P92 Low morbidity and no mortality of high-dose cyclophosphamide, thiotepa and mitoxantrone plus autologous peripheral blood stem cell support for high-risk breast cancer patients

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Objective: Women with breast cancer (BC) and >10 positive lymphnodes are at high risk for relapse and for metastatic disease. 55–85% of the patients (pts) develope relapse within 5 years under conventional adjuvant therapy. After high-dose chemotherapy 64–78% of the pts remained diseasefree after a follow-up of 5 years. The German Adjuvant Breast-Cancer Group (GABG) currently investigate the value of adjuvant high-dose chemotherapy in a randomized study (GABG-4/EH93). We report the toxicity of the pts treated with high-dose cyclophosphamide (6000 mg/m^2), thiotepa (600 mg/m^2) and mitoxantrone (40 mg/m^2) (CTM) according the GABG-4/EH-93 protocol.

Patients: 84 women with BC and >10 positive lymphnodes (including one pts with stage IV NED) received high-dose CTM with peripheral blood stem support after surgical therapy and preceeding anthracycline containing therapy. Peripheral blood stem cells were harvested after G-CSF mobilization and reinfused 2 days after completion of HD-CTM.

Results: Regimen related toxicity was scored according the Bearman-scale. 61 pts developed 2° mucositis demanding a continous infusion of morphine and 20 women 1 ° mucositis. 5 pts exhibited 2° and 10 pts 1° gastrointestinal toxicity. Two pts had 2° and one 1° CNS toxicity, and one pts 2° and 1° renal toxicity respectively. Hepatic toxicity 1° occurred in 6 women. Pulmonary toxicity 1° and 2° occurred in one pt each. 64 women had systemic infection during neutropenia resolving under antimicrobial chemotherapy or after engraftment. Severe 3° toxicity or therapy related mortality did not occur. A leukocyte count of >1/nl was seen after a median of 10 (8–30) days, a platelet count of >50/nl was seen after 12 (6–83) days. After a median follow-up of 281 (11–1333) days 65/84 (77%) pts are disease-free and 89% alive.

Conclusions: HD-CTM is a safe regimen for adjuvant therapy in high-risk BC pts. Completion of the randomised study comparing 4xEC plus 3xCMF versus 4xEC plus HD-CTM is necessary to confirm the superiority of HD-CTM.

P93 Gene replacement used as adjuvant therapy in primary chemoresistant adenocarcinoma of the breast

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Breast cancer is the most common and most dreaded malignancy in women, accounting for 24% of all cancers in females. Furthermore, it accounts for 18% of cancer deaths in females after a prolonged, painful and disabling period of disease. Cells from mucinous adenocarcinoma of the breast which is characterized by invasiveness, were ICC stained with a cocktail of monoclonal antibodies IgG1 which have the potentiality to cross react with epitopes in the middle region of exon 6 (AA212–217) and N-terminus (AA32–79) of mt p53. The fraction of positively stained nuclei was 75%. No morphological signs of apoptosis were observed by electron microscopy after incubation of 5 × 10^6 tumour cells with 10 μg of vinorelbine and 112 μg of gemcitabine for 4 hours at 37°C. To circumvent this inhibition of apoptosis due to mutant p53, we incorporate plasmid wt-p53 cDNA gene of pCMV- Neo-Bam vector in colloidal particles consisting of cationic lipids. These complexes at ratio 35 μg DNA/400 nmoles lipid were incubated with 5 × 10^6 tumour cells which had previously been incubated with the combined administration of cytostatic and cytotoxic drugs for 4 hours at 37°C. Morphological examination by transmission electron microscopy exhibited endocytosis of gold labeled colloidal particles via coated pit and non coated pit pathways leading to fusion of late endosomes with primary lysosomes forming secondary lysosomes where degradation of the internalized particles occurs, delivering the cDNA into the cytoplasm from where it enters the nucleus via the nuclear pores, exerting freely apoptosis such as progressive condensation of the cytoplasm around the nucleus, intense cell-shrinkage, condensation of nuclear chromatin, cell membrane blebbing and cytoplasmic vacuolization leading to irreversible D2 phase of apoptosis consisting of cellular fragmentation into discrete membrane bystander effect. Concluding, we have eradicated the chemoresistant mucinous adenocarcinoma cells of human breast, inducing apoptosis by the cytotoxic action of gemcitabine that intracellularly is phosphorylated to gemcitabine diphosphate and triphosphate which inhibit the activity of ribonucleotide reductase and CTP synthetase, affecting the level of cellular cytidine nucleotides. This cytotoxic action acts synergestically with the cytostatic action of vinorelbine which blocks the cell cycle at phase G2/M, after the wt-p53 function has been replaced by lipofection.

P94 Therapeutic efficiency of DNA-conjugated doxorubicin in chemotherapy of advanced stages of primary breast cancer

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Despite recent advances in early detection and management of primary breast cancer there is still a proportion of cases when tumours become inoperable due to metasthatic dissemination. At this generalized stage of the neoplastic process the use of conventional polychemotherapeutic approaches often becomes difficult due to frequent contraindications due to inhibition of leukopoiesis and weakness of such patients.

The present study has been conducted with the purpose of assessing the efficiency of Doxorubicin conjugated with native calf thymus DNA in treatment of patients with advanced primary breast cancer. 21 patients aged between 35 and 62 years (all with contraindications against anthracycline treatment) were treated with Doxorubicin conjugated with native calf thymus DNA. The conjugate was injected subcutaneously or intramuscularly in 8-day courses. Overall course doses of Doxorubicin and DNA were 100 mg and 750 mg respectively. Clinical indications of favourable dynamics after treatment were observed in 14 (66.6%) of cases, and stabilisation of leukocyte counts was documented in 15 (71.4%) cases. Progressive decrease in leukocyte counts in 6 (28.6%) patients was clearly associated with negative clinical changes.

Although only temporary remission (3–32 months) of the advanced neoplastic process was observed in this group of patients, we conclude that therapeutic application of DNA-conjugated Doxorubicin is entirely justified in the circumstances when conventional polychemotherapeutic schemes can not be applied.

P95 Long-term intraarterial chemotherapy for breast cancer

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Introduction: According to number of authors, the use of selective intraarterial chemotherapy is a promising approach in the treatment of patients with stage III-IV breast cancer.

Materials and Methods: We have developed a method of double-catheter superselective probing for breast tumor supplying arteries and their regional metastasis for conducting long-term intraarterial chemotherapy. A transfemoral approach was used for catheterisation of the respective subclavicular artery and angiographic investigation. Depending on the site of breast tumor and the routes of regional metastasis we introduced catheters into a. thoracica interna, a. thoracica lateralis, a. thoracoacromialis, r. thoracodorsalis a. subscapullaris and their ordinal branches. After establishing the sources of vascularization one catheter was placed in a dominant vessel feeding the tumor, while another in the artery supplying blood to the palpable lymph nodes. Cytostatic infusion was performed during 3 to 4 days. We used adriablastin at 30 mg/m^2 in combination with verapamil (50 mg), cysplatin at 40 mg/m^2. Administration of chemotherapeutic drugs was performed at the velocity of 2 to 2.5 ml per minute for 3–4 hours using a drug dosage unit. Preoperatively we performed 1–3 sessions of intraarterial chemotherapy with a 3 week interval. Radical mastectomy was carried out in 3 weeks following completion of treatment using selective intraarterial chemotherapy.

Results: Long-therm selective intraarterial chemotherapy was performed to 43 patients with breast cancer. After 1-6 courses of therapy 29 patients showed immediate clinical results, i.e. pain relief in affected breast, reduction and softening of the tumor, a decrease in the size affected lymph nodes. We have established angiographic signs of the direct therapeutic effect of intraarterial chemotherapy. Evaluation was made of life quality for inoperable patients for whom IACT was a major treatment. Radical mastectomy was performed to 14 patients following IACT. Analysis was made of the immediate treatment results for breast cancer patients using IACT. During selective evaluation of curative pathomorphosis the volume part of the viable tumor parenchyma amounted to about 20%.

Conclusions: Long-term superselective intraarterial chemotherapy results in tumor devitalisation, blocks the routes of metastasis, reduces the generally toxic effects of cytostatics on the host, enhances surgery ablasticity and improves patient life quality.