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First line chemotherapy for low or high risk metastatic breast cancer (LR/HR-MBC) – Are 3 (CMF/FEC) or 2 (NDOC) agents better than 1 (N)? – A multicenter clinical trial of the "IMA"

R. Souchon[1], E. Heidemann[2], W. Hirschmann[3], G. v. Minckwitz[4]. *For the German Interdisciplinary Breast Cancer Working Group ("IMA"); [1]AKH Hagen; [2]DiakonissKrkhs, Stuttgart; [3]Städt, Klinik Kassel; [4]UFK Frankfurt, Germany*

Purpose: In a multicenter randomized prospective clinical trial efficacy, impact on quality of life (QL) and toxicities of single (mitoxantrone (N)) vs multidrug chemotherapy (5-FU (F), epirubicin (E), cyclophosphamide (C) or N plus docetaxel (NDOC)) for HR-MBC-(visceral +/– further spread, age < 35 yrs, DFI < 18 months) and CMF for LR-MBC-(no HR-MBC-characteristics) patients were assessed.

Material and Methods: Between 7/92 and 3/99 340 HR-MBC-pts. received either N (12 mg/m^2) or FEC (F 500 mg/m^2, E 50 mg/m^2, C 500 mg/m^2) or – since 07/97 NDOC (N 12 mg/m^2, DOC 80 mg/m^2; each iv., d1, q22) until objective PD or CR + 2 cycles (NC: max. 12 or 6 cycles). During 7/92 and 6/97 111 LR-MBC-pts. received N (14 mg/m^2 iv, d1, q29) or CMF (C 600 mg/m^2, M (methotrexate) 40 mg/m^2, F 600 mg/m^2, iv, d1 + 8, q29). QL was assessed using a modified Brunner score.

Results: To date, data from 348 pts have been analyzed showing no clear differences in therapeutic efficacy between single drug or combination treatment using OS, RR and TTP as measurements. Looking at RR (CR + PR + NC), OS and TTP, LR-pts 70%, 18 and 6.4 months respectively) showed better results to HR-pts (60%, 13.7 and 5.2 months respectively). Toxicities, as well as a decrease in calculated therapeutic ratio and restrictions of QL were in favour of the single agent treatment (N).

Conclusion: These interim results justify continuation of this trial. An analysis, to be carried out in 1999 of N vs FEC and N vs CMF, will show whether or not prognostic risk factors are more important for pts. outcome than the chosen treatment for LH/HR-MBC-pts.

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Health-related quality of life (HRQL) in women with HER2-overexpressing metastatic breast cancer (MBC) in a phase III study of Herceptin (R) plus chemotherapy versus chemotherapy alone

J. Baselga[1], M. Kerrigan[2], M. Burchmore[3], M. Ash[3]. *[1]Hospital Vall d'Hebron, Department of Medical Oncology, Barcelona, Spain; [2]F. Hoffmann-La Roche, Basel, Switzerland; [4]Genentech Inc., South San Francisco, United States*

Purpose: To assess HRQL for patients treated with either chemotherapy (chemo) or Herceptin (H, trastuzumab) and chemotherapy (H + chemo).

Methods: 469 women with HER2-overexpressing MBC without prior chemo for MBC were randomised to receive H + chemo versus chemo alone. Randomisation was stratified by type of chemo regimen, which was anthracycline-cyclophosphamide (AC) in patients having received no prior adjuvant A, or paclitaxel (T) if the patient had previously received A. Doses used were A (doxorubicin = 60 mg/m^2 or epirubicin = 75 mg/m^2), C = 600 mg/m^2, T = 175 mg/m^2 every 3 hours. All were given every 3 weeks for 6 cycles. In the H + chemo arm, H was administered as an i.v. 4 mg/kg loading dose followed by i.v. 2 mg/kg per week. HRQL was assessed using the EORTC QLQ-C30 (V 1.0) with the breast cancer module (BR-23) at baseline, and at weeks 8, 20 and 32 (401/469 patients completed at least one questionnaire). Five prospectively defined domains (physical, role, social, global quality of life and fatigue) were defined as primary. All remaining domains were secondary (pain, nausea/vomiting, cognitive, emotional, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties, body image, sexual functioning, sexual enjoyment, future perspective, arm symptoms, breast symptoms, systemic therapy side effects and upset by hair loss). Data were analysed via repeated measures ANOVA using the last observation carried forward for inputting missing data.

Results: By week 32, there were trends for improvement in all five primary as well as secondary domains. None of these differences in the primary domains reached statistical significance. However, significant differences were found in the pain domain and dyspnoea question of the QLQ C-30 and the systemic therapy side effects domain of the BR-23, all favouring the H + chemo group.

Conclusions: Patients receiving H showed trends for improvement in primary and secondary HRQL endpoints by week 32. Results must be interpreted cautiously because of the multiplicity of testing.

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Cisplatin – epirubicin – paclitaxel (PET) weekly administration with G-CSF support in advanced breast cancer (ABC). A phase II study

G. Frasci, P. Comella, G. D'Aiuto, A. Apicella, R. Thomas, I. Capasso, G. Carteni, L. De Lucia, L. Maiorino, G. Comella. *Southern Italy Cooperative Oncology Group (SICOG) c/o National Tumor Institute of Naples, Italy*

Purpose: This study aimed at defining the antitumor activity of the PET regimen in ABC pts.

Patients and Methods: ABC pts with locally advanced (T4 or N2) or metastatic disease, who had not received prior chemotherapy (except adjuvant) were considered eligible. They received CDDP 30 mg/m^2, EPI 50 mg/m^2 and PTX 120 mg/m^2 weekly, plus G-CSF (d 3–5) for a maximum of 12 cycles.

Results: To date 60 pts have been recruited (32 locally advanced and 28 metastatic) 12 pts had visceral localizations, and adjuvant chemotherapy had been administered in 16 pts (anthracyline-based in 11). 51 pts are presently evaluable for response after at least 6 cycles. Overall, 15 CRs and 29 PRs have been recorded for a 86% ORR [95% C.I. = 74–94]. 10 CRs, 16 PRs have been recorded in the 28 evaluable pts with locally advanced disease (ORR = 93%) Surgery has been performed in 18 pts, and in 3/18 (17%) absence of invasive tumor has been found. 5 CRs and 13 PRs have been observed in the 23 evaluable pts with distant metastases (ORR = 78%) Grade 3–4 neutropenia, thrombocytopenia and anemia occurred in 33%, 4% and 10% of pts respectively. Severe vomiting, diarrhoea, skin toxicity and mucositis were observed in 5%, 9%, 8% and 10% of pts.

Conclusions: The weekly PET administration is a well tolerated and very effective approach in advanced breast cancer pts. The ORR even exceeds 90% in pts without distant metastases. The accrual of pts still continues until a final sample size of 70 pts.

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Intratumoral focused chemotherapy with cisplatin/epinephrine injectable gel for palliative treatment of metastatic breast cancer

I. Fernando, P.D. Eisenberg, S. Roshon, J. Mansi, G. Mills, E. de Vries. *The Solid Tumor Study Group; Queen Elizabeth Hospital, Birmingham, United Kingdom; Greenbrae, CA; Sandusky, OH, United States; St. George's Medical School, London, United Kingdom; LSU School of Medicine, Shreveport, LA, United States; Akademisch Ziekenhuis, Groningen, Netherlands*

Purpose: Phase III studies evaluated the safety and efficacy of intratumoral chemotherapy with cisplatin/epinephrine injectable gel (CDDP/epi gel) for local treatment of solid tumors of various histologies. The delivery system provides high tumor drug concentrations for extended periods.

Methods: Two open-label studies enrolled patients with breast cancer who had failed previous therapy. CDDP/epi gel was administered intratumorally (2 mg CDDP/cm^3 tumor) up to 6 times weekly in 8 weeks. Evaluations included attainment of a prospectively selected clinical benefit for the most troublesome tumor (MTT), tumor response for the MTT (≥50% tumor volume decrease), and adverse events.

Results: 30 patients with recurrent or metastatic breast cancer (95 evaluable tumors) were treated. Total patient cumulative dose of 1 to 215 mg CDDP (median 26.8 mg) was administered in 1–6 intratumoral injections. A total of 47% of the patients showed MTT responses [median duration, 85 d (29–250+)]. Clinical benefit [defined as improved function or disease management (wound care, pain control, tumor invasion)] was achieved by 40% of all patients and 57% of patients with MTT responses. Treatment was generally well-tolerated. Toxicities common with intravenous cisplatin (e.g., vomiting, nausea) were less frequent (<20%) with CDDP/epi gel and easily managed.

Conclusion: Local tumor control with CDDP/epi gel provides a new therapeutic tool for management of solid tumors as a single modality and holds promise for use in combination with standard therapies.