IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 12 Ver. IX (December. 2016), PP 93-98
www.iosrjournals.org

Comparative Study of Toxicity of Weekly versus Three -Weekly Regimen of Paclitaxel in Locally Advanced Breast Cancer

Dr.Jaijanani.R[1], Dr.Sangeetha Gopinath[2]
[1]*Assistant Professor, Pharmacology, SMC, Chennai, India*
[2]*Assistant Professor, SUT medical college, Trivandrum, India*

Abstract
Aim*: To compare the toxicity profile of two regimens namely three weekly paclitaxel followed by FAC (fluorouracil /doxorubicin /cyclophosphamide) and weekly paclitaxel followed by FAC in patients with locally advanced breast cancer.*
Methods*: Toxicities of both groups were recorded in the proforma following each cycle of treatment and at the end of treatment regimen. Grading of toxicities was done by WHO toxicity grading.*
Results: *Anemia, leucopenia, nausea, vomiting, stomatitis and diarrhoea were more with three weekly Paclitaxel regimen of which nausea and diarrhea were statistically significant whereas myalgia and peripheral neuropathy were more common with weekly Paclitaxel regimen but the difference was not statistically significant.*
Conclusion*: Patients on both regimens developed different pattern of toxicities and any one regimen cannot be considered better compared to the other regarding toxicities.*
Keywords*: breast cancer, chemotherapy, Paclitaxel, WHO toxicity criteria*

I. Introduction

Breast cancer is the most common cancer diagnosed in women in India. It accounts for about 27% of all cancers in India. Surgery, radiotherapy, chemotherapy, targeted therapy, and hormonal therapy are the major modalities of treatment. Chemotherapy given to patients after surgery is called adjuvant therapy. It is used to kill any undetected tumor cells (micrometastases) that may have migrated to other parts of the body. It reduces the risk of recurrence among women with operable breast cancer. The addition of a taxane, either in weekly or three weekly dose, to an anthracycline-containing regimen further reduces the risk of relapse. [1] Paclitaxel is an antitumor agent that acts by promoting tubulin dimerization and inhibiting depolymerization of the microtubules.[2] The challenge in cancer treatment is to use the various treatment modalities alone or together in a fashion that maximizes the chances for patient benefit. Interventions should be sought that will reduce side effects and increase the quality of life.

II. Objective

To compare the toxicity profile and to assess the grading of toxicities of two regimens namely three weekly paclitaxel (group 1) followed by FAC (fluorouracil /doxorubicin / cyclophosphamide) and weekly paclitaxel (group 2) followed by FAC in patients with locally advanced breast cancer.

III. Methods

This was a prospective observational study. Female patients diagnosed with stage 3 breast cancer (according to AJCC 7th edition) who were treated with either weekly or three-weekly Paclitaxel based regimen following surgery were recruited from Department of Radiotherapy, Government Medical College, Thiruvananthapuram (64 patients in each treatment group).
Sample size was calculated as 128 (64 in each treatment group) by expert statistician using the formula.
$n = p_1q_1 + p_2q_2 \quad F(\alpha, \beta) / d^2$
n =sample size, p_1 =proportion of patients with toxicity in weekly paclitaxel regimen, q_1=100 - p_1
p_2 =proportion of patients with toxicity in three weekly paclitaxel regimen, q_2 =100 - p_2
$d = p_1 - p_2$
$F(\alpha, \beta) = 16$ at 90% power

3.1Inclusion criteria

- Cytology proven locally advanced breast cancer patients (stage III) on three weekly and weekly Paclitaxel based regimens
- Female patients between 20-70 years of age.
- Patients with hematopoietic, cardiac, hepatic and renal function within normal limits.

3.2 Exclusion criteria

- Patients who are not willing to participate in the study.
- Patients with radiological evidence of metastasis.
- Patients on other chemotherapy regimens.

The study was carried out after approval from Institutional Ethics Committee. Written informed consent was obtained from all the subjects recruited in the study. Subjects fulfilling the inclusion and exclusion criteria were recruited in the study (64 patients in group 1 and 64 patients in group 2). Reports of all the relevant baseline investigations were collected in the structured proforma. The following was the detailed treatment regimen for group 1 and group 2 patients as prescribed by the treating oncologist.

3.3 Treatment regimen

Group 1: Patients assigned to three weekly arm received paclitaxel 225mg/m^2 as an intravenous infusion over 3 hours, this constitutes one cycle of therapy. Four cycles of paclitaxel administered at this dose every three weeks. It was followed by four cycles of FAC regimen in standard doses fluorouracil (500mg/m^2)/doxorubicin (50mg/m^2)/ cyclophosphamide (500mg/m^2) once in every three weeks.

Group 2: Patients assigned to weekly dose received paclitaxel 150mg/m^2 over a period of 3 hours every week for 3 weeks, followed by one-week rest. This constitutes one cycle of therapy. Four cycles of paclitaxel administered at this dose every week. It was followed by four cycles of FAC regimen in standard doses fluorouracil (500mg/m^2)/doxorubicin (50mg/m^2)/ cyclophosphamide (500mg/m^2) once in every three weeks. Patients on both groups received 50mg of Pheniramine (Avil), 8 mg of Dexamethasone, 300 mg of Ranitidine at night before and on the morning of each treatment day.

3.4 Toxicity assessment: Patients were subjected to hematology evaluation – Hb, TLC, DLC, blood sugar, blood urea, serum creatinine; liver function tests – SGOT, SGPT at the end of four cycles of Paclitaxel therapy and again at the end of four cycles of FAC therapy. Data collected was entered in the proforma sheet. Adverse drug reactions were collected from all patients during each visit and entered in the proforma sheet .The toxicities developed were graded according to the WHO toxicity criteria.

3.5 Statistical analysis: Statistical analysis Data analysis was done with the help of Excel 2007 and SPSS 16 statistical software. The toxicity grades were entered in the Excel 2007 worksheet for each variable. The highest toxicity during any cycle was considered as the toxicity grade for that patient. Chi square test was used to assess the difference between the two groups as the toxicity grading is a categorical variable.

IV. Results

4.1Demographic profile

4.1.1 Age: The age range of patients included in the study was between 32 years - 67 years. The maximum number of patients belonged to the age group 50-59. There was no statistically significant difference between the two treatment groups regarding age wise distribution (p value -0.22).

4.1.2 Menopausal status: In the present study, 71.4% of patients in three weekly regimen and 77.7% of patients in weekly regimen were premenopausal. Analysis showed no significant difference between the two treatment groups (p value – 0.42).

4.2 Toxicity Profile

4.2.1Overall comparison of toxicities: When overall toxicities were taken into consideration anemia, leucopenia, nausea, vomiting, stomatitis and diarrhoea were more common with group 1 patients whereas myalgia and peripheral neuropathy were more common in group 2.The difference was significant with regard to nausea and diarrhoea. (Table 1)

4.2.2 Haematological toxicity

4.2.2.1 Anemia: In the current study, out of the total 128 patients, 24 (18.8%) patients developed anemia. Among them, 12 received three weekly regimen and 12 were in weekly regimen. 8(14.3%) patients receiving three weekly treatment and 12(16.7%) in weekly regimen developed grade 1 anemia. Grade 2 anemia was seen only in patients who received three weekly paclitaxel regimen. None of the patients progressed to grade 3 or 4(Fig 1). There was no significant difference between the two treatment groups (p value – 0.49)

4.2.2.2 Leucopenia: Leucopenia developed in 12 patients taken up for the study. Comparison of the two regimens indicated that 8(14.3%) patients in group 1 developed leucopenia whereas only 4(5.6%) patients in group 2 developed leucopenia. 4(7.1%) patients in group 1 and 4(5.6%) patients in group 2 developed grade 1 leucopenia. Grade 2 leucopenia was not seen with group 2. None of the patients progressed to grade 3 or 4(Fig 2). There was no significant difference between the two treatment groups (p value – 0.09).

Table 1: Overall comparison of toxicities

Toxicity	Group 1		Group 2		P value
	N	%	N	%	
Anemia	12	21.4	12	16.7	0.49
Leucopenia	8	14.3	4	5.6	0.09
Thrombocytopenia	0	0	0	0	
Nausea	16	28.6	8	11.1	0.01
Vomiting	12	21.4	8	11.1	0.11
Stomatitis	12	21.4	8	11.1	0.11
Diarrhoea	4	7.1	0	0	0.03
Alopecia	56	100	72	100	
Myalgia	16	28.6	24	33.3	0.5
Peripheral neuropathy	8	14.2	16	22.2	0.3

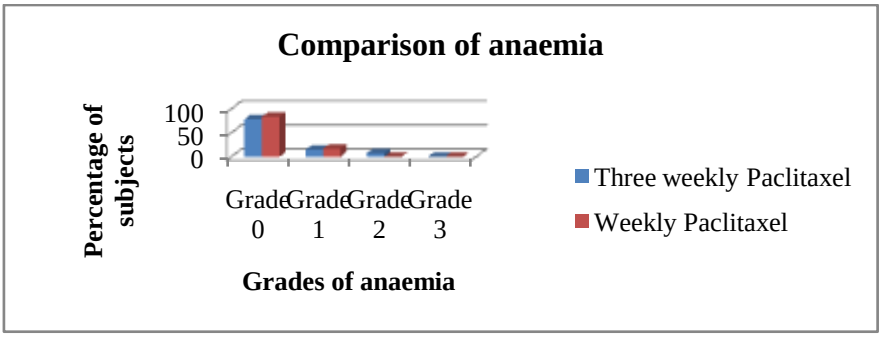

Fig 1: Comparison of anemia between three weekly and weekly regimen

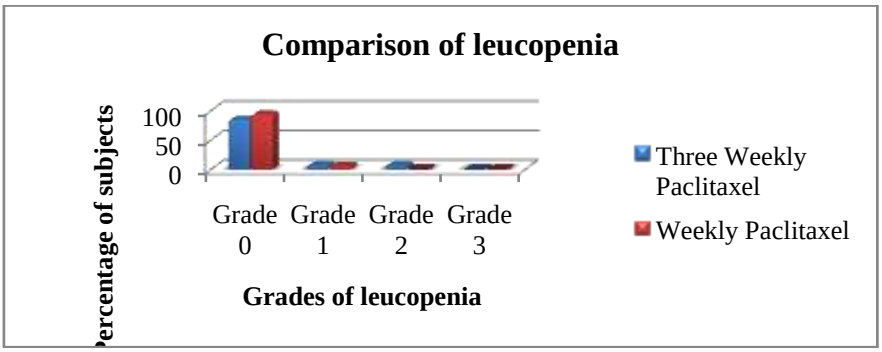

Fig 2: Comparison of leucopenia between three weekly and weekly regimen

4.2.3 Gastrointestinal toxicity

4.2.3.1Nausea : In this study, nausea was more common with group 1 patients. In group 1, 28.5% of patients developed nausea, whereas only 11.2 % had nausea in group 2. This difference is statistically significant (p value – 0.012). 12 (21.4 %) patients in group 1 and 4(5.6%) patients in group 2 developed grade 1 nausea. 4(7.1%) patients in group 1 and 4(5.6%) patients in group 2 developed grade 2 nausea. None of them developed grade 3 or 4 toxicity (Fig 3).

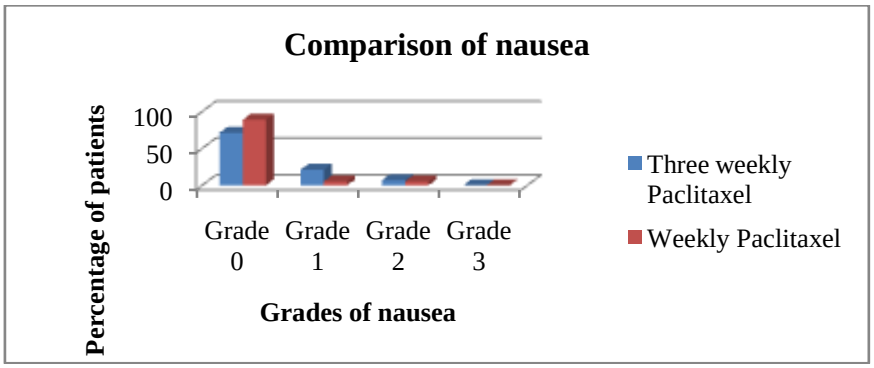

Fig 3: Comparison of nausea between three weekly and weekly regimen

4.2.3.2 Vomiting: Vomiting was seen in 12(21.4%) patients in group 1 and 8(11.1%) patients in group 2. All patients had vomiting of grade 1. None developed grade 2, 3 or 4 vomiting in both groups (Fig 4). The difference was not significant between the groups (p value – 0.11).

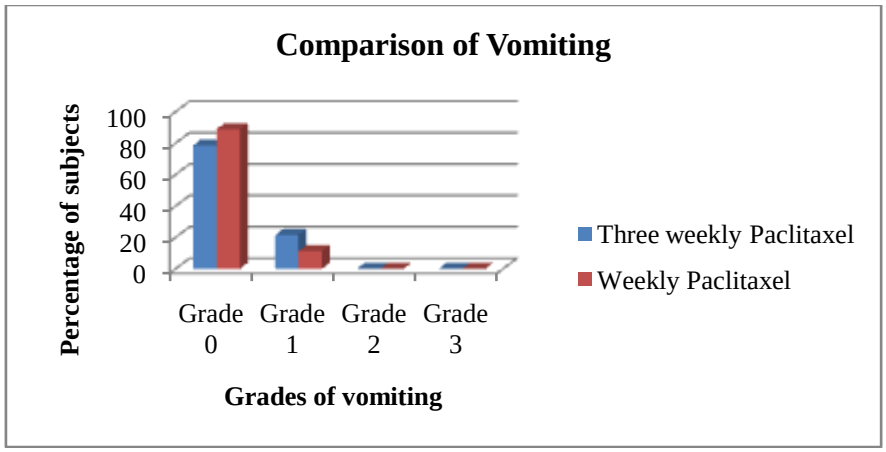

Fig 4: Comparison of vomiting between three weekly and weekly regimen

4.2.3.3 Stomatitis: Of the total 128 patients 20 developed stomatitis, more common in group 1 (14.3%) than the other (11.1%). None of the patients in either groups developed grade 2 toxicity (Fig 5). The difference was not significant (p value – 0.11).

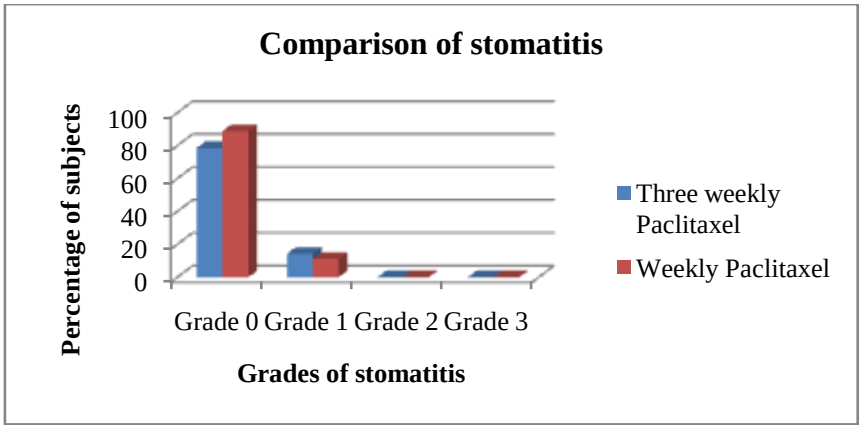

Fig 5: Comparison of stomatitis between three weekly and weekly regimen

4.2.3.4 Diarrhoea: Only 4 patients in group 1 developed diarrhoea and it was not seen with group 2. No patients went in for grade 2, 3 or 4 diarrhoea (Fig 6). The difference was statistically significant between the two treatment groups (p value – 0.034).

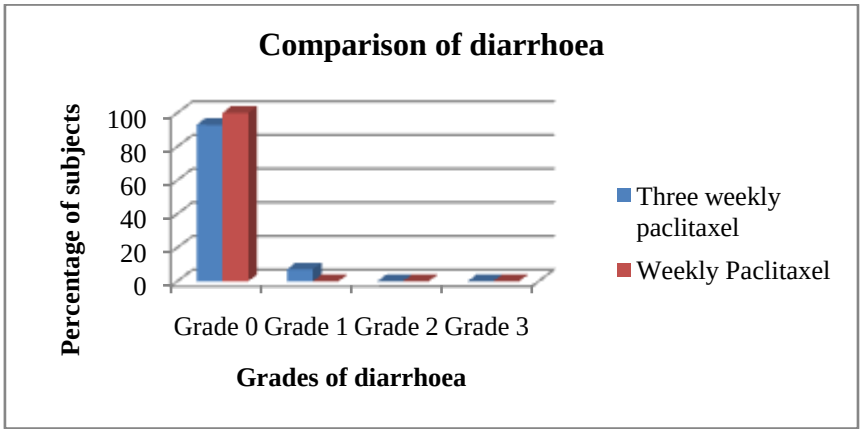

Fig 6: Comparison of diarrhoea between three weekly and weekly regimen

4.2.4 Dermatological toxicity

4.2.4.1 Alopecia: None of them was spared of this toxicity. Grade 2 toxicity was more common with both the regimens, 78.6% in group 1 and 94.4% in group 2 (Fig 7).

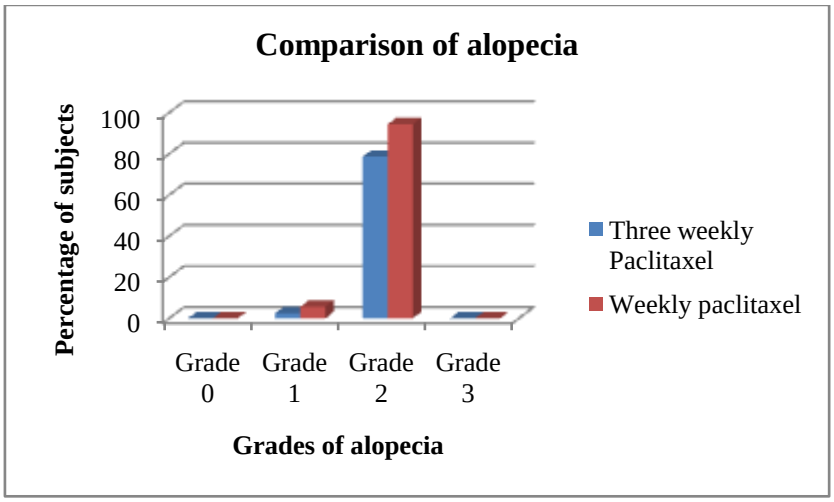

Fig 7: Comparison of alopecia between three weekly and weekly regimen

4.2.5 Musculoskeletal

4.2.5.1 Myalgia: 16(28.5%) patients in group 1 developed myalgia. In group 2, 24(33.3%) developed myalgia. There was no significant difference between the two treatment groups (p value – 0.56).This toxicity is not included in WHO toxicity grading.

4.2.6 Neurological toxicity

4.2.6.1 Paresthesia: This was seen in 16 patients on group 2 (22.2%) while only in 8 patients (14.2 %) in group 1. None of the patient in group 1 progressed to grade 2 toxicity (Fig 8). Difference in incidence of this toxicity was found to be statistically insignificant (p value -0.362).

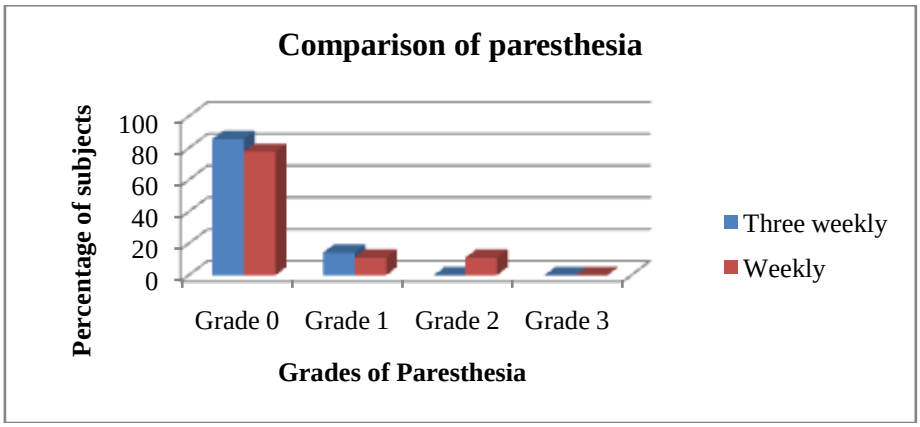

Fig 8: Comparison of paresthesia between three weekly and weekly regimen

V. Discussion

The aim of the study was to compare the toxicity profile of two popular regimens used for adjuvant chemotherapy in patients with locally advanced breast cancer. They were three weekly and weekly Paclitaxel regimen followed by FAC (5-fluorouracil, Adriamycin, Cyclophosphamide). Patients on both regimens developed toxicities, but the pattern of toxicities were different. Based on the observations from study, any one regimen could not be considered better than the other with regard to toxicities.

The demographic profile of patients in both regimens was comparable in the current study. The age range of patients included in the study was between 32 and 67 years. The majority of patients were more than 50 years old. In the study conducted by Majorie et al., the age range of patients was between 20 and 65. [3] Majority of patients belonged to the age group 36-50 years and the mean age was 44 years. In the current study, majority of patients were in premenopausal period in both the study groups. Similar findings were reported in the study by Trichopoulos et al. [4]

In this study out of the total 128 patients, 18.8% patients developed anaemia. Among them, 9.4% received three weekly regimen and 9.4% were in weekly regimen. Leucopenia was more common with three weekly regimen(14.3%) than weekly regimen (5.6%) ($p>0.05$). Thrombocytopenia was not seen in both the regimens in the current study. In the study by Abdel et al in Asian population, anemia was reported among 21% and 14% in three weekly and weekly regimen respectively. [5] In that study, leucopenia was observed in 21% of patients in three weekly regimen and 9.8% of patients in weekly regimen. Thrombocytopenia (2% in both) was seen in both study groups but there was no significant difference between them.

Gastrointestinal adverse effects like nausea, vomiting, stomatitis and diarrhoea were compared which showed that there was no significant difference in the incidence of development of vomiting and stomatitis between two groups. Nausea and diarrhoea were significantly high in patients receiving three weekly regimen than weekly regimen ($p<0.05$). In the study by Majorie et al, stomatitis and vomiting was not seen with weekly paclitaxel regimen. Equal incidence of nausea was seen with both the study groups in that study. There was no significant difference in the incidence of diarrhoea in both the study groups in that study.

All patients developed alopecia in both groups. Similar results were obtained in the study conducted by Majorie et al. The incidence of myalgia was 16% with three weekly regimen as compared to 24% of weekly regimen. This was concurrent with the results of study by Majorie et al.

Peripheral neuropathy was more common in patients receiving weekly (22.2%) regimen when compared to three weekly (14.2%) regimen. The difference in incidence of peripheral neuropathy was not statistically significant (p-0.362). In the study by Seidman et al paresthesia was seen in 24% of patients in weekly regimen while only in 12% of patients in three weekly regimen.[6] Also according to the studies by Majorie et al, the incidence of this toxicity was significantly higher in weekly regimen.

When overall toxicities were taken into consideration anemia,leucopenia were more common with three weekly regimen. Thrombocytopenia was not seen in both the study groups. Gastrointestinal toxicities like stomatitis, nausea, vomiting, diarrhoea were more common with three weekly regimen than the other in which the difference is statistically significant with regard to nausea and diarrhoea. Alopecia was seen in all the patients in both the study groups. The incidence of myalgia and peripheral neuropathy were more in weekly regimen than the other.

VI. Conclusion

Three weekly and weekly Paclitaxel regimens have different pattern of toxicities. Both regimens are equally efficacious according to previous studies results. Patient's predisposition to toxicities may govern the selection of regimen for treatment. The study period was short. So, delayed toxicities could not be monitored. The sample size was small. Larger sample size is needed for proper assessment of toxicity profile.

References

[1]. Sikov WM, Akerley W, Cummings F, et al: Weekly high-dose paclitaxel in locally advanced and metastatic breast cancer. Breast Cancer Res Treat 46:95, 1997
[2]. Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med. 1995; 332(15):1004–14.
[3]. Marjorie C. Green, Aman U. et al.Weekly Paclitaxel Improves Pathologic CompleteRemission in Operable Breast Cancer When Compared with Paclitaxel Once Every 3 Weeks.JClinOncol2005;23(25):5983-5992.
[4]. Trichopoulos D, MacMahon et al. Menopause and breast cancer risk. J Natl Cancer Inst 1972;48(3):605.
[5]. Abdel HalimI , El AshriM et al. Weekly paclitaxel versus standard 3-week schedule in patients with metastatic breast cancer. J ClinOncol 2011;29 (15) :627
[6]. Andrew D. Seidman, Donald Berry et al.Randomized Phase III Trial of Weekly Compared With Every-3-Weeks Paclitaxel for Metastatic Breast Cancer, With Trastuzumab for all HER-2 Overexpressors and Random Assignment to Trastuzumab or Not in HER-2 Nonoverexpressors: Final Results of Cancer and Leukemia Group B Protocol 9840.J ClinOncol2008; 26(10):1642-1649