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Clinical Trial Simulations to Assess Capecitabine Dose Reduction in Combination With Docetaxel in Second Line Treatment of Metastatic Breast Cancer

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Background: A phase II trial (NO16853) in patients with metastatic breast cancer (MBC) failed to demonstrate that capecitabine (CAP) 825 mg/m^2 in combination with docetaxel (DOC) 75 mg/m^2 was non-inferior (progression-free survival [PFS]) to 1250 mg/m^2 with DOC 75 mg/m^2 (Buzdar, Ann Oncol 2011). The aim of this project was to assess CAP dose response and to perform simulations to determine a CAP dose non-inferior to the registered dose 1250 mg/m^2 in combination with DOC in the 2nd-line treatment of MBC.
Methods: We updated a previously developed modeling framework (Claret, J Clin Oncol 2009) based on NO16853 and the pivotal phase III study in 2nd-line MBC, SO14999 (O'Shaughnessy, J Clin Oncol 2002), (888 patients in total). We first characterized the link between CAP dose intensity, tumour growth inhibition (TGI) (using an exposure-response TGI model based on longitudinal tumour size data), PFS and survival (using parametric models with change in tumour size from baseline at week 6 (CTS) as the main predictor). We then simulated response to a range of CAP starting doses (750 to 1250 mg/m^2) in combination with DOC. Multiple replicates of non-inferiority trials were simulated. The power of any trial with a given starting dose to show non-inferiority to the reference dose was calculated as the proportion of replicates with upper limit of PFS HR 95% CI exceeding 1.35 (Buzdar, Ann Oncol 2011).
Results: Baseline tumour size, ECOG performance status and CTS were significant predictors of PFS and survival. Clear dose-response was demonstrated in all simulated endpoints. Simulation of the NO16853 design showed it had little power to demonstrate non-inferiority (60%). Actually, no dose below 1250 mg/m^2 had 80% power to show non-inferiority to the reference dose level under the current study design. The power would reach 80% with a 1000 mg/m^2 starting dose and a slightly altered design (450 PFS events versus 350).
Conclusions: This is the first use of dose-efficacy simulation to extract information of a phase II clinical trial that did not meet its primary endpoint and to come to a conclusion that an intermediate dose that was not tested would have been successful to meet the primary end point of non-inferiority. The results support the current medical practice of using a lower than approved starting dose of CAP (1000 mg/m^2) in combination with DOC (75 mg/m^2) in the 2nd-line treatment of MBC without loss of efficacy and potentially with an improved safety profile.

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Modulation of Proliferation in MCF7 Cells by Regulated Expression of KLF2, 4, 6 and Ki-67 After Treatment With Zoledronic Acid

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Background: Bisphosphonates (BP) and the RANK-ligand antibody Denosumab (D) are antiresorptive drugs for the treatment of bone metastases. Primary target cells are osteoclasts but high concentrations of zoledronic acid (ZA) can induce tumour cell apoptosis via inhibition of the mevalonate pathway and/or accumulation of the ATP analog ApppI in cell culture. Actual clinical results have demonstrated a prevention of tumour relapse and increased overall survival with adjuvant treatment of zoledronic acic (ZA) in ER-positive breast cancer. Up to now, the underlying molecular mechanisms are still under debate.
Materials and Methods: MDA-MB-231 and MCF-7 breast cancer cells were treated for 3 h (pulse treatment) and 72 h (permanent treatment) with 5–100 μM ibandronate (Ibn), alendronate (Aln), risedronate (Ris) and ZA and 1–100 ng/ml D for comparison. Apoptosis and proliferation was determined after 72 h. Rescue experiments for the BP effects were done using geranylgeranyl-pyrophosphate (GGPP) and atorvastatin (Ator). Microarray hybridizations were performed to identify target genes in MCF-7.
Results: Permanent and pulse exposure to ZA induced apoptosis in MDA-MB-231 and inhibited proliferation in MCF-7 without affecting apoptosis. While Ibn, Aln and Ris were inferior to ZA in apoptosis induction in MDA-MB-231, they were equipotent in proliferation inhibition in MCF-7. GGPP rescued ZA effects in MDA-MB-231 but not the antiproliferative effects in MCF-7, while Ator rescued the latter. qPCR and immunocytochemistry identified KLF2, KLF4, KLF6 and Ki-67 as target genes of ZA in MCF-7. RANKL did not induce proliferation in MCF-7 cells and D did not affect the untreated or RANKL pretreated cells in terms of proliferation and apoptosis.
Conclusion: In summary, direct effects of ZA and other BP were shown on cell proliferation and expression of tumour relevant genes in MCF-7 cells, which are relatively resistant to ZA-induced apoptosis in comparison with MDA-MB-231. Ator but not GGPP rescued these effects, possibly indicating that these effects are rather due to the accumulation of ATP analogs than to the inhibition of protein prenylation. D had no effects under these basal conditions but future experiments should address the effects in the context of estrogens and gestagens and also in coculture with bone cells.

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Prognostic Factors of Breast Cancer Brain Metastases

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Background: Incidence of brain metastases (BM) from breast cancer has increased over the past decade, especially for HER2(+) tumours. The aim of this study is to determine the prognostic influence of biological subtypes, chemotherapy and anti-HER2 targeted treatments (TT) and to compare outcome predicted using different prognostic indexes.
Material and Methods: In this retrospective study conducted in Montpellier and Nice Cancer Centres, we have recorded 250 patients diagnosed with breast cancer BM with known HER2 and hormonal status and evaluated the association of overall survival with clinical and biological covariates using Cox models.
Results: After a median follow up of 4.5 years, median overall survival from BM diagnosis is 8.9 months (IC 95%, 6.9–10.3 months). When comparing the three prognostic indexes (Recursive Partitioning Analysis [RPA], Graded Prognostic Assessment [GPA] and Basic Score for BM [BS-BM]) in multivariate analysis, only RPA and GPA have a statistically significant prognostic value. Predictability of outcomes in patients with short and long term survival appears better using RPA index.
Patients with HER2(+) disease treated by anti-HER2 directed therapies have a longer survival (15.5 months (IC 95%, 11.9–20.2 months)) from BM diagnosis than patients with HER2(+) disease not treated by anti-HER2 TT (3.6 months [IC 95%, 1.4−5.9 months]), with triple negative disease (5.9 months [IC 95%, 4−9.5 months]) and hormone receptor (+)/HER2(−) disease (8.3 months [IC 95%, 4.7−10 months]) ($p < 0.001$). In a multivariate analysis not including chemotherapy, data significantly correlated with overall survival are RPA score, LDH level, protidemia and HER2(+) disease treated by anti-HER2 TT after BM diagnosis. In a second multivariate analysis including chemotherapy and limited to patients with good performance status, negative prognostic factors are the RPA score of 2 or 3, a high LDH level and liver metastases, whereas a normal protidemia, chemotherapy, HER2(+) disease treated with anti-HER2 targeted therapies after BM diagnosis and RH(+)/HER2(−) disease are associated with a better survival.
Conclusions: Survival for patients with breast cancer BM is significatively associated with the RPA score, the biological subtype of the primitive tumour, LDH and protidemia levels.
Our results show that, even after BM diagnosis, chemotherapy and anti-HER2 treatments for HER2(+) disease are associated with prolonged survival.

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Clinicopathological, Therapeutic and Prognostic Features of the Triple-negative Tumours in Moroccan Breast Cancer Patients (Experience of Hassan II University Hospital in Fez)

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Background: Triple-negative breast cancer (TNBC) is defined as a group of breast carcinomas that are negative for expression of hormone receptors