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Nab-Paclitaxel weekly or Q3Wks compared to Docetaxel Q3Wks as first-line therapy in patients with metastatic breast cancer: an economic analysis of a prospective randomized trial

G. Dranitsaris[1], R. Coleman[2], W.J. Gradishar[3]. *[1]Princess Margaret Hospital, Breast Cancer Disease Site Group, Toronto, Canada; [2]Weston Park Hospital, Academic Unit of Clinical Oncology, Sheffield, United Kingdom; [3]Northwestern University, Medical Oncology, Chicago, USA*

Background: In patients with metastatic breast cancer developing disease recurrence following treatment with adjuvant anthracyclines, the current practice in many countries is to offer first line chemotherapy containing a taxane, usually docetaxel. However, docetaxel is associated with dose limiting toxicity often requiring dose reductions, delays and in some circumstances the initiation of prophylactic hematopoietic growth factors. An albumin-bound formulation (nab) of paclitaxel (Abraxane™) was recently developed to overcome the safety drawbacks of docetaxel and to provide additional efficacy. A randomized phase II trial comparing nab-paclitaxel 100 or 150 mg/m^2 weekly 3 out of 4 and nab-paclitaxel 300 mg/m^2 q3w to docetaxel 100 mg/m^2 q3w reported improved efficacy and reduced toxicity with the former regimens at the interim analysis (Gradishar, 2006). To measure the economic value of the nab-paclitaxel regimens, an economic analysis from the perspective of the UK National Health Service was conducted. Nab–paclitaxel 100 or 150 mg/m weekly 3 out of 4 and nab-paclitaxel 300 mg/m q3w to docetaxel 100 mg/m q3w reported improved efficacy and reduced toxicity with the former regimens at the interim analysis (Gradishar, 2006). To measure the economic value of the nab-paclitaxel regimens, an economic analysis from the perspective of the UK National Health Service was conducted.
Methods: The first part of the study utilized the randomized trial database available at the interim analysis (Gradishar, 2006). Resource utilization data contained within the database were converted into cost estimates. This consisted of costs for chemotherapy, drug delivery, monitoring, supportive care drugs and hospitalization due to toxicity. Univariate and multivariate regression analysis was conducted to compare the total cost of therapy in patients randomized to each of the four regimens.
Results: Hematopoietic growth factor use, hospital days for side effects management and toxicity induced protocol discontinuations were higher in the docetaxel group. When all of the cost components were combined for the entire population (n = 300), patients in the nab-paclitaxel 100 mg/m^2 wkly and 300 mg/m^2 q3wk groups had comparable costs to the docetaxel control group (£10,091 vs. £10,915 vs. £9,652; p = NS). The nab-paclitaxel 150 mg/m^2 weekly arm had overall costs of £14,277 and efficacy that was no better than the 100 mg/m^2 weekly regimen. As a result, the 150 mg/m^2 weekly dose will not be taken forward into phase III clinical trials.
Nab–paclitaxel 100 mg/m wkly and 300 mg/m q3wk groups had comparable costs to the docetaxel control group (£10,091 vs. £10,915 vs. £9,652; p = NS). The nab-paclitaxel 150 mg/m weekly arm had overall costs of £14,277 and efficacy that was no better than the 100 mg/m weekly regimen. As a result, the 150 mg/m weekly dose will not be taken forward into phase III clinical trials.
Conclusions: Given its more favorable safety profile, superior efficacy and comparable economic impact, nab-paclitaxel (100 mg/m^2 wkly or 300 mg/m^2 q3wk) can be considered a preferred option over docetaxel (100 mg/m^2 q 3 wk) as first-line chemotherapy in metastatic breast cancer.

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Detection of metastatic disease in breast cancer – Comparison between [^{18}F]fluorodeoxyglucose positron emission tomography, computed tomography and conventional imaging

S. Mahner[1], S. Schirrmacher[1], V. Müller[1], C. Habermann[2], W. Brenner[3], F. Jänicke[1], J. Dose Schwarz[1]. *[1]Universitätsklinikum Hamburg-Eppendorf, Gynecology, Hamburg, Germany; [2]Universitätsklinikum Hamburg-Eppendorf, Radiology, Hamburg, Germany; [3]Universitätsklinikum Hamburg-Eppendorf, Nuclear Medicine, Hamburg, Germany*

Background: The presence of distant metastases is a key prognostic factor in breast cancer patients and plays a central role in therapeutic decisions. To detect distant metastases, chest X-ray, abdominal ultrasound, bone scintigraphy and computed tomography (CT) are performed as standard of care in many centers. [^{18}]Ffluorodeoxyglucose positron emission tomography (FDG-PET) detects metastatic disease in various tumors with high accuracy, but the diagnostic value in breast cancer still needs to be defined. The aim of this study was to compare the diagnostic performance of FDG-PET with conventional imaging and CT.
Materials and Methods: In 119 breast cancer patients who presented for restaging, whole-body FDG-PET was compared with chest X-ray, bone scintigraphy, abdominal ultrasound and CT. Each imaging modality was independently assessed and classified as 'negative', 'equivocal' and 'positive' for metastasis. The imaging results were compared with histopathology and clinical follow up, which together served as the reference standard.
Results: For findings classified as 'positive', FDG-PET detected distant metastases with a sensitivity of 87% and a specificity of 83%. In contrast, the sensitivity and specificity of combined conventional imaging procedures were 43% and 98%, of CT 83% and 85% respectively. The positive and negative predictive values were 89% and 82% for FDG-PET, 96% and 69% for conventional imaging and 95% and 58% for CT. Combining 'equivocal' and 'positive' results, the sensitivity and specificity of FDG-PET was 93% and 76%, respectively, compared to 61% and 86% for conventional imaging and 90% and 62% for CT. The positive and negative predictive values were 86% and 88% for FDG-PET versus 77% and 75% for conventional imaging and 90% and 58% for CT.
Conclusions: FDG-PET is superior to conventional imaging procedures and CT for detection of distant metastases in breast cancer. However, the use of combined PET/CT needs to be addressed in future studies comparing anatomical vs. metabolic staging procedures in breast cancer patients.

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A phase I study of trastuzumab-DM1, a first-in-class HER2 antibody-drug conjugate, in patients with HER2+ metastatic breast cancer

I.E. Krop[1], M. Beeram[2], S. Modi[3], N. Rabbee[4], S. Girish[4], J. Tibbitts[4], S.N. Holden[4], S.G. Lutzker[4], H.A. Burris[5]. *[1]Dana-Farber Cancer Institute, Medical Oncology, Boston MA, USA; [2]Institute for Drug Development, Medical Oncology, San Antonio TX, USA; [3]Memorial Sloan-Kettering Cancer Center, Medical Oncology, New York NY, USA; [4]Genentech Inc., BioOncology, South San Francisco CA, USA; [5]Sarah Cannon Research Institute, Medical Oncology, Nashville TN, USA*

Background: Antibody-drug conjugates (ADCs) utilize tumor-specific and/or over-expressed surface antigens that undergo internalization to deliver highly potent anti-tumor agents via linkage to antigen-specific monoclonal antibodies (MoAbs). Trastuzumab-DM1 (T-DM1) contains a highly potent antimicrotubule agent (DM1) derived from maytansine, conjugated to the humanized anti-HER2 MoAb trastuzumab (T). T in combination with chemotherapy prolongs survival in HER2+ breast cancer (BC). Maytansine has induced responses in patients (pts) with breast and lung cancer; principal adverse events (AEs) were nausea, vomiting, diarrhea, and neuropathy. The linker molecule MCC employed in T-DM1 provides a stable bond between T and DM1 that is designed to prolong exposure and reduce the toxicity of T-DM1 while maintaining activity; T-DM1 is the first ADC with an MCC linker in clinical trials. T-DM1 has activity in HER2+ BC xenografts that are unresponsive to T; its principal preclinical toxicities were reversible transaminase elevations, reversible decreases in platelets, and neuropathy.
Methods: This ongoing first-in-human phase I study is evaluating the safety and pharmacokinetics (PK) of T-DM1 given IV q3 weeks to pts with HER2+ metastatic BC who have progressed on a T-containing regimen.
Results: Eighteen pts [median age 52.8 (range 35−70); all PS 0−1]; median number prior chemo regimens 7.5 (range 2−18) have received 75 doses of T-DM1 at 6 dose levels (0.3−4.8 mg/kg). Related grade (gr) 2 AEs include elevations in hepatic transaminases (1 pt), fatigue (1 pt), anemia (2 pts), and thrombocytopenia (TCP, 5 pts). Related gr 3−4 AEs have been limited to rapidly reversible TCP (gr 3, 1 pt; gr 4, 2 pts). There has been no cardiac toxicity or peripheral neuropathy. Clearance of T-DM1 decreased in a dose-dependent fashion, as predicted by preclinical modeling. Four pts at 2.4 or 3.6 mg/kg have achieved a partial response. Two have been confirmed and are ongoing after 2 and 4 months; the others are unconfirmed but ongoing.
Conclusions: At these initial doses, gr $\geqslant$ 2 AEs related to T-DM1 have been infrequent and manageable; gr 4 (dose-limiting) TCP was seen in 2 pts at 4.8 mg/kg. T-DM1 PK is consistent with q3-week dosing. Objective tumor responses have been observed at tolerable doses. Enrollment is ongoing to determine the maximum tolerated dose of q3-week T-DM1. Phase II trials are planned; weekly dosing will also be explored.