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Correlation between 99mTc-DPD bone scan findings and Ca 15–3 values in breast cancer patients after neoadjuvant chemotherapy

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Aim: The aim of this study was to evaluate the correlation of Ca 15–3, bone scan and complementary imaging methods (Rtg, Ct and MRI) in follow up of breast cancer patients after neoadjuvant chemotherapy.
Patients and methods: Sixty three patients with histologically proven breast cancer were included (mean age 58, range 41–82) and followed for having positive bone scan findings. Information was confirmed with other imaging methods: Rtg, Ct and MRI. Ca 15–3 values were measured in the same time with bone scan, using same commercial test over the follow-up period. Bone scan were classified as negative (group 1), diffuse increased uptake in calvaria (group 2), solitary hor spot lesion (group 3), benign disorder (group 4), mixed benign and malignant patterns (group 5), multiple-3 and more metastatic involvement (group 6).
Results: Number of patients in group 1 to 6 were: 13, 5, 18, 6, 4, 17 respectively and had mean Ca 15–3 value U/ml: 17.6 (range 9.2–43.3), 12.7 (range 6.9–18.5), 74.26 (range 7.3–469.2), 92.9 (range 10.0–480.0), 52.8 (range 15.1–150.0), 404.8 (range 8.9–3160.0). Five patients in group 6 had normal Ca 15–3 values. Metastatic involvement: pulmonary, liver, skin was respectively 27.8%, 27.8%, 5.6% in group 3 and 11.8%, 35.3%, 5.9% and brain %.9% in group 6. The statistical difference was not evident in groups 1 vs. 2+3+4+5 but was excellent ($p < 0.01$) in group 6 vs. 2+3+4+5 (Mann-Whitney test). Multiple metastatic bone scan were confirmed with radiology 50% (Rtg 6 in 14, Ct 2 in2(; benign lesions 100% (Rtg); 20% (Rtg) in calvaria; solitary hot spot lesions 53% (ribs 6 in 8, pelvis 2 in3, vertebra 1 in 1 with Rtg and MRI 100% 2 in 2) and 8 of them solitary malignant lesions.
Conclusion: Normal Ca 15–3 value does not exclude bone metastases, and cannot be helpful in confirming solitary lesions. It has excellent specificity, and is good predictor of a progressive disease, during follow up period. Bone scan pathological findings require careful radiographic evaluation, for early diagnosis.

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High-dose chemotherapy and autologous peripheral blood stem cell transplantation in locally advanced breast cancer. Updated results of a single center

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Introduction: High-dose chemotherapy is not standard in the treatment of breast cancer, neither in the adjuvant nor in the metastatic setting. In this retrospective study, we aimed to review the interim data of locally advanced breast cancer patients who underwent high-dose chemotherapy (HDC) and autologous peripheral blood stem cell transplantation (APBSCT) in our BMT center.
Material and methods: Between March 1997 and June 2004, 54 breast cancer patients with at least 10 metastatic axillary lymph nodes were treated with HDC and APBSCT. Their ages ranged from 26 to 66 years with a median age of 43 years. The time from diagnosis to transplant ranged from 60 to 550 days with a median of 131 days. The number of their previous chemotherapy cycles ranged from 3 to 7 with a mean of 4. Their preparative regimens were: CNV (n = 44): Cyclophosphamide 2.4 g/m^2, mitoxantrone 35 mg/m^2, etoposide 250 mg/m^2/d for 6 days; ICE (n = 6): Ifosfamide 2.5 g/m^2/d for 6 days, carboplatin 250 mg/m^2/d for 6 days, etoposide 250 mg/m^2/d for 6 days; CNP (n = 2): Cyclophosphamide 60 mg/kg/d for 2days, mitoxantrone 35 mg/m^2, carboplatin 200 mg/m^2/d for 6 days; TCM (n = 2): Thiotepa 250 mg/m^2/day for 2 days, melphalan 50 mg/m^2/day for 2 days, carboplatin 450 mg/m^2/day for 3 days. In the post transplant period, 35 patients received G-CSF, 12 patients GM-CSF, and 7 patients received no GF.
Results: Recovery to $\geqslant 1 \times 10^9$ leukocyte/L occurred at a median of 10 days, platelet recovery to $\geqslant 20 \times 10^9$/L was 12 days. A mean of 2.7 units of red cell suspensions and a mean of 1 unit of platelet suspension were transfused. The mean hospitalization duration was 12 days. After median follow-up of 925 days (range 5–2580 days), the five-year survival rate was 58%, and disease-free survival rate was 34%. The transplant related mortality was 3.7%.
Conclusion: Our data show that HDC and APBSCT is rather safe treatment in locally advanced breast cancer. The place of this treatment is still unsolved question in this indication. Further randomized studies with more patients and longer follow-up will clarify this issue.

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Phase II study of gemcitabine and cisplatin in women with taxane-failed metastatic breast cancer (MBC)

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Background: Taxanes are considered as one of the most active cytotoxic drugs in breast cancer which often are used as first-line treatment to anthracyclines – failed MBC. Now AC followed by Taxol (T) and TAC (taxotere T) regimens have been standard adjuvant therapy according to NCCN guildline. However, at present there are no standard therapeutic methods when patients relapse following taxane-based chemotherapy. We have desiged this study to evaluate the efficacy and safety of gemcitabine and cisplatin in women with taxane-failed MBC.
Methods: Major eligibility criteria: pathology diagnosis of breast carcinoma, prior taxanes therapy, adequate marrow, hepatic and renal function. Gemcitabine 1000 mg/m^2 was given on day1 and 8 and Cisplatin 100 mg/m^2 was devided into 3 days. Cycles were repeated every 3 weeks. RECIST was used for efficacy evaluation.
Results: From July 2004 until April 2005, 25 patients were enrolled. The median age was 45 years (range 30–69years). 25 qualified for safety analysis, 24 for efficacy assessment. Dominant site of disease was visceral in 60%. 88% pts had previously received anthracyclines and taxanes. A total of 63 cycles were delivered with a median of 2 cycles. 13 patients had PR, 7 patients had SD and 3 patients had PD. Overall response rate was 52%. Median survial and median time to progression has not been reached. Grade 3/4 toxicities were listed in table 1. There were 3 patients who had I-II ototoxicity with tinitus and acouesthesia.

Table 1: Grade 3/4 toxicities

	Grade III, n = 63 cycles		Grade IV, n = 63 cycles	
	cycles	%	cycles	%
Neutropenia	20	31.7	3	4.7
Anemia	2	3.1	1	1.5
Thrombocytopania	7	11.1	3	4.7
Nausea	15	23.8	3	4.7
Vomitting	11	17.4	5	7.9

Conclusions: The gemcitabine-cisplatin regimens appear to have high efficacy and manageable toxicity in women with taxanes-failed MBC.

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Results from a pilot study of goserelin plus fulvestrant in premenopausal women with advanced, hormone-sensitive breast cancer

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Background: Fulvestrant is an oestrogen receptor (ER) antagonist with no agonist effects available for the treatment of postmenopausal women with hormone-sensitive advanced breast cancer (ABC). Our study evaluated the efficacy and safety of fulvestrant in premenopausal women with hormone-sensitive ABC rendered postmenopausal with continuous goserelin treatment.
Materials and methods: This prospective study included 14 patients with ER-positive and/or progesterone receptor-positive ABC; two patients also had human epidermal growth factor receptor 2 (HER2)-positive disease. Patients received at least 3 doses of fulvestrant 250 mg via monthly intramuscular injection plus goserelin 3.6 mg via monthly subcutaneous depot injection. Treatment continued until disease progression or intolerability. Tumour response was assessed every 3 months.
Results: Fourteen patients (median age 41 years, range 28–49 years) were included. One patient received goserelin+fulvestrant as 1st-line endocrine therapy, seven as 2nd-line, five as 3rd-line, and one as 4th-line treatment, respectively. Eleven patients (78.6%) had received adjuvant chemotherapy and eight patients (57.1%) had received adjuvant

endocrine therapy (tamoxifen). Prior palliative chemotherapy had been given to six patients (42.9%) and prior palliative endocrine therapy to 13 patients (92.9%) (goserelin+anastrozole and/or exemestane). Three patients (21.4%) had clinically apparent non-visceral metastases only, one patient (7.1%) had clinically apparent visceral metastases only and 10 patients (71.4%) had both. Eleven patients are currently evaluable for response: one patient had a partial response (PR) and four patients (36.4%) had stable disease (SD) $\geqslant$ 6 months, resulting in a clinical benefit rate of 45.5%. Also one patient had SD > 3 months but < 6 months. Both patients with HER2-positive disease experienced SD $\geqslant$ 6 months. Median time to progression was 5 months (range 2–12+ months). No local or systemic adverse events were reported.
Conclusions: Goserelin+fulvestrant appears to be an effective and well-tolerated treatment for premenopausal women with ABC including those with asymptomatic visceral metastases and HER2-positive disease. These data compare very favourably with similar data reported with fulvestrant treatment in naturally postmenopausal women with ABC. Further evaluation of fulvestrant in premenopausal women with iatrogenic menopause is supported in controlled clinical trials.

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Phase II study of vinorelbine (VRL) alternating i.v. and oral in combination with docetaxel (DTX) as 1st line chemotherapy (CT) of metastatic breast cancer (MBC)

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Background: VRL and DTX are targeting tubulin-microtubule system, either inhibiting tubulin polymerisation (VRL) or microtubule depolymerisation (DTX). Both agents have proven activity in MBC.
Material and methods: This study was designed to evaluate the efficacy and the tolerance of the combination of i.v. VRL 20 mg/m^2 with DTX 60 mg/m^2 on day 1 and oral VRL 60 mg/m^2 on day 15 of a three-week cycle in first line treatment MBC for a maximum of 6 cycles (recommended dose established in Phase I study, abstract no. 684, ASCO 2004). Prior adjuvant CT was allowed if completed at least 12 months before study entry. At least one bidimensionnally measurable lesion (WHO criteria) was required.
Results: 49 patients (pts) were treated: with a median age of 53 years; 31 pts (63.3%) had received prior adjuvant chemotherapy; 44 pts (89.9%) had a KPS *80%; and 22 pts (44.9%) had *3 sites involved. A total of 261 cycles were given (median 6). Median relative dose intensities (RDI) of i.v. VRL and DTX were over 99% and median RDI of oral VRL was 76.4%. Neutropenia was the major side effect: grade (G) 4 in 51% of pts and 22.1% of cycles but only complicated in 5 pts: 4 febrile neutropenia (8.2%) and one neutropenic infection (2%). In terms of non-haematological related toxicity (all grades), the most frequent events reported were alopecia (61.2%), fatigue (22.4%), weight loss (18.4%), stomatitis (16.3%) and constipation, diarrhoea and nausea (14.3% each). Only one patient experienced G4 dehydratation. G3 events were stomatitis, vomiting and amenorrhea (4.1% each) and fatigue, constipation, diarrhoea, nausea, infection, syncope and abdominal pain (2% each). The combination was highly effective with 24 responses documented and validated by an independent panel review, yielding a response rate of 49% [95%CI: 34–64] in the 49 enrolled pts. Median duration of progression-free survival was 5.5 months [95%CI: 4.2–7.2]. Median duration of overall survival has not been reached with a median duration of follow-up of 9.7 months.
Conclusions: This combination with oral VRL on day 15 avoiding hospitalisation is highly efficient and manageable in contrast with previous Phase II studies having used higher doses and different schedules. VRL i.v./oral D1/D15-DTX D1 every 3 weeks is an attractive option to combine DTX and VRL at doses which are convenient for every day practice in MBC.

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Low value of serum Ca 15–3 and CEA in monitoring trastuzumab-based therapy of advanced breast cancer

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Background: Trastuzumab therapy has recently become standard management of HER-2 positive patients with advanced breast cancer. There are particularly few data on the usefulness of serum Ca 15–3 and CEA in monitoring of this management. We present here the relationship between serum levels of both markers and the outcomes of trastuzumab-based therapy assessed in a single-institutional retrospective study.
Material and methods: Study group included 43 patients (median age 50 years; range 31–71 years) with recurrent or advanced HER2/neu overexpressing breast cancer who were administered trastuzumab with or without additional systemic therapies. Serum levels of CEA and Ca 15–3 were measured prior to initiation of therapy and every 3 months during treatment. Samples were tested using ELISA assays. Ca 15–3 and CEA values below 30 U/ml and 5 ng/ml, respectively were considered normal. 36 patients were evaluable for this analysis, of whom 22 (61%) responded to treatment. The median follow-up in the entire group was 9 months (range 3 to 24 months). Correlation between serum levels of both markers and clinical outcomes was computed using linear regression analysis.
Results: Baseline Ca 15–3 and CEA levels were elevated in 62% and 48% patients, respectively. Changes in serum levels of both markers during therapy did not predict for relapse. Elevation of Ca 15–3 and CEA levels occurred in 7 (35%) and 6 (30%) of patients with progression, respectively, and the correlation factor for both markers was 0.34 and 0.30, respectively. Combined analysis of CEA and CA 15–3 did not increase their predictive value.
Conclusion: Monitoring trastuzumab therapy of advanced breast cancer patients with serum Ca 15–3 and CEA, considered as single tests or in combination is of limited clinical value.

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Cellular immunotherapy with reactivated autologous Memory T-Cells from bone marrow in late stage breast cancer patients

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Tumorspecific Memory T-cells (MTC) can be found in the bone marrow (BM) in the majority of primary and metastatic breast cancer (BC) patients by using ELISpot-analysis. Upon specific restimulation with tumourantigen-pulsed dendritic cells (DC) those autologous T-cells exert specific effector functions like IFN-gamma or perforin production and specific cytotoxicity. Furthermore we have shown in NOD/Scid-mice that reactivated MTC are able to infiltrate autologous and heterologous tumor tissue, proliferate and kill tumor cells by induction of apoptosis, leading to a marked or complete tumor rejection within 21 days after transfer (Nature Med, 2001). Endocrine and cytostatic cancer therapies only have a limited influence on the frequency of tumorspecific MTC in BM of BC patients.
In a phase-I trial 11 patients with metastatic BC (inclusion criteria) were treated with autologous reactivated MTC of BM. Primary objective were feasbility, and toxicity, secondary were clinical response, and immunomonitoring. After testing patient's BM for presence of tumorspecific MTC those cells were reactivated by incubating them in vitro with autologous DC pulsed MCF-7 lysate for 12 days. Reactivated T-cells and pulsed DCs were injected once intravenously. Follow Ups were done after 7, 14, 21, 28, and 120 days. Study design was feasible in every way.
There were no side effects found during and after T-cell injection. There was a partial response in 3 of 5 measurable patients. In 5 Patients – who received a maximum of reactivated T-cells – we were still able to find these cells 7 days after vaccination.
We conclude that cellular immunotherapy with autologous reactivated MTC is an innovative way of BC treatment. We thus prepare a phase-II trial in metastatic and primary BC patients.

459 PUBLICATION

Risk factors for brain metastasis in patients with advanced breast cancer (abc)

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Background: Incidence of brain metastasis is apparently rising in pts with ABC, possibly due to better therapeutic approach and longer survival. Occurrence of brain relapse severely affects quality of life and is associated with extremely poor prognosis.
Patients and Methods: A retrospective analysis of 84 consecutive pts with brain metastasis and ABC was performed (March 1999-December 2004). Evaluated variables were: age at diagnosis, staging and nodal status, oestrogen and progesterone receptor status, c-erbB2 over-espression, site of first relapse, previous chemotherapy.
Results: Thirty-three percent of pts aged less than 45 years (13% less than 35 years). Thirty-nine percent had T1 tumour, 28% T2 tumour, 41% had N0 disease and 46% N1 at diagnosis, therefore stage seems not a risk factor for developing subsequent cerebral metastases. Twenty-one percent of pts were metastatic at diagnosis. Brain metastases occurred more frequently in pts with lung (24%), bone (27%) and liver (20%) metastasis