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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.

Methods: Between August 2003 and April 2006, 40 patients (pts) with HER2+ MBC (IHC 3+ or FISH+) have been included in the study. Pts received Trastuzumab (loading dose of 4 mg/kg/wk and 2 mg/kg/d following wks), Paclitaxel (80 mg/m^2) and Carboplatin (AUC 2) all given weekly $\times$ 3 followed by 1 week of rest. Treatment was given until disease progression or unacceptable toxicity.

Results: 40 pts had baseline data available. Median age was 54 yrs (range 29−75). 38 (95%) pts received prior adjuvant or neoadjuvant treatment. 11 (27.5%) pts have received one prior CT line for metastatic disease. 87.5% pts had PS 0 or 1 at study entry. Disease sites were liver 16 (40%), bone 12 (30%), lymph nodes 13 (32.5%) and lung 8 (20%). 19 (47.5%) had >2 lesions. 97.5% had measurable disease.

36 patients have been evaluated for response: 11 CR (31%, 95% CI: 15−46%), 11 PR (31%, 15−36%), 9 SD (25%, 9−36%), 5 PD (14%, 2−26%) and 4 NE resulting in an ORR of 61% (95% CI: 45−77%) and tumor growth control rate (RR+SD) of 86% of patients (95% CI: 75−97%). Median TTP was 12.1 mo (95% CI: 8.8−19.9 mo) and median duration of response have not been reached yet. For a time of observation of 41.8 mo, the median OS is 33.1 mo (95% CI: 18.9−. . .). At a median follow-up of 39.4 mo from the inclusion, 14 pts (35%) developed CNS metastases: 9 pts (22.5%) as first progression site and 5 pts (12.5%) as later progression. For CNS met. pts TTP was 17.3 mo (r 2.2−44.2), and OS was 27.7 mo (r 12−48).

37 patients have received 194 cycles with a median of 5 cycles. Grade 3−4 toxicities/pts were: 3 (7.5%) anaemia, 2 (5%) leucopenia, 8 (20%) neutropenia, 1 (2.5%) febrile neutropenia, 1 (2.5%) trombopenia, 2 (5%) asthenia, 2 (5%) diarrhea, 3 (7.5%) nausea, 2 (5%) vomiting, 3 (7.5%) mucositis.

Conclusions: This interim analysis shows an interesting activity with this regimen. One week of rest may be of better convenience for the patient and hospital but also may improve the tolerability profile and efficacy of the combination. We observed a incidence of CNS metastases similar to that reported in other trials, but the survival is longer than in patients unselected for Her-2 status. The better control of extracranial disease reported in our experience is probably the cause of the longer survival of these CNS metastatic patients. Further results would be available for presentation.

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Metronomic oral vinorelbine and temozolomide, after whole brain radiotherapy, for the treatment of breast cancer patients with brain metastasis. A phase II study

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Background: The incidence of Central Nervous system (CNS) metastases has been reported to be 15−25% in patients with breast cancer. Whole Brain Radiotherapy (WBRT) remains the mainstay of therapy for brain metastasis of solid tumours not amenable to surgical resection. Temozolamide (TMZ) is a new orally administered imidazo-tetrazine with proven activity in Brain metastasis. Vinorelbine The recently introduced oral form of this vinca alkaloid derivative, Vinorelbine, has disclosed new and useful perspectives particularly for elderly patients.

Methods: Patients with breast cancer and newly diagnosed, inoperable, brain metastases (BM) were eligible. We have treated 19 consecutive patients (mean age: 55.2 + 22.4 yrs; median age: 57.9 yrs) affected by brain metastases with WBRT at 3 Gy/day administered over a two-week period (on wks 1–2), total dose 30 Gy, and an induction with TMZ 75 mg/m^2/day during this period, followed by 4 weeks off-therapy and subsequent original schedule with TMZ administration at 75 mg/m^2 on days 1–21 every and oral Vinorelbine (VNR) 70 mg/m^2 fractionated in days 1, 3 and 5, one week on-one week off, every four weeks up to twelve additional cycles. Pts who received at least one cycle of TMZ and VNR were assessable for response.

Results: All patients were subjected to the induction therapy and 86 cycles were performed, mean cycles 4.7. Two grade three, twelve grade II ad ten grade I neutropenia (CTC), five grade II anemia, seven grade I and four grade II thrombocytopenia and nine grade I alopecia were recorded. Fourteen grade I and 7grade III, nausea and vomiting were observed, moreover, liver or renal toxicity were never recorded in our series being the schedule well tolerated in all patients. two CR (10%), and 8 PRs (42%) were recorded while a clinical benefit was achieved in other four patients (21%). The Objective Response rate was 52% (C.I. 42.7−64.9%), while the disease control rate was 73% (C.I. 61.7−82.4%). Nine still alive patients, who achieved a PR and a SD, had an overall survival between 19 and 9 months, respectively. At the present, in our series, overall survival was 59% at 1 year. Patients continue to be followed to evaluate long term effects of the treatment. Our study found a high level of satisfaction for QoL.

Conclusions: These preliminary results show that some of the pts who received complete treatment plan could achieve prolonged disease control and survival. The schedule was safe and well tolerated (also in old pts.) and has suggested an encouraging activity in brain metastases from breast cancer. Final data analysis will be presented.

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All-oral vinorelbine (NVBo) and capecitabine (X) combination for chemotherapy-naïve HER2-negative metastatic breast cancer (MBC) patients: efficacy and safety in an international phase II study

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Background: NVBo and X have shown single-agent activity in MBC and combination of these two oral agents with non-overlapping key toxicities is logical. We report the latest efficacy and safety data from an international phase II study of all-oral NVBo plus X.

Methods: Eligible patients had measurable HER2-negative MBC, had received no prior chemotherapy for MBC, had relapsed greater than or equal to 6 months after completing (neo)adjuvant chemotherapy and had Karnofsky PS greater than or equal to 70%. Patients received 3-weekly cycles of NVBo 80 mg/m^2 (first cycle at 60 mg/m^2, escalating in the absence of G3/4 neutropenia) d1 and d8 in combination with X 1000 (750 if greater than or equal to 65 years) mg/m^2 twice daily d1−14. Treatment was continued until progression or unacceptable toxicity. The primary endpoint was response rate (RR) by RECIST.

Results: Baseline characteristics of the 55 enrolled pts (one not treated) were: median age 58.5 years (41% greater than or equal to 65); chemotherapy for early breast cancer 63% (predominantly anthracyclines, 85% with a taxane in 18%); prior hormone therapy 76%; visceral involvement 78% greater than or equal to 3 metastatic sites 46%. Patients received a median of 7 cycles (range 1–45). Median relative dose intensity was 87% for both agents and 94% received the escalated NVBo dose. G3/4 NCI CTC v2 adverse events in >5% of patients were: leucopenia 28%, neutropenia 49%, vomiting 9%, stomatitis 7%, fatigue 7%, febrile neutropenia 6%, infection with neutropenia 6%. The RR in 47 evaluable pts was 51% (95% CI: 36−66), including one complete response (2%). Stable disease (SD) was reported in an additional 30%. The clinical benefit rate (CR + PR + SD for >6 months) was 64%. After median follow-up of 21.1 months, median progression-free survival is 8.4 months. Median overall survival has not been reached.

Conclusions: The all-oral combination of NVBo and X is an effective and well-tolerated first-line therapy for MBC. Treatment was continued for up to 45 cycles. The efficacy of this combination with the added benefit of oral administration has led to initiation of a randomised trial versus i.v. combinations in the first-line setting.

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Is HER-2 over expression associated with brain metastases in Chinese breast cancer patients?

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Background: Brain metastases occur in 10−15% of metastatic breast cancer patients and are associated with poor prognosis. This study aims to identify tumor characteristics of the primary breast cancer which are related to brain metastases in Hong Kong Chinese patients.

Material and Methods: A retrospective study of patients with invasive breast cancer receiving treatment in a university hospital from January 2001 to December 2005 was performed. Clinico-pathological factors of those patients with brain metastases were compared with those without. HER-2 over expression was confirmed either by 3+ protein over expression using immunohistochemistry or by HER-2 gene amplification using fluorescence in situ hybridization.

Results: 787 patients with invasive breast cancer were treated during the study period. 30 patients were found to have distant metastases to brain. The median age of the patients at the diagnosis of brain metastases was