Thursday, 22 March 2012 12:30–13:30

POSTER SESSION

Locally Advanced and Metastatic Disease

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A Review of Clinical Endpoints and Use of Quality of Life Outcomes in Phase III Metastatic Breast Cancer Clinical Trials

R. Tatla[1], D. Landaverde[2], J.C. Victor[3], D. Miles[4], S. Verma[2]. [1]*University of Toronto, Faculty of Medicine, Toronto, Canada;* [2]*Sunnybrook Odette Cancer Centre, Department of Medical Oncology, Toronto, Canada;* [3]*University of Toronto, Dalla Lana School of Public Health, Toronto, Canada;* [4]*Mount Vernon Cancer Centre, Department of Medical Oncology, London, United Kingdom*

Background: The management of metastatic breast cancer (MBC) is often considered to be palliative, with most interventions intended to relieve disease symptoms, minimize treatment effects and prolong patient survival. The impact of disease and treatment on a patient's functional abilities has led to the emphasis of incorporating quality of life (QoL) measures into clinical trials. The primary objective of this study is to evaluate phase III clinical trials in MBC, and assess the inclusion of QoL as an endpoint, in addition to conventional progression and survival endpoints.

Methods: A structured PubMed search was conducted to identify phase III clinical trials published between Jan. 1990 and Aug. 2011, which evaluated systemic treatment in MBC patients. Data pertaining to treatment regimens, study endpoints and clinical findings were collected, with a particular focus on progression-based (PB), overall survival (OS), and QoL endpoints. The instrument(s) used in evaluating QoL were also noted (when applicable).

Results: Of 520 publications identified, 122 phase III MBC clinical trials met the inclusion criteria. Of these studies, 98.4% and 95.9% included PB and OS respectively, as clinical endpoints, while QoL was assessed in only 46 (37.7%) studies. 14 instruments were identified as QoL measurement tools among these studies, with EORTC QLQ-C30 and FACT-B accounting for 54.7% of the instruments used. While the inclusion of QoL was not associated with the significance of PB results, there was an association between the inclusion of QoL and OS results, with 59% of significant OS studies and 32% of non-significant OS studies including QoL as a clinical endpoint ($p = 0.016$). When stratified by treatment arm, it was found that studies favouring standard therapy were more likely to include QoL (75%, $p = 0.045$), compared to those favouring the intervention (56%), and those without significant differences (32%).

Conclusions: Although the importance of QoL is often emphasized in MBC management and treatment decisions, only one-third of identified phase III clinical trials included an assessment of QoL. About half of these trials showed no statistically significant differences in QoL endpoint; of note, instruments of varying validity were utilized. There needs to be greater emphasis on the evaluation of QoL, with the use of standard and validated QoL tools in MBC clinical trials, especially as we increasingly focus on progression-based endpoints.

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Evaluation of Megasterol Acetate in Locally Advanced and Metastatic Breast Cancer in the era of Aromatase Inhibitors

A. Ramadan[1], L. Rivett[1], M. Wong Ah-See[1], N. Hussain[1]. [1]*Luton & Dunstable Hospital, Luton Bedfordshire, United Kingdom*

Background: There is no cure from metastatic breast cancer and the aim of treatment is to palliate symptoms, delay disease progression & prolong survival [1]. Median overall survival approaches two years, with a range from a few months to many years [2]. Megestrol Acetate (MA) is a progestin which has activity in Tamoxifen refractory, oestrogen receptor (ER) positive breast cancer, but the efficacy of MA following the use the 3rd generation aromatase inhibitors is unknown [3]. We performed a retrospective audit of the efficacy of MA in metastatic & locally advanced breast cancer patients who had progressed following treatment with aromatase inhibitor.

Materials and Methods: Breast cancer patients who had received treatment with MA at the Luton & Dunstable Hospital between 2001 & 2011 were identified from the Oncology Unit patient letter database by searching for the word 'Megace'. Treatment received and clinical outcomes were obtained from the patient notes. Progression free survival was evaluated.

Results: 49 patients were identified with a median age 67 years (range 39–100). All patients had received MA 160 mg daily orally following 3 or more lines of endocrine therapy, which included at least one aromatase inhibitor. 44 (90%) of patients had metastatic disease and 5 (10%) patients had locoregional disease only. All patients had ER positive disease and the HER2 status was: 36 (74%) negative, 3 (6%) positive, 10 (20%) unknown. The tumour pathology was: 35 (71%) Invasive ductal, 13 (27%) invasive lobular, 1 (2%) tubulo-lobular. The median PFS was 12 weeks with a range of 2–110 weeks. Median PFS in patients with 2 or more sites of metastatic disease was 10 weeks (range 2−20 weeks). There was no difference in PFS according to tumor pathology ($p = 0.46$).

Conclusion: Patients with locally advanced or metastatic ER positive breast cancer can obtain clinical benefit from treatment with MA following disease progression with a 3rd generation aromatase inhibitor. No difference was seen in DFS according to tumor pathology, but patient numbers were small. A prospective audit is underway to further evaluate MA in this patient group.

References

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The Prognosis and the Validity of Early Detection of Bone Recurrence After Breast Cancer Surgery

Y. Koyma[1], E. Sakata[1], M. Ikarashi[1], C. Toshikawa[1], N. Manba[1], M. Hasegawa[1], K. Hatakeyama[1]. [1]*Niigata University School of Medicine, Division of Digestive & General Surgery, Niigata, Japan*

Background: Intensive routine diagnostic evaluation including bone scans after surgery for breast cancer is not considered appropriate because of less cost-effectiveness. However, bone is the most popular metastatic site, and the patient with bone recurrence alone seems to have better prognosis than the patient with lung or liver metastasis. In the present study, we examined the prognosis of patients with bone reccurrence to clarify the validity of bone examination as a routine Follow-up after breast cancer surgery.

Materials and Methods: Four hundred and sixteen patients who underwent operation for primary breast cancer at Niigata University Hospital during 1999–2008 were entered into the present study. Patients with distant metastasis at surgery were excluded. Almost all the patients entered in the present study have received annual bone scan. The patients records were examined, and the patients with distant recurrences were divided into 3 groups by the first recurrence site; group B included the patients of bone recurrence as the first recurrence site, group BM included both bone and other distant recurrence as first site, and group M included distant recurrences except bone as the first sites. The disease free survival (DFS) and overall survival (OS) were analyzed and compared among these three groups. Statistical analysis was performed by Logrank test, and the statistical significance was defined as $p < 0.05$.

Results: Among 416 patients, distant recurrence was recognaized in 52 patients; 13 patients belonged to group B, 4 patients belonged to group BM and 35 patients belonged to group M. There was no statistical differrence in DFI or OS among the three groups. In group B, despite all 5 patients who finally progressed distant recurences outside bone have died, all 8 patients who showed bone metastases alone have alived. Moreover, DFI was significantly prolonged in these alived 8 patients compared with died 5 patitents in group B ($p < 0.05$). Among alived 8 patients of bone recurrence in group B, 6 patients were asymptomatic, and bone metastases were detected at first with follow-up bone scintigraphy.

Conclusion: Our results suggest that the prognosis bone metastasis alone after breast cancer surgery may present good prognosis in some caces. Because the recent management with anti- cancer drugs such as chemo-, hormonal, molucular-targeting drugs, and bisphosphonates have been progressing, the early detction of bone recurrence seemed to be valid.

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A Phase II Study of Pegylated Liposomal Doxorubicin Combined with Cyclophosphamide / 5-fluorouracil as Second Line Chemotherapy in Patients with Metastatic Breast Cancer Who Failed Previous Taxane-based Treatment

H.K. Chang[1], Y.C. Lin[1], K.M. Rau[2], Y.Y. Chen[2], K.D. Lee[3], C.H. Wang[4]. [1]*Chang Gung Medical Foundation, Medical Oncology, Taoyuan County, Taiwan;* [2]*Chang Gung Medical Foundation, Medical Oncology, Kaohsiung, Taiwan;* [3]*Chang Gung Medical Foundation, Medical Oncology, Chiayi, Taiwan;* [4]*Chang Gung Medical Foundation, Medical Oncology, Keelung, Taiwan*

Background: Although antracycline and taxanes are frequently used in both adjuvant and metastatic setting of breast cancer, treatment

failure would still occur. This has raised the need for new drugs or combination regimen in the treatment of metastatic breast cancer (MBC). Unfortunately, based on limited data in the oncology literature, several agents including vinorelbine, capecitabine, ixabepilone and pegylated liposomal doxorubicin had only minimal antitumor activity (response rates ranged 10−20 %) in patients with MBC who progressed on first-line taxane-based treatment. There are limited published data demonstrating favorable response in MBC after the failure of taxane-based treatment or rechallenging with anthracyclines which were previously used in the adjuvant setting. Pegylated liposomal doxorubicin (Lipo-Dox®) is a non-toxic alternative agent to doxorubicin. The aim of this study is to evaluate the efficacy and safety of pegylated liposomal doxorubicin combination as second line treatment in patients with MBC who failed previous taxane-based treatment.

Material and Methods: From Aug. 2005 to Jul. 2010, 43 patients with MBC who progressed after prior treatment with taxane-containing regimen were recruited in this prospective, multicenter, single-arm, phase II trial. Treatment with pegylated liposomal doxorubicin 40 mg/m^2, cyclophosphamide 500 mg/m^2 and 5-Fluorouracil 500 mg/m^2 were delivered every 3 weeks until disease progression or the appearance of intolerance toxicity. The primary endpoint of this study is objective response rate and the secondary objectives are to evaluate progression free survival (PFS), duration of response, overall survival (OS) and safety profiles.

Result: Forty-three patients were included in the analysis. The median age was 52.5 years (36–67.5) and ECOG performance status was 0−2. 77.8% of patients had visceral metastases and 55.6 % of patients had equal or more than three metastatic lesions. An objective tumor response was observed in 18 patients (41.9%), stable disease in 18 patients (41.9 %) and the clinical benefit rate (objective response rate plus stable disease greater than 6months) in 26 patients (60.47%). The median progression free survival (PFS) and overall survival (OS) were 8.2 and 36.6 months, respectively. The majority of adverse event were mild to moderate. Grade 3/4 neutropenia and leucopenia were observed 14% and 9% by cycles. 12% patients had grade 2−3 mucositis, but only 7% patients experienced grade 2/3 hand and foot skin reaction by cycles.

Conclusion: The pegylated liposomal doxorubicin, cyclophosphamide and 5-fluorouracil combination regimen showed promising response rate and manageable side effects. The regimen could considered to be a treatment option for patients with MBC who failed previous taxane-based treatment.

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Oral Vinorelbin (osVNR) − An Observational Study on Practical Matter in Three Italian Oncology Centers

G. Mustacchi[1], S. Cinieri[2], M. Caruso[3]. *[1]Università di Trieste, Centro Oncologico, Trieste, Italy; [2]Ospedale Perrino, Oncologia Medica, Brindisi, Italy; [3]Humanitas, Oncologia Medica, Catania, Italy*

Background: osVNR is more expensive than iv VNR but according to several Authors it is much less time consuming for Patients (Pts), Nurses (drug preparation and administration) and Oncologists (Taylor, Proc NCRI 2005, Abs 435), preferred by Patients (Lju JCO 1997; Catania, BRCT 2005) and, actually, more cost/effective (Lelay, 2002, Mantovani 2005). Several variables as type of Institution (public or private), geographical situation and site of blood drowing could modify the final evaluation of osVNR in clinical practice.

Patients and Methods: we measured time spent by Pts and accompaniyng person (when applicable) for transfers, waiting and treatement, time of Nurses and Oncologists, toxicities (evaluated both by Oncologist and Pts) and overall Pts 's feeling in 287 osVNR administrations (60 mgs/sqm dd 1,8−21 in 75.3%; metronomic 80 mgs/sqm dd 1,3 and 5/week qq 4 weks, in 24.7%) (169 cycles in Trieste and 87 in Brindisi public Hospitals, 31 in Catania Humanitas private Hospital) in 44 metastatic breast cancer Pts.

Results: 80% of Pts had an accompaniyng person in all Centers. The ratio access/cycle is similar in public Institutions (0.94), higher in the private one (1.2). Similarly the time of Oncologist, 16 min/cycle versus 31. Blood drowing was done at home/near-home in 83.4% of cases in Catania, 63.2% in Brindisi and 16,6% in Trieste. Overall dosing mistakes were reported in 32.3% of cycles (16.7% Trieste; 43.8 Brindisi; 33.4 Catania). No difference between Centers in Nurse 's time (13 min) was recorded. Pts transfer time is similar in Trieste and Catania (50 min) vs 136 min in Brindisi. G3 toxicity rate was 0% with metronomic dosing and 30% with the classic one, viceversa toxicity G1/2 was higher (92,9% vs 73%), mainly nausea and diarrhoea. The overall toxicity was 70.5% for G1/2 and 18.2% for G3.

Pts toxicity evaluation was excellent in 74.5% of cases with classic dosing and 99% with the metronomic one. Overall more than 90% Pts appreciated the higher autonomy level.

Conclusions: osVNR is safe and very appreciated in metastatic breast cancer Pts. Our experience confirm that the oral route is time sparing both for Pts and Institutions. There is little difference between public and private institutions. Under an overall point of view of Pts, Families and Oncology Centers this is an important added value wich strongly reduces the pure cost for drug. There is margin of improvement working on logistics for blood drowing and further reducing the number of accesses.

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Final Results of a Phase II Study of the Combination of Oral Vinorelbine (NVBo), Capecitabine (X) and Trastuzumab (H) in HER2-positive Metastatic Breast Cancer (MBC)

L. Petruzelka[1], V. Ganju[2], P.F. Conte[3], N. Tubiana-Mathieu[4], F. Majois[5], M. Espie[6], A. Llombart[7], M. Gil Gil[8], G. Villanova[9], A. Chan[10]. *[1]Charles University, Oncology Department, Prague, Czech Republic; [2]Frankston Hospital, Frankston, Australia; [3]Policlinico de Modena, Modena, Italy; [4]CHU Dupuytren, Limoges, France; [5]Hopital Jolimont, Haine Saint Paul, Belgium; [6]Hopital St Louis, Paris, France; [7]Instituto Valenciano de Oncologia, Valencia, Spain; [8]ICO − Hospital Duran I Reynals, L'Hospitalet de Llobregat, Spain; [9]Institut de Recherche Pierre Fabre, Boulogne-Billancourt, France; [10]Mount Hospital, Perth, Australia*

Background: Chemotherapy (CT) plus trastuzumab (H) is the standard first-line treatment for HER2-positive MBC. H plus vinorelbine regimen is among the most active and well-tolerated options in this setting. The all-oral CT combination of NVBo and X has shown activity and good tolerability in MBC. In this abstract, we report the final results of an international phase II trial evaluating NVBo + X + H in HER2-positive MBC.

Material and Methods: Main eligibility criteria included: HER2-positive disease (3+ IHC or FISH+), measurable metastatic disease previously untreated by CT, Karnofsky PS $\geqslant$70. Study treatment (until progression): NVBo was given as a 80 mg/m^2 dose (following a first cycle at 60 mg/m^2) D1 & D8 every 3 weeks, X at 1000 (750 if $\geqslant$65 y) mg/m^2/bid D1−D14 every 3 weeks, H at 4 mg/kg on D1 (loading dose) then 2 mg/kg i.v. weekly starting on D8.

Results: Main patient (pt) characteristics in the full population (n = 50): median age: 53.5 years (18% $\geqslant$65); prior (neo)adjuvant CT 54%; visceral involvement 82%; >2 metastatic sites 34%; median number of cycles: 10 (range:1−81); 72% of pts received more than 6 cycles, 58% more than 8 cycles and 32% more than 16 cycles; median number of NVBo administrations: 20 (range:1–161); median number of H administrations: 30 (range:1–251); median relative dose intensity: NVBo 76%, X 78%, H 96%; G3/4 adverse events per pt: neutropenia 71%, hand-foot syndrome 20%, diarrhoea 16%, vomiting 12%, asthenia 8%, febrile neutropenia 8% (0.5% of cycles), infection 6%, LVEF decline 4%, alopecia (grade 2) 14%. Efficacy (n = 44 evaluable pts): objective response rate (RECIST) 77% (95% CI [62−89]), CR 21%, PR 57%, SD 18%, PD 5%, disease control (CR+PR+SD $\geqslant$6 months) 93% (95% CI [81−99]); median duration of response was 13.3 months (95% CI [9.8–15.7]). Median progression-free survival was 12.8 months (95% CI [10.8–16.9]) and median overall survival was 47.0 months (95% CI [30.5–64.3]). 3 pts are still receiving full study treatment.

Conclusions: The oral regimen of NVBo and X combined with H has shown high anti-tumoral efficacy in pts. with HER2-positive MBC. Toxicity profile was acceptable, with, in particular, a very low rate of alopecia. Full treatment could be maintained until progression of the disease in the majority of pts.

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Tartrate-resistant Acid Phosphatase and C-terminal Telopeptide of Type I Collagen as Serum Tumor Markers in Women with Bone Metastases From Breast Cancer

F. Lumachi[1], F. Marino[2], U. Basso[3], G.B. Chiara[4], S.M.M. Basso[4]. *[1]University of Padova School of Medicine, Department of Surgical & Gastroenterological Sciences, Padova, Italy; [2]University of Padova School of Medicine, Department of Pathology, Padova, Italy; [3]Istituto Oncologico Veneto (IOV) IRCCS, Medical Oncology 1, Padova, Italy; [4]S. Maria degli Angeli Hospital, Chirurgia 1, Pordenone, Italy*

Background: Breast cancer (BC) remains one of the first leading causes of death in women over the age 50. Bone is the first site of distant metastases in patients with BC. Bone lysis induced by cancer cells invading the bone and promoting degradation of mineral matrix, together with the production of PTH-like peptides represent the mechanisms of cancer-induced hypercalcemia. Bone metastases (BMs) are a frequent complications in BC. They are usually detected by whole body bone scintigraphy, which unfortunately presents low sensitivity and specificity, visualizing areas of increased osteoblastic activity. In patients with BMs a number of urinary and serum markers are altered. Tartrate-resistant acid phosphatase (TRACP5b), specifically derived from osteoclasts, is a promising marker of bone resorption. Moreover, increased concentrations of carboxy-terminal telopeptide of type I collagen (ICTP), a cross-linked