5096 POSTER

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.

5097 POSTER

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.

5098 POSTER

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.

5099 POSTER

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

and Her2. So, we distingue in this group the basal-like suptype (ER−, PR−, Her2−, cytokeratin (CK) 5/6+ and/or Her1+) and unclassified subtype (ER−, PR−, Her2−, Her1− and CK5/6−).
The aim of this study is to determine the clinicopathological, histological, therapeutic and prognostic features associated with this type of breast cancer.
Material and Methods: This is a retrospective study of 366 Breast cancer females diagnosed between January 2007 to June 2010 at the Department of pathology. Epidemiological, clinical, histological, therapeutic and evolutive data were analyzed: the histological grade is determined and based on the Scarff-Bloom-Richardson grading system (SBR). For Her2, immunohistochemical was carried out using with HercepTest, All Her2 score 2+ cases were analysed by FISH.
OS and DFS rates were estimated by Kaplan–Meier analysis and a log-rank test to estimate outcome.
Results: 17.5% of all breast cancer women (64 women) were identified TNBC, 12.6% were basal-like, 4.9% were unclassified subtype. The median age is young (45 years) and the median tumour size is high (4.3 cm).
TNBC were associated most often with a high grade; 49.2% grade III (53% for unclassified subtype, 47.6% for basal-like). Vascular invasion was found in 26.6% of cases (22% for unclassified subtype and 28.3% for basal-like subtype). For the lymph node involvement: 51% had positive lymph nodes, and 22.4% had distant metastases. For the AJCC staging, 17.2% were classified stage I, 20.7% stage IIA, 13.8% stage IIB, 10.3% stage IIIA, 15.5% stage IIIB, and 22.4% were stage IV. For treatment modalities, we have 94% of TNBC underwent surgery. Although, neoadjuvant chemotherapy was administered to 18% patients with 6% of complete pathologic response and adjuvant chemotherapy to 82%. 98% received anthracycline based regimen and only 30% received taxanes.
The Kaplan–Meier curves based showed the lowest survival probability (49% of OS, and 39% at the 3-years DFS).
Conclusion: TNBC is associated with young age, high grade tumours, advanced stage at diagnosis, important lymph node involvement, and distant metastases. Critical to optimal future management are accurate identification of truly triple negative disease and adequately powered prospective TNBC trials to establish treatment efficacy and define predictive biomarkers.

5100 POSTER

Relationship Between Survival, Hormone Receptor Rate, and Ca 15−3 Serum Levels in Patients With Isolated Liver Metastases From Breast Cancer

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Background: Breast cancer (BC) is the is the most common cancer in women, and the liver is one of the site of distant metastases, accounting for about 15% of patients with BC. Isolated liver metastases (LMs) are uncommon, and the presence of extra-hepatic disease usually represents a contraindication to liver resection. Liver metastasis of BC origin is usually life limiting, and the patient needs treatment. Surgical resection of parts of the liver is considered the only potentially curative therapy, but unfortunately only few patients are suitable for liver resection. The 5-year survival of patients with LMs from colorectal cancer ranges from 20% to 25%, while the survival period after resection to manage LMs from BC is unclear, due to the limited number of studies, ranging between 36−42 months. The aims of this study were (1) to identify factors predictive of survival of women with LMs from BC who underwent liver resection, and (2) to evaluate the relationship between survival, age, primitive tumour size, number of LM, serum carbohydrate antigen (CA) 15−3, estrogen receptor (ER) and progesterone receptor (PR) rate.
Patients and Methods: Medical reports of a group of 11 women (median age 57 years, range 39−67 years) with LM and no evidence of extra-hepatic disease who had undergone curative surgery for BC were reviewed retrospectively. All patients received 6−12 cycles of neoadjuvant chemotherapy (anthracyclines) alone or chemotherapy plus hormone therapy (tamoxifen or aromatase inhibitors) prior to liver resection (wedge resection or segmentectomy), and those with disease progression were excluded. The following parameters were recorded: age of the patients, size (maximum diameter measured by the pathologist) and number of the LMs, size of the primitive tumour, preoperative CA 15−3 serum levels, ER and PR rate.
Results: All LMs were metachronous, 7 patients had a single LM, 3 had two LMs, and 1 had three LMS. The baseline data were: size of the primitive BC = 25.8±6.4 mm, number of LMs = 1.4±0.68, ER = 6.6±33.8%, PR = 48.3±34.2%, CA 15-3 = 84.7±33.1 U/mL. The median survival rate was 32 months (range 12−77 months). There was a significant correlation between ER and both PR ($R = 0.95$, $p < 0.001$) and CA 15-3 ($R = 0.64$, $p = 0.034$), and between CA 15-3 and both PR ($R = 0.67$, $p = 0.024$) and number of LMs ($R = 0.69$, $p = 0.017$). At univariate analysis younger age, number of LMS, and size of the primitive tumour were associated with poorer prognosis, while at multivariate analysis only the age ($R = 0.81$, $p = 0.002$) of the patients was an independent factor of survival.
Conclusions: The survival of patients with BC and LMs is independent of hormone-receptor status and serum CA 15-3 levels at the time of liver resection.

Poster Presentations (Sun, 25 Sep, 14:00−16:30)
Breast Cancer − Early Disease

5101 POSTER

86 Cases of Early-onset Breast Cancer in Hungary − Retrospective Analysis of Immunohistochemistry (IHC) and Family-history Data − Assessing the Risk of Carrying BRCA1 and BRCA2 Mutation

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Background: It has long been debated whether breast cancer diagnosed at a young age is a clinically and etiologically distinct disease from breast cancer diagnosed later in life.
The aim of the present study was to retrospectively investigate clinicopathological characteristics and prognosis, as well as to assess the probability of carrying BRCA mutations in our group of young breast cancer patients.
Material and Methods: We included women diagnosed with invasive breast carcinoma younger than/or at the age of 35 years. Between 2000–2009 eighty-six (86) cases were selected from the files of the 2nd Department of Pathology, Semmelweis University.
Family history, clinicopathological and follow-up data were analyzed. BRCAPRO software analyses were performed to assess the probability of BRCA1 and BRCA2 mutations.
The tissue specimens were reviewed for histological type, nuclear/histological grade, tumour size, lymph node status, estrogen receptor (ER), progesterone receptor status (PR), Ki67, p53, HER2 and CK5/6.
Results: The mean age in the study group was 31.49 years at the time of diagnosis. Analyzing the family history in 41 cases 54 malignant tumours, mainly breast carcinomas (48%) were recorded. In the two most affected families 5−5 malignancies were found in each family. Based on the IHC results we grouped the examined tumours according to the four main molecular subtypes. Out of 81 patients, 37.05% were luminal A; 16.05% luminal B; 28.4% triple negative; and 18.5% HER2.
Evaluating the results of the BRCAPRO software we found higher than 10% of carrier probability in 14 cases (32.56%) regarding BRCA1 and in 2 cases (4.65%) concerning the BRCA2 gene. From the data provided we got to know that 24 of our 86 patients died already.
Conclusions: Despite the relatively short period of follow-up, more than one-fourth of our patients have already died, and there were a large amount of malignancies among the families involved.
According to our results luminal A and triple-negative subtype was the most common breast cancer subtype in this group of young patients. Carrier probabilities determined by BRCAPRO raised the necessity of the detection of the mutations of BRCA genes among the examined cases.
Sequencing the 5 most common BRCA1 and BRCA2 mutations occurring in Hungary is under progress in our study group.

5102 POSTER

Gene Expression Patterns in Canine Mammary Osteosarcomas Versus Osteosarcomas of the Head and Trunk

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Background: Tumours in the breasts or mammary glands affect women, dogs, cats and rodents. In addition to the frequent carcinomas there are other types, such as sarcomas that by definition originate from mesenchymal tissues. Breast sarcomas usually appear as fibrosarcomas and osteosarcomas and, to the best of our knowledge, only in humans and dogs. However, the origin of mammary sarcomas is not fully