893 PUBLICATION

Prognostic significance of the biologic features of breast tumors

N. Güler[1], A. Sungur[2], H. Canpinar[1], I. Sayek[3], Z. Öner[3], S. Kilic[1], E. Baltah[1]. [1]Department of Medical Oncology; [2]Department of Pathology; [3]Department of Surgery, Hacettepe University School of Medicine, Ankara, Turkey

Purpose: Behaviour of breast cancer is variable of patients presenting at the same clinical stage. In this prospective study, prognostic significance of clinical and pathologic parameters, hormone receptors, c-erbB-2 oncogene, p53, PCNA score, ploidy and S phase fraction (SPF) were evaluated in breast cancer patients.

Methods: c-erbB-2 oncogene, p53 tumor-supressor gene, PCNA score, estrogen and progesterone receptors were studied with immunohistochemical method (IHC) in the primary breast cancer specimens of 52 patients. Ploidy and SPF were determined with flow cytometry in the fresh tissue samples. Prognostic significance of all these parameters and coventional prognostic factors (age, menopausal status, tumor size, positive axillary lymph nodes, tumor grade, stage, etc) were evaluated at the end of the 3 years follow-up period.

Results: c-erbB-2 positivity was 69%; p53 positivity was 35%; ER positivity was 62%; PR positivity was 71%; aneuploidy was 27%; median SPF was 20.9% (range: 0–91.6%) and median PCNA score was 25% with a range of 0–98%. Median follow-up period was 29 months with a range of 1–35+ months. In univariate analyses tumor size, positive axillary lymph nodes, stage and grade were found to be significant on DFS and OS. In stage 2 disease, grade was found an important prognostic factor on DFS and OS. In stage 3 disease, grade and positive axillary lymph nodes were important for DFS. Grade and p53 were found to be significant for DFS and grade for OS in multivaried analyses.

Conclusion: According to our study results, conventional prognostic factors are more powerfull than new prognostic factors on DFS and OS. Larger prospective studies will helpfull to understand the prognostic significance of these new prognostic factors.

894 PUBLICATION

Prognostic significance of telomerase activity in breast cancer

A. Hoos, H.H. Hepp, S. Kaul, T. Ahlert, D. Wallwiener, G. Bastert. *University Hospital for Obstetrics and Gynecology, University of Heidelberg, Germany*

Purpose: Increase of telomerase activity has been observed in various types of human malignancies. But little is known whether telomerase activity could serve as a predictor for clinical course and patient survival. In order to investigate the prognostic significance of telomerase activity in breast cancer the activity of the enzyme was measured quantitatively in tumor material of breast cancer patients of whom the clinical course was known.

Methods: Tumor tissue from 19 primary breast tumors and 6 secondary tumors was enzymatically separated into single cells, counted and stored in liquid nitrogen. For each patient an identical number of cells was quantitatively analysed for telomerase activity using the Telomerase-PCR-ELISA based on the Telomerase Repeat Amplification Protocol (TRAP). 25 Patients were divided into 3 prognostic categories: *I:* tumor-resection and no recurrent disease, *II:* tumor-resection and a postoperative tumor-free interval followed by local recurrence or metastases, *III:* palliative surgery in systemic disease.

Results: No relation was found between prognostic categories and telomerase activity in primary tumors nor in metastases. Also disease-free interval wasn't significantly related to enzyme activity. Primary tumors displayed an approximately 3-times higher telomerase activity than metastases ($p = 0.02$). Nodal status was significantly better in patients with low telomerase activity in primary tumors ($p = 0.01$).

Conclusion: These results don't indicate a clear relation between telomerase activity and prognosis in breast cancer. However these data seem to show a higher enzyme activity in tumors with potential for lymphatic spreading than in limited local disease. Future studies with a higher number of cases are needed to further determine the prognostic value of telomerase activity in breast cancer.

895 PUBLICATION

Mammary carcinoma: Prognostic value of histology, proliferative indicators receptor status and expression of oncogen products in node-free patients

A. Niezabitowski, J. Ryś, B. Lackowska, A. Gruchala, A. Sokołowski, A. Kruczak, A. Wasilewska, W. Szklarski. *Department of Pathology, Center of Oncology, Cracow, Poland*

Purpose: In node-free breast cancer patients analysis of multiple clinicomorphological parameters is of value for prognosis and strategy of treatment. Predictive value of numerous morphological factors was analysed in a retrospective study.

Methods: The study was performed in 150 node-free breast cancer patients with known age and hormonal status treated by radical or modifite mastectomy and followed-up at least ten years. Histological parameters (tumor type and differentiation, percentage of intraductal constituent and necrosis, type of invasion, infiltration of nerves by cancer cells. vascular invasion of tumor surrounding and involvment of breast with cancer cells distantly from tumor mass) and mitotic index were evaluated on routine HE sections. Estrogen receptor content, expresion of proliferative antigens (MIB1, PCNA), c-erb-B2 and p53 proteins were assessed by immunohistochemistry. Flow cytometry DNA analysis was performed on tumor tissue obtained from paraffin bloks. In the statistical analysis long-rank- and Cox-tests were used.

Results: MIB1 index and microfocal invasion type influenced independently on disease free survival. Tumor diameter, tumor type (considered in three categories), Bloom-Richardson score, percentage of intraductal constituent, mitotic and MIB1 indices and involvment of breast by cancer cells distantly from tumor mass were significantly correlated with total survival.

Conclusions: Proliferative indicators, in particular MIB1, are of great predictive value for disease free and total survival in node-free breast cancer patients.

896 PUBLICATION

The value of new prognostic factors for the prediction of disease free interval for women with primary breast cancer in comparison with histopathological variables

G. Alex, M. Neises, F. Lenz, F. Melchert. *Department of Obstetrics and Gynaecology, University Clinic Mannheim, Germany*

Purpose: A great number of factors with putative value for the prediction of tumour recurrence for women with primary breast cancer has been described. The aim of the study was to assess their prognostic value also in comparison with histopathological ones.

Methods: 203 women underwent surgery for unilateral primary breast cancer in the years 1992–1995 at the gynecological university clinic Mannheim. In June 1996 23 of these patients suffered from recurrences. We determined at the time of operation: tumour size and stage, lymph node involvement, grading, age, menopausal status, estrogen-, progeseterone-receptor, epidermal-growth-factor-receptor, erb B2, cathepsin D, cycling-index, p 53, s-phase-fraction and ploidy. To assess the value of each prognostic factor a univariate analysis and after this a multivariate analysis for the significant factors was performed and Kaplan Meier curves calculated.

Results: The histopathological factors all showed prognostic significance, which did only epidermal-growth factor-receptor and cycling index in the group of tumour biological factors. In multivariate analysis cycling index could not reach significant level as a independent prognostic factor.

Conclusions: We could confirm the value of histopathology for the prediction of disease free interval for women with primary breast cancer. Most of the new variables failed to show prognostic significance in our collective.

897 PUBLICATION

Evolution of biological parameters in patients with breast cancer treated with primary chemotherapy

M. Donadio[1], E. Manzin[1], O. Dal Canton[1], E. Berardengo[2], C. Bumma[1]. [1]Department of Medical Oncology, Osp. S. Giovanni Antica Sede, Torino; [2]Department of Pathology, Osp. S. Giovanni Antica Sede, Torino, Italy

The administration of primary chemotherapy is an innovative model of study in order to value the interactions beetween cytotoxic drugs and tumor biology. We conducted a study to evaluate the evolution of biomarkers such as hormone receptor status (ER, PgR), Ki 67 during primary chemotherapy

(CT). 40 consecutive patients (pts), bearing T2–T4, N0–1, M0 primary breast cancer received 3 cycles of either epirubicin 120 mg/sqm (38 pt) or CMF regimen (2 pts) as neoadjuvant chemotherapy before surgery. All pts were assessed, immediately before and after 3 cycles of CT, for several biological parameters (ER, PgR, Ki 67) using immunocytochemistry on fine-needle aspiration biopsy material. Clinical response to treatment was assessed after primary CT; the overall response rate was 24/40 pts (60%). The evolution of biomarkers was examined in 39 pts. Ki 67 changed in 11/31 pts (35.5%); ER changed in 16/38 pts (42.1%); PgR changed in 18/39 pts (46.1%) In responder pts ER changed in 27.2%, PgR in 39% and Ki 67 in 41% whereas non responders showed variations in hormone receptor status in 62% of pts and in Ki 67 in 28.6% of pts. Primary CT with antracycline produces significant tumor reduction (60%).

At present the study is ongoing; non responder pts seem to present greater variations in hormone receptor status than responder pts, while a decrease of Ki 67 has been observed in responder pts.

898 PUBLICATION

Tc-99m MIBI uptake in advanced breast cancer: Predictive value of response to chemotherapy

L. Delgado[1], O. Alonso[2], I. Alonso[1], G. Lago[2], Y. Afonzo[1], M. Núñez[2], G. Sabini[1], J. Gaudiano[2], I. Musc[1], E. Touya[2]. *Department of Clinical Oncology; [1]Nuclear Medicine Center; [2]Clinical Hospital of the University of Uruguay, Montevideo, Uruguay*

Purpose: Multidrug resistance (MDR) is a major therapeutic problem limiting advanced breast cancer (BC) treatment. Tc-99m MIBI has been reported to be extruded from tumoral cells by the P-glycoprotein (Pgp), encoded by the MDRI gene. The aim of this study was to investigate the possible relationship between MIBI uptake and response to chemotherapy in advanced BC.

Methods: We studied 14 pts with biopsy proven BC; 8 with advanced locorregional disease, 3 with locorregional and metastatic disease and 3 with recurrent disease. MIBI scintigraphy was performed 2–8 days prior chemotherapy. Images were acquired 10 minutes and 1 hour post injection of 740 MRq of Tc-99m MIBI. Tumor-to-normal tissue uptake ratios (T/N) were calculated in each evaluable lesion. All pts received combination chemotherapy containing doxorubicin for at least 2 cycles.

Results: Twenty-two BC lesions were evaluable for response to chemotherapy. Early T/N were significantly higher in lesions that showed a complete or partial remission than in non responding lesions (1.85, 1.5–2.9 vs. 1.40, 1.3–1.6; median, range respectively; p = 0.0006). No lesion with a T/N < 1.5 responded to chemotherapy.

Conclusion: These preliminary results suggest that Tc-99m MIBI scintigraphy may be a valuable tool for guiding chemotherapy in BC pts.

Brain tumours in children and adults

899 ORAL

Radiation therapy of intracranial pure germinoma: Results of the German prospective trials MAKEI '83, '86, '89

R.D. Kortmann[1], M. Bamberg[1], G. Becker[1], G. Calaminus[2], U. Göbel[2], C. Meisner[3]. *[1]Department of Radiotherapy, Univ. of Tübingen; [2]Children's Hospital, Univ. of Düsseldorf; [3]Institute for Medical Information Processing, Univ. of Tübingen, Germany*

Purpose: The trials (MAKEI '83/'86/'89) were conducted to assess the therapeutic outcome in pure intracranial germinoma after radiotherapy of the neuroaxis alone at reduced radiation doses.

Methods: 64 pat. were enrolled. In the MAKEI '83/'86 study (n = 12) the total dose was 36 Gy (neuroaxis) and 14.0 Gy (tumour site). In the MAKEI '89 study (n = 51) the dose was reduced to 30 and 15 Gy, resp..

Results: The 5 year relapse-free survival rate was 87.5% +/− 4.8% at a median follow-up of 50 months. The 5 year overall survival rate was 93.0% +/− 3.9%. 6 to 33 months (mean 16.3 months) after diagnosis relapses occurred in 6 pat. (9.5%), in 1 pat. a spinal recurrence in 1 pat. cerebral and spinal metastases and in 4 pat. metastases outside the CNS. Salvage chemotherapy achieved a second complete remission in 5 pat.. 2 pat. died of disease (3.2%) and 1 pat. (1.6%) of septicemia.

Conclusion: Radiotherapy alone is highly effective. Decreased dose levels were successful in local tumor control and prevention of spinal seeding. We advocate the irradiation of the neuroaxix and to continue to reduce the dose prescription to avoid major adverse effects of irradiation. The results were introduced in the current European prosp. study SIOP-CNS-GCT 96 with a further dose reduction to 24 Gy and 16 Gy, resp. to reduce acute and long term side effects.

900 ORAL

Treatment of carcinomatous meningitis (CM) with intra-CFS sustained-release encapsulated cytarabine (DEPOCYT™) vs. methotrexate (MTX)

M. Glantz[1], S. Phupanich[2], K. Jaeckle[3], L. Swinnen[4], T. Campbell[5], B. Maria[6], S. LaFollette[7], M. Chamberlain[8]. *DepoCyt Study Group; [1]Brown Univ. School. Med., Providence, RI; [2]Moffitt Cancer Ctr, Tampa, FL; [3]M.D. Anderson Cancer Ctr. Houston, TX; [4]Loyola Univ. Chgo, IL; [5]Sharp Healthcare, San Diego, CA; [6]Univ FL, Gainesville, FL; [7]Rush Cancer Inst Chgo, IL; [8]UCSD, San Diego, CA, USA*

Neoplastic infiltration of the leptomeninges is a serious complication of cancer, and current intra-CSF (I-CSF) chemotherapy must be administered by frequent bolus injections. DepoCyt has an increased half-life in the CSF compared to MTX leading to reduced peak exposure with sustained cytotoxic CSF levels of ara-C, which allows for markedly decreased frequency of dosing. A randomized, Phase III, open-label, multicenter trial of DepoCyt vs. MTX was conducted in patients (pts) with CM. 61 pts were randomized to DepoCyt (31) or MTX (30). Primary neoplasms included breast (22), central nervous system (14), non small cell lung cancer (6), small cell lung cancer (4), melanoma (5), and other (10). Pts received either I-CSF DepoCyt (50 mg q14d x 2. [Induction]; 50 mg q28d x 4 [Consolidation]) or I-CSF MTX (10 mg 2×/wk × 8 [Induction]; 10 mg 1×/wk × 8 [Consolidation]). Cytological responses were noted in 9 of 23 (39%) DepoCyt and 7 of 24 (29%) MTX pts evaluable for response (p = 0.34). A Kaplan-Meier estimate of survival between treatment groups (log rank, p = 0. 12) showed median survival of 105 (DepoCyt) vs. 87 days (MTX); mean survival of 195 (DepoCyt) vs. 128 days (MTX). At 6 months, the number of surviving pts was 11 (35%) DepoCyt and 5 (17%) MTX pts. I-CSF DepoCyt provides a more convenient dosing schedule than MTX, results in a cytological response rate that is at least comparable to MTX, and may offer a survival advantage over conventional I-CSF chemotherapy.

901 ORAL

Phase II study of intravenous RMP-7 and carboplatin for chemotherapy naïve recurrent malignant glioma

A. Gregor, M. Lind, C. Osborn. *On behalf of the UK RMP-7 Glioma Study Group; University of Edinburgh, Clinical Oncology, Western General Hospital, UK*

RMP-7, a selective bradykinin analogue, transiently increases the permeability of the blood brain barrier and the delivery of hydrophilic agents into brain tumours.

Aim: To assess clinical and 3-D MRI response to and toxicity of RMP-7 (300 ng/kg) + carboplatin (AUC 7) in treatment of recurrent glioma, WHO histology III + IV.

Methods: 45 patients (median age 42, Karnofsky 80%) were treated q 28 days. Neurological impairment, performance status and steroid use were measured over 4 cycles, plus tumour volume by 3-D MRI at the end of cycles 2 & 4.

Clinical response = stable or improved compared to baseline, and steroids stable or reduced, for ≥2 cycles. Primary evaluation of first 4 cycles.

Results:

Responding by Assessment Tool: Intent to Treat Analysis

Assessment	All	Grade III	Grade IV
EFIT[1]. improved/stable (n = 41)	39/22	47/20	35/23
Karnofsky: stable + improved (n = 45)	74	80	70
MRI volume· CR/PR/SD[2] (n = 43)	7/21/51	12/35/30	4/12/65
CR+PR+SD	79	77	81

[1] an objective, validated measure of neurological impairment. [2] CR ≥ 95% volume reduction + off steroids; PR > 50% reduction + stable or reduced steroids; PD > 50% increase, SD all other situations; all maintained ≥2 cycles.

Toxicity: no toxic deaths, 1 thrombocytopaenic withdrawal. Thrombocytopaenia and/or neutropaenia CTC grades 3/4: 2% at baseline; 27% at cycle 1; 29% at cycle 2; 45% at cycle 3; 35% at cycle 4. 3 patients had treatment-associated transient focal seizures.

Conclusions: Clinical and MRI response to RMP-7 and carboplatin combination is promising and toxicity is mild.