracyclines. This randomized phase III trial was designed to compare taxanes (docetaxel and paclitaxel) and anthracyclines (Epirubicin and doxorubicin) at approved doses and schedule.

Patients and methods

Patients Eligibility

This randomized, controlled, multicenter, open-label, phase III study was designed to compare the antitumor activity and toxicity. Women 18–75 years old with histologically- or cytologically confirmed and previously untreated locally advanced or metastatic breast adenocarcinoma awere eligible for the study. Prior adjuvant or neoadjuvant chemotherapy with an anthracycline-based regimen was allowed if it had been completed>1 year before enrollment. Other eligibility criteria included the presence of measurable disease (RECIST criteria), performance status of zero to two (World Health Organization criteria), adequate hematological (absolute granulocyte count>1.5 · 1029/l and platelet count >100 · 1029/l), renal (creatinine level <1.5 mg/dl) and hepatic [transaminases <1.5· the upper normal limit (UNL), alkaline phosphatases <2.5 UNL and bilirubin <UNL] function and normal left ventricular ejection fraction (LVEF >50%). Prior hormonal therapy or radiation therapy was allowed if they had been completed at least 1 month before enrollment and if <25% of the active bone marrow had been irradiated. Prohibited prior treatments included taxanes, bone marrow transplantation or stem-cell support, recent radiotherapy to bone marrow, surgery within the prior 2 weeks, and an investigational drug within 4 weeks of study registration. Bisphosphonate therapy was permitted. Exclusion criteria included active central nervous system metastases, history of serious cardiac disease contraindicating the use of anthracyclines, history of previous cancer (except treated basal cell and squamous cell carcinoma of the skin or cancer of the uterine cervix) and other serious concomitant illness. The concurrent administration of other antineoplastic treatment was not allowed. Patients with HER2-positive disease were excluded from the study. Written informed consent was obtained from each patient beforeenrollment. The protocol was approved by the Ethics and Scientificc Committees of all participating centers. The study was conducted in accordance with the Declaration of Helsinki and the applicable guidelines on good clinical practice.

Study design

Chemotherapy consisted of Epirubicin 75mg/m^2 and docetaxel (75 mg/m^2)1-hour intravenous (IV) infusion every 21 days, Epirubicin 75 mg/m^2 and paclitaxel (175 mg/m^2) 3-hour IV infusion every 21 days, Intravenous bolus injections of doxorubicin (50 mg/m^2)and docetaxel(75 mg/m^2) administered as a 1-hour intravenous infusion every 21 days and doxorubicin (50 mg/m^2) and paclitaxel (175 mg/m^2) administered as a 1-hour intravenous infusion every 21 days. For docetaxel patients, premedication consisted of dexamethasone 8 mg by mouth twice daily beginning on the day before the infusion and continuing for a total of 5 days. For paclitaxel patients, premedication included dexamethasone 20 mg by mouth administered 12 and 6 hours before the paclitaxel infusion, diphenhydramine 50 mg IV, and either ranitidine 50 mg IV or cimetidine 300 mg IV administered 30 to 60 minutes before the infusion. Treatment continued until tumor progression, unacceptable toxicity, or withdrawal of consent. Dose reductions (docetaxel 75 mg/m^2 then 55 mg/m^2; paclitaxel 130 mg/m^2 then 100 mg/m^2) were implemented after recovery from grade 3/4 toxicities. Patients experiencing grade 2 neuropathy were treated without delay, but at a reduced dose. Treatment delays due to toxicities were limited to 2 weeks; if patients did not recover, they were taken off study.

Patients were evaluated every 3 weeks, and tumor response was determined by clinical assessments of bi dimensionally measurable disease using standard response criteria. Patients were withdrawn from the study in the event of intolerable adverse events as judge by the investigator or the patients, recurrent grade ¾ toxicity despite dose modification, tumor progression after a minimum of two cycles of chemotherapy, or if there was evidence of metastatic disease.

Baseline and follow-up evaluations

Baseline evaluation included patient history, physical examination, chest Xrays, complete blood count (CBC) with differential , blood chemistry with CA 15-3 and carcinoembryonic antigen (CEA) measurement, electrocardiogram (ECG), echocardiography or multiple gated acquisition scan (MUGA) with LVEF measurement, computed tomography (CT) scan of chest and abdomen and a bone scan. CBCs were repeated weekly for all patients throughout the treatment or daily in case of grade 3–4 neutropenia, thrombocytopenia or febrile neutropenia and until hematological recovery occurred.

Before each cycle, evaluation included patient history, physical examination, CBC, blood chemistry with CEA and CA 15-3 determination and an ECG. Other tests were carried out when clinically indicated. Cardiac monitoring consisted of physical examination and ECG carried out every 3 weeks and LVEF measurement every three cycles of treatment (DE regimen). Evaluation of response was carried out after each cycle if measurable disease was assessable by physical examination or after every three cycles of treatment by repeating the CT scans. All objective responses, assessed by two independent radiologists, had to be maintained for at least 4 weeks. Long-term follow-up included patient history, physical examination, CBC, blood chemistry and radiological assessments every 3 months until disease progression occurred and every 6 months

thereafter until death. Response to treatment was assessed by using RECIST.

Statistical Methodology and Analysis

The primary end points were the objective response rate and toxicity. Secondary end points included duration of response, time to progression (TTP), overall survival (OS), and quality of life (QOL). The sample of ~170 patients for this study was chosen to provide adequate power to detect an improvement of 10% in progression free-survival with the dose-dense regimen with an expected proportion of relapse of ~30% after 5 years in the standard treatment arm. The ITT population included all randomly assigned patients, including those who did not receive treatment, with analyses performed based on the treatment assigned.

Eligible patients included all patients with no major inclusion or exclusion criteria deviations.

Patients assessable for response included those who met major eligibility criteria; received at least two cycles of treatment, unless progression occurred before the second cycle, in which case the patients were considered to have progressive disease; had at least one complete tumor assessment after the second cycle; and had no major protocol violations. All patients who received at least one dose of study drug were assessable for safety assessment; safety analyses were performed based on the actual treatment administered.

Response rate was defined as the sum of the percentage of patients who achieved a complete response or partial response in each treatment group. Duration of response was defined as the time from the first documentation of response to the date of disease progression or the date of death as a result of any cause if death occurred within 1 month after the last dose of study drug. TTP was defined as the time interval between the date of random assignment and the date of disease progression or the date of death as a result of any cause if death occurred within 1 month after the last dose of study drug. For response duration and TTP analyses, patients were censored at the time of last clinical contact if they were lost to follow-up, died later than 1 month after the last dose of study drug, or did not experience disease progression or die before the cutoff date for the analyses. Patients were also censored on the date that they received any subsequent anticancer therapy before documented tumor progression.

OS was calculated from the date of random assignment to the date of death or to the date of last contact.

Results

Patients enrollment and baseline characteristics

A total of 170 previously untreated patients with advanced breast cancer (ABC) were enrolled onto this study between July 2020 to December 2020. Thirty patients were excluded because they did not meet the eligibility criteria and 140 patients were registered and 10 patients randomly assigned to ED, 10 patients randomly assigned to EP, 50 patients randomly assigned to DD and 50 patients assigned to DP. Five patients assigned to ED, 2 patients assigned to EP, 10 patients assigned to DD and 3 patients assigned to DP withdrew their consent before initiation of therapy and did not receive study treatment. 10 patients received ED, 10 patients received EP, 50 patients received DD and 50 patients received DP. The median age at randomization was 46 years (range 18-75 years). All baseline characteristics were well balanced between the four treatment groups.

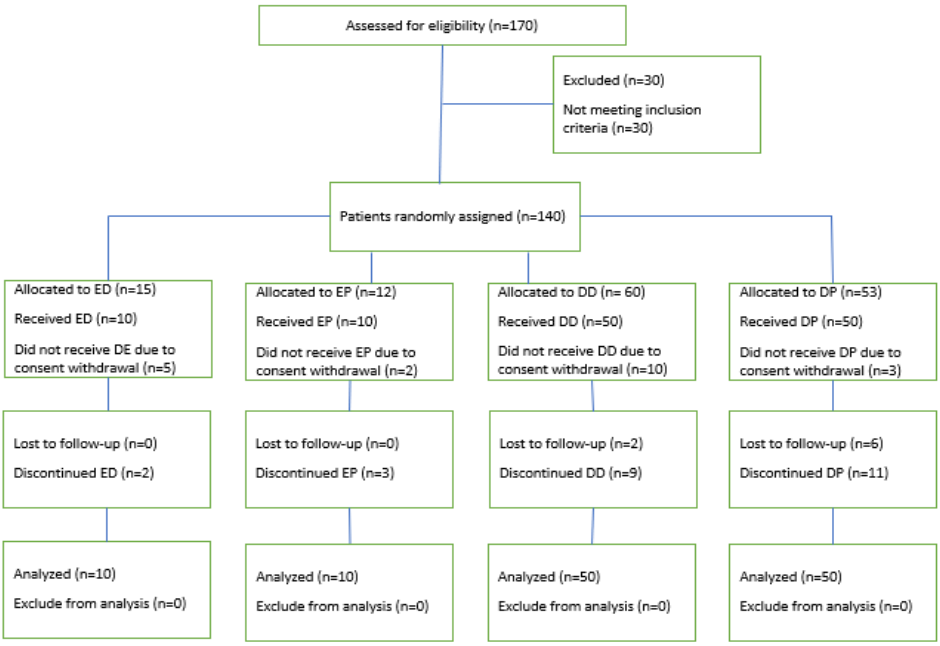

Figure 1: CONSORT diagram of the study

Table 1: Baseline Patients characteristics

689	ED	EP	DD	DP
Patients	10	10	50	50
Age (years)				
Median (range)	46.5 (18-75)	47 (19-75)	48.5 (21-76)	48 (20-76)
Menopausal status				
Premenopausal	2 20	1 10	8 16	12 24
Postmenopausal	8 80	9 90	42 84	38 76
Histological tumor type				
Ductal	5 50	5 50	27 54	30 60
Lobular	3 30	4 40	20 40	15 30
Other	2 20	1 10	3 6	5 10
Prior treatment				
Surgery	5 50	6 60	35 70	33 66
Radiotherapy	3 30	2 20	21 42	23 46
Hormonotherapy	3 30	5 50	16 32	20 40
Chemotherapy	4 40	5 50	20 40	11 22
Receptor status				
ER and PR positive	4 40	6 60	36 72	33 66
ER and PR negative	4 40	3 30	11 22	12 24
Unknown	2 20	1 1	3 6	5 10

Efficacy

The overall response rate was 60% (95% CI 50% to 70%) with ED versus 70% (95% CI 60% to 80%) with EP (p=0.80) and 34% (95% CI 30% to 38%) with DD versus 36% (32% to 42%) with DP (p=0.032). The median duration of response was 10.5 months on ED versus 10 months on EP and 10.5 months on DD versus 11 months on DP. The median TTP was 10 months on ED versus 11 months on EP and 8.5 months on DD versus 9 months on DP. The OS does not differ significantly between the ED was 36.7 and EP was 35.5 (p=0.03) two groups respectively. The OS slight differ in DD was 26 versus DP was 21 (p=0.031).

Table 2: Response, time to progression and overall survival

	ED	EP	DD	DP
Response				
CR	2	2	13	10
PR	4	5	21	26
SD	3	2	12	11
PD	1	1	4	3
Overall response rate				
% Pattients	60	70	34	36
Duration of response				
Median, months	10.5	10	10.5	11
Time to progression				
Median, months	10	11	8.5	9
Overall survival (estimated)				
Median, months	36.7	35.4	26	21

Chemotherapy details

A total of 50 patients received 275 cycles of DD (mean, 5.5 cycles) , 50 patients received a total of 280 cycles of DP (mean, 5.6 cycles), and 10 patients of each ED & EP received 60 cycles (mean, 6 cycles). Twelve patients received fewer than the maximum of six cycles of chemotherapy with DD because of toxicity (n=2), disease progression (n=1), with the reminder proceeding to surgery after fewer than six cycles at the investigator's discretion (n=9). Ten patients received fewer than the maximum of six cycles of chemotherapy with DP because of toxicity (n=1), disease progression (n=2), with the reminder proceeding to surgery after fewer than six cycles at the investigator's discretion (n=7). Similarly 2 patients received fewer than the maximum of six cycles of chemotherapy with ED and

EP because of toxicity (n=1), and investigator's discretion (n=1).

Dose reduction was necessary with 36 cycles of DD (22%) in eleven patients, 38 cycles of DP(26%) in thirteen patients, 6 cycles of ED (20%) in two patients and 7 cycles of EP(20%) in two patients. In contrast, dose delay was necessary with 24 cycles of DD (14%) in seven patients, 27 cycles of DP (16%) in 8 patients, 9 cycles of ED& EP (30%) in three patients.

Toxicity

Toxicity of chemotherapy was recorded as the number of patients who experienced grade 3-4 toxicity shown in table 3. Hematological and non hematological toxic effects were generally mild and were similar in all treatment groups. Grade3-4 leukopenia was observed in 2 patients (4%) with DD versus 1 (2%) with DP. Grade3-4 neutropenia was observed in 2(20%)patients with ED versus 1 (10%) patient with EP (p=0.069) and 10 (20%) patients with DD versus 11 (22%) patients with DP (p=0.03). Grade3-4 anemia occurred in 1 (10%) receiving ED versus 3 (30%) patients on EP (p=0.002) and 19 (38%) patients on DD versus 17 (34%) patients on DP (p=0.021). Hand foot syndrome grade 3-4 observed none of the group arm , no patients developed congestive heart failure. Non hematological toxicities were mostly grade 1-2. Grade 3-4 diarrhea toxicity was observed 4 (8%) on receiving DD versus 2 (4%) on DP and in one patients on ED. Neurotoxicity grade 3-4 was observed none of the patients with ED and EP but 1 (2%) patient on DD versus 3 (6%) patients on DP (p=0.022) was observed.

Table 3: Grade 3 and 4 Toxicity Recorded As the Number of Events for All Cycles of Chemotherapy

	ED		EP		DD		DP	
Toxicity grade	3-4		3-4		3-4		3-4	
	n	%	n	%	n	%	n	%
Hematological								
Leukopenia	0	0	0	0	2	4	1	2
Neutropenia	2	20	1	10	10	20	11	22
Anemia	1	10	3	30	19	38	17	34
Thrombocytopenia	3	30	1	10	9	18	12	24
Non-hematological								
Diarrhea	1	10	0	0	4	8	2	4
Nausea	2	20	1	10	3	6	0	0
Vomiting	0	0	0	0	1	2	0	0
Mucositis	0	0	0	0	2	4	1	2
Neurotoxicity	0	0	0	0	1	2	3	6

Discussion

Anthracyclines and taxanes are recommended for the adjuvant treatment of women with operable advanced breast cancer. Several regimens are being used by clinicians, including standard dose sequential, concurrent and dose-dense sequential [10].The combination of anthracyclines (Epirubicin, doxorubicin) and taxanes (docetaxel, paclitaxel) has demonstrated significant activity as first-line chemotherapy in ABC. The rationale for combining taxanes with anthracyclines rests on a number of observations. Individually they have the greatest single agent activity in and have largely non-overlapping patterns of commonly encountered adverse events [11].

The primary objective of this study, which was to show a large superiority in TTP, ORR, OS for the ED regimen compared with EP and DD regimen compared with DP, was not met; the study lacks power to rule out smaller differences. Nevertheless, our results indicate that the activity and efficacy of the two regimens as first line therapy are similar in terms of overall survival rate, durations of response, TTP and OS. The clinical response rates with ED (60%), EP (70%), DD (34%), and DP (36%) reported here are comparable to the overall clinical response rates reported in some previous study---. There is no significant difference in quality of life scores between the ED versus EP and DD versus DP. Non-hematological toxicity was significantly more frequent in arm DD, as well as grade 3-4 mucositis. Neurotoxicity occurred more frequently in arm DP as compared to arm DD. The efficacy results are shown in table 2. and demonstrated that the paclitaxel or docetaxel combination with doxorubicin were not significantly different in terms of quality of life scores and efficacy, but had different toxicity profiles[12].

The median duration of response (10-11 months), TTP (8-11 months) and OS (21-36 months) in our trial are very acceptable for patients with an incidence of visceral metastases of approximately 65% and a high rate of adjuvant chemotherapy, including anthracyclines. Furthermore, the results are very similar to those found in other studies using a conventional 3-week schedule[13].This study does not support the proposed relationship of tumor oxygenation and sensitivity to cytotoxic agents. In the mean time studies, have raised concerns about inferior long-term outcomes if erythropoietin -stimulating agents were used to increase hemoglobin but not if the intension was to prevent severe anemia.[14].

The rational behind this choice was centered on the dose-density theory based on the reduction of the intervals

between chemotherapy doses to restrict the opportunity for cancer cells to become resistant to drugs and to target cell clones with differing growth rates. Furthermore, weekly administration of chemotherapy in a dose-dense schedule is understood to have an anti-angiogenesis effect, constricting the blood supply to tumors and restricting their growth. Thus, the weekly schedule was designed to allow administration of a total dose of drug greater than or equal to that administered with the conventional 3-week schedule, to enhance cumulative cytotoxic activity while reducing the toxicity of the treatment, providing greater therapeutic benefit together with a more favourable tolerability profile [15-17].

This study has limitations due to its small sample size; which should be mentioned. The sample size is not large enough to detect a small but clinically meaningful difference even it was originally calculated to have sufficient power for DFS and pCR. Treatment duration and drugs of the four chemotherapy arms are not completely identical.

In conclusion, this multicenter randomized study indicates that the DD and DP regimens have similar efficacy but different toxicity as first line treatment of ABC and in ED &EP regimen is difficult to compared the efficacy and toxicity because of small sample size. Until individualized therapy becomes a reality in everyday clinical practice, either regimen can be used for the treatment of women with HER2-negative ABC who due to aggressive disease might benefit from combination chemotherapy.

References

1. Wilson KA, Waugh A (2006). Ross and Wilson Anatomy and Physiology in Health and Illness. Edinburgh, Churchill Livingstone pp 53-4.
2. Wafa Majeed, Bilal Aslam et al. 2014 Breast Cancer: Major Risk Factors and Recent Developments in Treatment Asian Pac J Cancer Prev, 15 (8), 3353-3358.
3. Nadia Harbeck1, Frédérique Penault- Llorca, Javier Cortes, 2019 breast cancer researchgate DOI: 10.1038/s41572-019-0111-2fef.
4. W.J.Gradishar, taxanes for the treatment of metastatic breast cancer, Breast cancer: Basic and clinical research 2012:6, 159-171.
5. Nabholtz J-M, Tonkin K, Smylie M, et al: Chemotherapy of breast cancer: Are the taxanes going to change the natural history of breast cancer? Exp Opin Pharmacother 1::187,2000-206.
6. Ghersi D, Wilcken N, Simes RJ. A systematic review of taxen- containg regimens for metastatic breast cancer. Br J Cancer 2005;93(3)293-301.
7. Joseph A. Sparano, et al, Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer, N Engl J Med. 2008 Apr 17; 358(16): 1663–1671.
8. A Hern Rp, Smith IE, Ebbs SR (1993) Chemotherapy and survival in advanced breast cancer patients: the inclusion of doxorubicin in Cooper type regimens. Br J Cancer 67: 801-805.
9. Swain S, Whaley F, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97:2869–79.
10. Saloustros E, Malamos N, Boukovinas I, et.al. (2014) Dose-dense paclitaxel versus docetaxel following FEC as adjuvant chemotherapy in axillary node-positive early breast cancer: a multicenter randomized study of the Hellenic Oncology Research Group (HORG). Breast Cancer Res Treat 148: 591–597.
11. Nabholtz JA (2003) Docetaxel–anthracycline combinations in metastatic breast cancer. Breast Cancer Res Treat 79: S3– S9.
12. Cassier P, Chabaud S, Triller lenoir Vet al. a phase II trial of doxorubicin and paclitaxel in metastatic breast canceer: results of the ERASME 3 study. Breast Cancer Res Treat 2008;109:343-50.
13. T Gamucci, AM D'Ottavio, E Magnolfi et al.Weekly epirubicin plus docetaxel as first-line treatment in metastatic breast cancer, British Journal of Cancer (2007) 97, 1040 – 1045.
14. leyland-Jones B, Semiglazov V, Pawlicki M et al. maintaining hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first line chemotherapy; a survival study. J Clin Oncol 2005; 23: 5960-5972.
15. Norton L (1988) A Gompertzian model of human breast cancer growth. Cancer Res 15: 7067–7071.
16. Norton L (2005) Conceptual and practical implications of breast tissue geometry: toward a more effective, less toxic therapy. Oncologist 10: 370–381.
17. Stammler HJ, Gutschow K, Sammer H, Malekmohmmadi M, Kentenich CH, Forstpointner R, Geuenich S, Bischoff J, Hiddemann W, Heinemann V (2001) Weekly docetaxel in patients with metastatic breast cancer. Ann Oncol 12: 1393–1398.