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Vinorelbine and 5 fluoro-uracil/folinic acid versus docetaxel as first line treatment for patients with metastatic breast cancer

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Background: Vinorelbine (V) and 5-Fluorouracil (5FU) is an effective combination for the treatment of metastatic breast cancer (MBC). Available Phase II clinical data reports response rates ranging from 60−64% in first-line MBC. Single agent Docetaxel (D) is also an effective treatment for MBC, demonstrating an objective response rate of 48% in a pivotal phase III trial. We evaluated the efficacy and safety of V + 5FU (Arm A) versus D (Arm B) in patients (pts) with MBC relapsing after adjuvant anthracycline-based treatment.

Materials and Methods: 100 pts (50% Arm A, 50% Arm B) were enrolled between July 2003 and March 2005. All pts had measurable MBC (WHO) recurrent after adjuvant anthracycline treatment, WHO PS $\leqslant 1$, adequate bone marrow, renal and hepatic functions. Pts were randomized to Arm A: Vinorelbine i.v. 25 mg/m^2 D1, D3 + folinic acid 100 mg/m^2 D1, D2, D3 + 5FU 350 mg/m^2 D1, D2, D3 or Arm B: Docetaxel 100 mg/m^2 D1 with optional prophylactic G-CSF. Cycles were repeated every 3 weeks. Pts with PD went off study while those with CR, PR, or SD continued treatment for a maximum of 8 cycles.

Results: Median age (Arm A; Arm B): 53 & 50 years; median WHO PS 0 (range 0−1) in both arms. Previous adjuvant therapy: anthracycline (100%), hormone-therapy (60% & 47% in Arms A & B respectively). Median disease free interval (Arm A; Arm B): 5.4 & 4.6 years. Main metastatic sites (Arm A; Arm B): lymph nodes (56%; 56%), liver (56%; 58%), lung (44%; 48%) and bone (34%; 20%). Number of metastatic sites (Arm A; Arm B): One (2%; 6%), Two (42%; 52%), Three (50%; 38%), More than 3 (6%; 4%). Total number of cycles delivered (Arm A: 281, Arm B: 282). Median number of cycles per patient: 6 in both arms. An objective tumor response of 64% & 68% and a complete response of 26% & 22% were achieved in arms A & B respectively. Median time to progression & overall survival: Arm A: 15 & 27 months, Arm B: 15 & 30 months. No WHO grade Gr 3−4 toxicities were noted in Arm A. Gr 3 alopecia (18%) & Gr 3 liver enzymes elevation (2%) were noted in Arm B.

Conclusions: Our results suggest that Vinorelbine–5FU combination and single agent docetaxel demonstrate similar efficacy as first line treatment for MBC. Vinorelbine–5FU is however better tolerated besides being a less costly therapeutic option in Egypt. A comparative Phase III trial is needed to confirm these results.

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Weekly paclitaxel and carboplatin as first line treatment of metastatic breast cancer: correlation of response with p53 status

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Background: Weekly paclitaxel plus carboplatin being a non-anthracyclin regimen lacking cardiotoxicity is an appealing approach as first line treatment for advanced breast cancer. The sensitivity of tumors overexpressing p53 to paclitaxel is a matter of debate.

Purpose: To evaluate weekly paclitaxel/carboplatin in patients with metastatic breast cancer in terms of response rate, relation of response to p53 status, time to progression & toxicity.

Patients and Methods: Forty patients with metastatic breast cancer were included in this study with a median age of 53 years (range, 40−63) and all patients had an ECOG performance status of 0−2. In addition to the routine workup, pathology specimens were evaluated for p53 status by immunohistochemistry (IHC). All patients received weekly paclitaxel 100 mg/m^2, one hour IV infusion and carboplatin AUC 2 IV infusion over $\frac{1}{2}$ an hour as first line treatment. Twenty-four patients (60%) received adjuvant chemotherapy, 19 (52.5%) received adjuvant radiotherapy & 15 (37.5%) received adjuvant hormonal treatment.

Results: p53 overexpression was found in 15 of the 40 studied patients (37.5%). The overall response rate among the 34 patients assessable for response was 55.9% (n = 19) of which 2 patients (5.9%) achieved CR and 17 (50%) achieved PR. Overexpression of p53 had a significant (p = 0.014) negative impact on response to treatment, where only 3 of the 13 patients (23.1%) overexpressing p53 responded to treatment, all of which were PRs compared to 16 of the 21 patients (76.2%) having normal p53 status including 2 CRs. The median time to progression was 4.2 months. Grade 3 & 4 toxicities included neutropenia (25%), neuropathy (10%), anemia (5%) and thrombocytopenia (2.5%).

Conclusions: The 55.9% overall response rate achieved with weekly paclitaxel plus carboplatin is among the highest achieved in metastatic breast cancer. However, the poor response rate seen in patients with p53 overexpression suggests that these patients should be encouraged to participate in clinical trials investigating other combinations.

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Randomized comparison of nab-paclitaxel weekly or every 3 weeks compared to docetaxel every 3 weeks as first-line therapy in patients (pts) with metastatic breast cancer (MBC)

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Background: Nanoparticle albumin-bound paclitaxel (nab-pac; Abraxane®) allows the preferential delivery of paclitaxel to tumors based on preclinical models and reduces the risk of hypersensitivity reactions induced by solvent-based paclitaxel (sb-pac). Nab-pac demonstrated an overall response rate (ORR) almost double that of sb-pac (p = 0.001) and a longer time to progression (>6 weeks longer; p = 0.006) in a phase III study in pts with MBC. This current phase II study was designed to evaluate the toxicity and antitumor activity of nab-pac administered every 3 weeks (q3w) or weekly (qw) and solvent-based docetaxel in pts with MBC.

Material and Methods: Patients with previously untreated MBC were randomized to receive nab-pac (A) 300 mg/m^2 q3w; (B) 100 mg/m^2 qw, 3/4 wks; (C) 150 mg/m^2 qw, 3/4 wks; or (D) solvent-based docetaxel at the highest dose for MBC, 100 mg/m^2 q3w.

Results: All nab-pac arms demonstrated higher ORR than docetaxel. Significantly higher ORR compared to docetaxel were observed for the nab-pac qw arms (63%, 74% vs 39% for B, C vs D; p = 0.002 and p < 0.001, respectively). A significant difference in progression-free survival (PFS) was observed (14.6 mo, nab-pac 150 mg/m^2 qw; 7.8 mo, docetaxel; p = 0.012). A numerical increase in PFS was observed for nab-pac 300 mg/m^2 q3w compared to docetaxel (10.9 vs 7.8 mo, p = NS). No difference in PFS was observed between nab-pac arms A and C, suggesting that this study was underpowered to show a difference between these arms. Nab-pac 100 mg/m^2 qw and docetaxel resulted in similar median PFS. The most frequent hematologic adverse event was neutropenia, with significantly lower rates of grade 3/4 neutropenia in all nab-pac arms (grade 4 neutropenia, 5%, 5%, 9%, 75% for arms A, B, C, D, respectively). Nab-pac also had lower rates of febrile neutropenia (1%, 1%, 1%, 8% for arms A, B, C, D, respectively) and fatigue (grade 3 fatigue, 5%, 0, 3%, 19% for arms A, B, C, D, respectively) compared to docetaxel. Peripheral neuropathy was similar in the nab-pac and docetaxel arms.

Conclusions: The nab-pac arms demonstrated improved safety and increased efficacy compared with docetaxel. All 3 arms of nab-pac resulted in lower rates of neutropenia, febrile neutropenia, and fatigue than docetaxel. The most effective nab-pac arm, based on significantly improved PFS and ORR, was nab-pac 150 mg/m^2 qw. Based on the results of this study, a phase III study of nab-pac 150 mg/m^2 qw versus docetaxel 100 mg/m^2 q3w will be conducted.

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Multicenter study of weekly trastuzumab, paclitaxel and carboplatin followed by a week of rest every 28 days in patients with HER2+ metastatic breast cancer – incidence of central nervous system metastases

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Introduction: The addition of Carboplatin to Trastuzumab and Paclitaxel improves the efficacy in HER2+ metastatic breast cancer (MBC). We have conducted a multicenter Phase II study to investigate the efficacy and safety of this combination given weekly $\times$ 3 followed by 1 week of rest. Primary endpoint was objective response rate and secondary endpoints were time to progression, overall survival and to study the toxicity profile of the combination.