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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