357 POSTER

Antibody-mediated cytotoxic therapy eradicates chemoresistant breast cancer

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Breast cancer is one of the most fatal cancers due to its extremely high chemoresistance. Highly metastatic breast cancer cell line extracted by the collagenase method from human malignant tissue has exhibited aberrations of the p53 tumour suppressor gene by PCR-SSCP analysis. Furthermore, PCR has exhibited high expression of MRP gene, low expression of bax oncogene and overexpression of the tyrosine kinase receptor erbB2 (HER-2/neu), which is a functional membrane protein, playing an important role in the pathogenesis of breast cancer. Monoclonal antibodies directed against c-erbB2 have been conjugated on the surface of liposomes. In the lipophilic bilayer of these immunoliposomes we entrap paclitaxel molecules and we incubate with the tumour cells. As controls we incubate tumour cells with empty liposomes. After incubation for the test samples we observe by PCR upregulation of bax oncogene. Furthermore, analysis by TEM exhibits morphological evidence of liposomal binding onto the cell surface, and subsequent endocytosis leading to lysosomes, where disintegration of liposomes occurs, releasing paclitaxel molecules into the cytoplasm, exerting their oncolytic action.

Furthermore, morphological apoptotic signs are observed, such as pyknotic nuclei, condensed and marginated chromatin of the nucleus forming distinct crescents, segregated nucleus, cell shrinkage, denser nucleus and cytoplasm, cytoplasmic megavacuolization and budding of cell surface, resulting in the formation of apoptotic bodies. Also, these results are confirmed biochemically, where metabolic activity is reduced according to MTT analysis and DNA synthesis is proportionally reduced according the BrdU analysis, compared to control samples.

Conclusion: We achieved to eradicate chemoresistant breast cancer cells by targeting specifically immunoliposomes, circumventing drug efflux pumps such as MRP, and protecting chemotherapeutic molecules from biological milieu interactions, such as HDL attach or albumin binding. Most importantly, this apoptotic induction is independent of p53 mutation, probably due to upregulation of bax-gene caused by paclitaxel.

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Frequency domain laser scanning mammography of the breast – First clinical evaluation study

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We recently demonstrated feasibilty and contrast features of frequency-domain laser scanning mammography (FLM). We now report the first clinical evaluation of this new diagnostic method.

The FLM instrument was equipped with two laser diodes, emitting at 690 nm and at 810 nm, modulated at 110,080 MHz and 110,100 MHz respectively. Breast scans were performed in a reproducible slab geometry in two perpendicular views. Amplitude and phase signals were measured by lock-in amplification and heterodyne detection for each pixel. Edge-effect corrected images (N-algorithm) were calculated based on both amplitude and phase signals. Positivity of FLM was judged by two independent reviewers, if correlating images were discernible on both views.

133 symptomatic patients were investigated, 92 of those (59 malignant 20 benign tumours, 13 mastopathy only) are evaluable for correlation between FLM and histological results. FLM revealed 2/9 non-invasive cancers, 37/50 invasive cancers, 3/20 benign tumours and 0/13 mastopathy lesions. 2/3 mammographically occult cancers were visualized. There was no correlation between FLM imaging contrast and radiological contrast, tumour grade, or age of the patient.

FLM provides independent and complementary information to conventional imaging. The reproducible geometry of the system will allow for further technological improvements as to sensitivity, i.e. by 3-dimensional reconstruction.

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Sequential adriamycin (A), docetaxel (D) and CMF in the adjuvant treatment (AT) of breast cancer (BC)

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In preparation for a phase III trial evaluating D and dose-intensity in the AT of BC, we studied the feasibility of these regimens: 1) non-accelerated (NA): A 75 mg/m^2 q 3 wks × 3 → D 100 mg/m^2 q 3 wks × 3 → CMF days 1, 8 q 4 wks × 3; 2) accelerated (ACC): A 75 mg/m^2 q 2 wks + lenograstim (G) × 3 → D 100 mg/m^2 q 2 wks + G × 3 → CMF (as NA). Radiotherapy was given during/after CMF. 48 pts are evaluable: 19 treated with NA and 29 with ACC. Pt characteristics are: median age 48 (29–66), stage II/III untreated BC 43/5. 164 and 165 cycles were delivered so far in NA and ACC, respectively. Median relative dose-intensity is 100% in both arms. Skin toxicity occurred in 62% of pts receiving ACC (17% G3–G4) and consisted of erythematous plaques in different body areas. Skin lesions appeared during treatment with A in 24% of cases.

Treatment (n° pts)	N° Pts Withdrawn			% Pts
	radiodermatitis	bone pain	skin toxicity	
NA (19)	1	–	–	5
ACC (29)		1	4	17

This study shows that: 1) ACC is not feasible as adjuvant treatment; 2) NA can be safely given at full doses. The phase III trial will start in June 1997.

360 PUBLICATION

Optimal duration of neoadjuvant chemotherapy: 3 or 4 versus 6 cycles in 3 schemes for operable breast cancer

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Most studies use 3 or 4 cycles of induction chemotherapy, in contrast with adjuvant therapy (most often 6 cycles). From 01/82 to 06/96, 283 patients (pts) (stage II and IIIa) received primary chemotherapy in our center with 3 different regimens (all doses mg/m^2): AVCF/AVCFM, 157 pts (adriamycin 30, vincristine 1 d1, cyclophosphamide 300, fluorouracil 400 d2–d5 and methotrexate 20 d2 and 4, every 28 d); NEM, 83 pts (navelbine 25, epirubicin 35, methotrexate 20 d1 and d8, every 28 d); TNCF, 43 pts (THP-adria 20, d1–d3, navelbine 25 d1 and d4, cyclophosphamide 300, fluorouracil 400 d1–d4, every 21 d). All patients were evaluated after 3 or 4 and 6 cycles by 3 methods: clinical, mammography and ultrasound. The clinical complete (CR) and overall (OR) response rates were:

	AVCF/AVCFM		NEM		TNCF	
Evaluation after	3	6	3/4	6	3/4	6 cycles
CR (%)	6	27^{-}	19	26N	41	58N
OR (%)	39	64^{-}	78	89•	88	90*

N $p < 0.05$, • $p < 0.01$, $^{-}$ $p < 0.001$, * non significative

Similar differences were found with the other 2 evaluations. In conclusion, a significative difference between 3 versus 6 cycles was observed with AVCF/AVCFM and NEM. For TNCF regimen, OR was already important after 3 cycles, but 6 cycles seem necessary to improve CR and therefore pathological complete response (ECCO 8, S13, 53).

361 PUBLICATION

COLLATE: A collaborative authoring tool for the development of clinical oncology guidelines

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ECOLE/GRIP (European Collaboration in Oncology Literature Evaluation/Getting Research Into Practice) is a European project whose goal is to develop a telematics infrastructure to support the development and dissemination of evidence based, quality assured Clinical Practice Guidelines in Oncology. The project involves National Cancer Organisations from