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Capecitabine dose modification minimises side effects without compromising efficacy in pretreated metastatic breast cancer (MBC)

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Background: Randomised studies and retrospective analyses have demonstrated that dose modification of capecitabine (X) in patients with MBC receiving monotherapy, or X−docetaxel (XT) combination therapy, minimises side effects while maintaining efficacy. The twice-daily, oral administration of X allows dose adjustments to be made easily. Here we report the findings of a retrospective review of 971 patients with pretreated MBC to reinforce the available information on the effect of dose modification on the efficacy and safety of X.

Methods: We reviewed data from 830 patients receiving X in four phase II monotherapy trials (X 1,255 mg/m^2 b.i.d. every 14 days q3w) and a phase III XT combination trial (X 1,250 mg/m^2 b.i.d. every 14 days, T 75 mg/m^2 day 1, q3w). The clinical records of 141 consecutive patients receiving X were also analysed, grouped according to starting dose: full dose (1,250 mg/m^2 b.i.d.), a 10% reduction (1,125 mg/m^2 b.i.d.), or a 20% reduction (1,000 mg/m^2 b.i.d.). The dose of X was modified in the clinical trials following the appearance of NCIC-CTC $\geqslant$ grade 2 treatment-related adverse events (O'Shaughnessy et al. J Clin Oncol 2002;20:2812−23), with an initial dose reduction of 25%, increased to 50% where necessary.

Results: In the four monotherapy trials, 41% of patients (n = 131) required dose reductions to 941.25 mg/m^2 b.i.d. X, compared with 65% of patients (n = 163) in the XT combination trial (80% of these patients had doses of both X and T reduced, to ~950 mg/m^2 b.i.d. and ~55 mg/m^2, respectively). In all of the studies analysed, similar, or even slightly longer, time to disease progression and overall survival were noted in patients receiving lower rather than full dose X. The incidence of treatment-related adverse events (hand-foot syndrome, diarrhoea, and stomatitis) was also lower in patients receiving reduced X doses.

Conclusions: This retrospective review demonstrates that, when used as monotherapy or in combination with T, X can be dose reduced without compromising time to progression or overall survival benefits. These data support the feasibility of dose reducing X, and the possibility of starting at a lower dose of X (<1,250 mg/^{2} b.i.d.) to reduce the incidence of adverse events.

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Efficacy of first-line capecitabine 1,000 mg/m^2 b.i.d. in patients with metastatic breast cancer (MBC)

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Background: Capecitabine (Xeloda®; Xel) 1,250 mg/m^2 b.i.d. on a standard intermittent schedule (days 1−14 of a 21-day cycle; SIS) was licensed >10 years ago. Physicians have since gained experience of adverse event management through dose modification, and more recent studies have used a starting dose of Xel 1,000 mg/m^2 b.i.d.

Methods: Efficacy and safety of first-line Xel 1,000 mg/m^2 b.i.d. in patients with MBC were reviewed from three clinical studies (ANZBCTG 0001 Xel vs classical cyclophosphamide/methotrexate/5-FU [CMF]; MoniCa; RIBBON-1).

Results: In the ANZBCTG 0001 trial, Xel 1,000 mg/m^2 (SIS), an equivalent-dose continuous schedule of 650 mg/m^2 b.i.d. (cont), and CMF were compared in a randomised, multicentre, phase III trial in 323 women. Treatment was continued until disease progression (PD) or unacceptable toxicity. Overall response rate (ORR) was similar with Xel-SIS, Xel-cont, and CMF (22%, 20% and 18%, respectively). Progression-free survival (PFS) was similar with Xel and CMF (6 months), but overall survival was significantly prolonged with Xel (22 vs 18 months; p = 0.02). Xel demonstrated lower incidences of grade 3/4 neutropenia, febrile neutropenia and stomatitis (J Clin Oncol 2007; 25(Suppl.18): 39s [Abst 1031]). In the MoniCa phase II trial, 165 patients received Xel 1,000 mg/m^2 (SIS) until PD or unacceptable toxicity. Rates of complete response, partial response and stable disease were 7.9%, 17.6% and 37%, respectively. Median time to disease progression was 32.2 weeks (95% CI 29.58–34.81). In a subgroup analysis, patients aged >65 years or those with hand-foot syndrome showed superior efficacy. The regimen was associated with a favourable tolerability profile. In the Xel cohort of the randomised, placebo-controlled phase III RIBBON-1 study, 615 patients received Xel 1,000 mg/m^2 (SIS) with (n = 409) or without (n = 206) bevacizumab (A). Xel-A combination achieved a significantly greater PFS than Xel plus placebo (HR = 0.69; p = 0.0002; 8.6 vs 5.7 months), and the PFS benefit was afforded irrespective of baseline risk group. ORR (35.4% vs 23.6%; p = 0.0097) and median duration of response (9.2 vs 7.2 months) were also greater with the Xel-A combination.

Conclusions: There is an ever-increasing body of evidence that Xel is effective at the low starting dose of 1,000 mg/m^2 b.i.d. The Xel-A combination provides greater clinical benefit than Xel alone. Without compromising efficacy, low-dose Xel would be expected to also reduce the incidence of adverse events.

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Primary breast cancer phenotype associated with propensity for leptomeningeal metastases

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Background: The incidence of breast CNS metastases seems to have increase in recent years probably due to increased incidence of breast cancer, improvement of diagnosis techniques and longer survival of patients with metastatic disease. Leptomeningeal metastases (LM) occur in 12 to 34% of breast cancer. Early detection of LM is needed to improve quality of life and survival. The aim of this study was to identify clinicopathologic characteristics associated with of LM in breast cancer.

Material and Methods: This retrospective study evaluated clinical and initial histological (before any cancer treatment) data from 60 breast cancer patients with LM diagnosed at Lille Cancer Center between 2005 and 2008. Patients were matched with of a control group of breast cancer patients without CNS metastases, according to age at breast cancer diagnosis, year of breast cancer diagnosis and used of chemotherapy during initial breast cancer treatment. Comparisons between groups were done using Wilcoxon, Chi2 or Fisher exact tests.

Results: The median age at the time of diagnosis of breast cancer was 48.5 years and the median age at the time of LM diagnosis was 52 year. In LM group, 26% patients had invasive lobular carcinoma (ILC). 60% of the tumors were grade 2 tumors, 38% T2, 67% N+, 20% M+. 40% of the tumors had negative estrogen receptor (ER−), 62% had negative progesterone receptors (PR−) and 23% had HER2 positive status. 27% tumors were triple negative. 85% of patients had received either neoadjuvant treatment or adjuvant treatment. LM was the site of first recurrence in XX patients. Parenchymal metastases were associated in 48%. The median time from breast cancer diagnosis to LM was 53 months. The comparison between matched groups with or without LM revealed a that risks factors of LM were ILC type (p = 0.02), PR− tumors (p = 0.04) and presence of metastases at breast cancer diagnosis (p = 0.005). ER negative tumors (p = 0.08) and HER2 overexpressed tumors were not significantly related to LM.

Conclusions: Our results confirm that the lobular type and the hormonal receptor negative status are risks factors for the development of LM. HER2 positive breast cancers, prone to developing parenchymal CNS metastases, were not associated with LM complication. Triple negative tumors were not significantly associated with LM evolution, but we observed triple negative tumors in 23% of cancers with LM evolution versus 15% of the general population of breast cancer.

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Evidence from the phase III AVADO study reveals no increase in tumour malignant potential following treatment of metastatic breast cancer (mBC) with bevacizumab (BV) and docetaxel (D)

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Background: The anti-VEGF antibody BV has shown significant clinical benefit in combination with chemotherapy in a range of tumours and in

three phase III trials in mBC. Recent preclinical data suggest that some anti-angiogenic agents (VEGFR tyrosine kinase inhibitors [TKIs] or VEGFR antibodies) increase the malignant potential of tumours (Pàez-Ribes; Ebos: Cancer Cell 2009:15). Although BV has a distinctly different mechanism of action, exploratory analyses to investigate these findings were performed on data from AVADO, a placebo (PL)-controlled study in first-line mBC.

Materials and Methods: Patients (pts) were treated with D (100 mg/m^2) q3w for up to 9 cycles, in combination with PL or BV (7.5 or 15 mg/kg) q3w until disease progression (PD) or unacceptable toxicity. Mortality rates were calculated at 30-day intervals up to day 210 after discontinuation of PL or BV for any reason. For pts discontinuing PL or BV for toxicity, PFS was analysed using Kaplan-Meier methods. In the overall population, the proportion of pts with new metastatic lesions was analysed at PD.

Results: As of 30 April 2009, 91 pts had discontinued PL or BV for toxicity; median PFS from discontinuation was longer in the BV arms than the PL arm. Mortality rates in pts stopping BV or PL for any reason (n = 463) were similar or lower in the BV arms than the PL arm at all 30-day intervals for the first 210 days after discontinuation, the timeframe over which the analyses were performed. At PD, fewer BV than PL pts had developed new lesions.

	PL + D	BV 7.5 mg + D	BV 15 mg + D
ITT population, n	241	248	247
Pts with PD, n (%)	208 (86)	212 (85)	210 (85)
Pts with PD & new lesion, n (%)	160 (77)*	154 (73)*	138 (66)*
All pts discontinuing BV or PL, n	139	153	171
Mortality, n (%)			
day 90	28 (21)	25 (17)	14 (9)
day 150	35 (26)	34 (23)	27 (17)
day 210	43 (33)	45 (32)	37 (24)
Pts discontinuing BV or PL due to toxicity, n	29	27	35
PFS from discontinuation of BV or PL			
median, months	3.3	6.4	6.8
HR vs PL		0.71	0.73
[95% CI]		[0.40–1.27]	[0.42–1.24]

*% of pts with PD.

Conclusions: Although preclinical data suggest that anti-angiogenic therapy may increase tumour malignant potential, exploratory data from a large clinical trial of BV do not support this theory. PFS in AVADO was longer after discontinuation of BV than after discontinuation of PL. Mortality rates up to day 210 after PL/BV discontinuation were similar. The proportion of BV pts with new metastatic lesions at PD was lower than that of PL pts, suggesting that metastatic spread was not increased.

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An indirect comparison of aromatase inhibitors (AIs) in the first line treatment of post menopausal women with hormone receptor positive (HR+) metastatic breast cancer (MBC)

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Background: Tamoxifen has in the past been the most widely used 1st line hormonal therapy for post-menopausal patients with HR+ MBC. Third-generation AIs, which have shown superior efficacy in early and advanced disease compared with tamoxifen, have been insufficiently explored in head-to-head trials in the 1st line setting. Hence, an indirect comparison was made of the relative effects of 2 non-steroidal (letrozole, anastrozole) and 1 steroidal (exemestane) AI.

Methods: Seven databases, from database inception to Jan. 2009, were searched for randomized controlled trials of AIs. Letrozole, anastrozole, and exemestane were compared, using tamoxifen as the common comparator, via the Bucher et al method (J Clin Epidemiol 1997; 50:683–691).

Outcomes were overall survival (OS), progression free survival (PFS), time to progression (TTP), objective response rate (ORR), adverse events (AEs) and quality of life (QOL).

Table: Hazard and Odds Ratios (HR) with 95% CIs

	Treatment 1 vs Treatment 2*		
	Anastrozole vs Letrozole	Exemestane vs Letrozole	Exemestane vs Anastrozole
OS	HR = 1.08 (0.87, 1.32)	1.18 (0.86, 1.61)	1.10 (0.79, 1.52)
PFS/TTP	HR = 1.22 (0.96, 1.54)	1.24 (0.95, 1.62)	1.02 (0.79, 1.35)
ORR	OR = 1.68 (1.12, 2.52)	0.96 (0.57, 1.62)	0.57 (0.35, 0.95)

*Hazard or odds ratio <1 indicates greater likelihood of better response on treatment 1.

Results: Four trials were included: 2 comparing tamoxifen with anastrozole (Bonneterre & Nabholtz 2001), 1 with letrozole (PO25) and 1 with exemestane (EORTC 10951). No significant differences were observed among the 3 AIs in OS, PFS/TTP or AEs; only ORR showed some advantage for letrozole and exemestane over anastrozole. QOL could not be compared as it was only reported for PO25.

Conclusions: Paucity of data in head-to head comparisons between AIs in this population make it difficult to conclusively differentiate between the drugs. Hence these AIs appear to be used interchangeably in clinical practice. Though results of this study need to be interpreted with caution because they are based on indirect comparisons, they suggest a class effect for all AIs.

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Analysis of risk factors associated with early development of brain metastases in breast cancer

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Background: Different groups reported an increased incidence of brain metastases (BM) from Her2-positive breast cancer in recent years; similar results were observed in triple-negative disease. Longer survival as well as the inability of most anti-cancer drugs to pass through an intact blood–brain barrier may add to this phenomenon. Furthermore, based on preclinical data, it was suggested that the Her2-positive subtype itself featured higher propensity to brain tissue.

We tried to correlated clinical and histopathological risk factors with early development of brain metastases, as such high-risk patients may derive the largest benefit from strategies of screening or prophylaxis.

Material and Methods: 230 patients with BM were identified at two Austrian centres. Patients received whole brain radiotherapy (WBRT) with or without boost irradiation or surgical resection. Data concerning case history and histology were available. Time to development of BM was defined as primary study endpoint. Multivariate analyses (Cox regression model; binary logistic regression model) were used in order to identify risk factors associated with early development of BM and BM as first site of disease progression (age; hormone receptor [HR] status; Her2-status; histological subtype; grading; stage 4 at primary diagnosis; adjuvant treatment; time to recurrence <12 months; visceral metastases; palliative chemotherapy; trastuzumab).

Results: Median age was 50 years; median time to development of BM was 36 months (mo), 95% CI 32.33–39.67. Overall survival following WBRT was 8 mo, 95% CI 6.06–9.94. HR-negative disease ($p = 0.043$; OR 1.68) and time to recurrence <12 mo ($p < 0.0001$; OR 3.57) predicted for early development of brain metastases, while palliative chemotherapy had a preventive effect ($p < 0.0001$; OR 0.31). Lobular histology correlated with BM as first site of disease progression ($p = 0.033$; OR 1.22).

Conclusions: Risk factors for development of BM were already published. We tried to identify a population at risk for early development of BM.

While Her2-positive disease shows increased risk for BM, our data suggest that Her2-status is not correlated with early development of BM or BM as first site of tumour progression. HR-negative disease and early disease recurrence predicted for shorter time BM. As those are typical features indicating a more aggressive tumour phenotype, we were not able to define reliably risk factors predicting for early development of brain metastases.

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Retrospective database analysis of the effect of zoledronic acid on skeletal-related events and mortality in women with breast cancer and bone metastasis in a managed care plan

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Background: Breast cancer (BC) patients with malignant bone lesions (BM) often experience skeletal-related events (SRE) including pathologic fracture, spinal cord compression, hypercalcemia of malignancy, which require radiotherapy and/or surgery to bone and are associated with significant morbidity and mortality and reduced quality of life. Zoledronic acid (ZOL) and pamidronate disodium (PAM), from the drug class bisphosphanates (BP), have proven to reduce and delay incidence of SREs