ThT 19

IS CONTINUATION OF THE BMFT MULTICENTER TRIAL JUSTIFIED BY THE PROBLEM'S CURRENT UNRESOLVED STATUS?

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Manifold uncritical statements in the media kindled the discussion on the treatment of primary breast cancer thus causing more confusion than clarification. At times those discussions suggest that conservative breast cancer therapy is a standard treatment. Thus the BMFT-sponsored multicenter study "treatment of small breast cancer" could be regarded as outdated. Ethically and scientifically this view must be vigorously rejected. Apart from a large number of colleagues not having any experience in breast preservation treatment, a broad range of questions is still open. Preliminary results of other studies might suggest that conservative and radical therapy provide equal survival rates, but scientific proof is still lacking. Although the quality of radiation therapy has improved substantially conclusions still cannot be drawn as to side-effects like damage of neighbouring organs, secondary tumors, etc. In our study, special emphasis will be given to prognostic factors which may exclude certain tumors from conservative therapy from the outset. Another open question is the quality of life based on the applied treatment modality. The strict patient selection criteria of our protocol guarantee progress on these questions. Two years after activation of the BMFT-Study, patient recruitment is still underway, so that results would be premature. As of October 1985, 56 hospitals had entered 320 patients into the trial.

At present the following positive aspects can be summarized:

- an increased conscientiousness in operative techniques as well as the histopathological work-up of the specimens removed.
- a significant improvement in radiotherapy standards.

These are the absolutely necessary conditions for performing conservative breast cancer treatment without bringing discredit on this therapeutic modality - a consideration that per se justifies our study's continuation, apart from the scientific obstacles outlined above.

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CPh 01

DNA-METABOLISM IN HUMAN BONE MARROW CELLS: THYMIDINE-KINASE-ACTIVITY AS A MARKER OF LEUKEMIC BLAST POPULATIONS AND NUCLEOSIDE-INCORPORATION-ACTIVITY FOR PREDICTION OF PROGNOSIS AND RESPONSE TO CYTOSTATIC TREATMENT

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Bone marrow aspirates of normal individuals and of adult patients with acute lymphoblastic and non-lymphoblastic leukemias were analysed for some parameters representing DNA-synthesis activity: biochemical determiantion of thymidine-kinase(TK) in the cytosol and of thymidine(dTR)- and deoxyuridine(dUR)-incorporation into the acid insoluble material (=DNA) after incubation with intact cells. The most interresting result was the high TK in acute leukemic blast populations. TK seems to be a relevant tumor marker for these populations. The table shows the results.

TK in bone marrow cells (nmoles/min x 10^{10} cells)				
	N	TK ± S	p vs.norm.	p vs.remiss.
normal marrow	26	12.5± 8.7	---	<0.0001
acute leukemia	87	61.3±60.1	<0.0001	<0.0001
complete remission	172	19.3±18.4	<0.0001	---
1-2 mo.bef. relapse	13	33.1±28.6	<0.0001	<0.02
acute leuk. relapse	56	60.3±45.5	<0.0001	<0.0001

TK has also some prognostic significance indicating a soon relapse by rising 1 to 2 months before a relapse can be diagnosed morphologically in the bone marrow aspirates. With respect to treatment outcome, dTR and dUR correlated better than TK. The incorporation rates were significantly higher in patients who did not achieve complete remission. In patients who achieved complete remission dTR and dUR decreased significantly 3 to 11 days after the beginning of polychemotherapy. This was not found for patients who did not go into complete remission after treatment.

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CPh 02

CLINICAL RELEVANCE OF IN VITRO CHEMOSENSITIVITY TESTING IN ACUTE LEUKEMIAS:

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The ready availability and convenient isolation procedures of leukemic blast cells makes human leukemia a favourable target for in vitro drug testing. For clinical use long term tests are insufficient as therapy has to be initiated within one or two days. - We have analyzed leukemic blasts for in vitro responsiveness to cytostatic agents in terms of suppression of labeled nucleoside precursor incorporation into cellular nucleic acids in a short term test with results available within 24 hours. Cell-line experiments showed that the percentage inhibition of precursor incorporation in independent from the proliferative activity of the cells.

In previous retrospective studies the test system proved to be clinically applicable (Cancer 53:390,1984). Thus, criteria prospectively indicating sensitivity or resistance of the blasts were evaluated. Using these new criteria cells from 46 leukemia patients (15 ALL, 21 AML, 6 AMML,1 AUL, 3 CML-BC) were tested in a prospective "single blind" study.

Our data show that 89% of the patients with in vitro sensitivity to one or more of the drugs used for therapy responded with complete or partial remission, A treatment failure correlated in 70% with in vitro resistance. In this small number of patients we also observed a trend that the probability to respond to therapy increased with the number of in vitro active drugs. - No correlation was found between in vitro results and the number of blast cells in peripheral blood or bone marrow. We also could not predict the duration of remission. However, it is interesting to note, that some individual patients with extremly high in vitro sensitivity (very high inhibition of precursor uptake) seemed to relapse earlier.

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CPh 03

LIMITED POTENTIAL OF THE HUMAN TUMOR-NUDE MOUSE SYSTEM FOR PRE-THERAPEUTIC DRUG TESTING

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Out of 500 human tumors of different origin 51% grew progressively after 3 months after subcutaneous transplantation in nude mice. Most of these tumors were suitable for drug testing in subsequent animal passages. In order to investigate if a tumor responds in nude mice in a similar way than in the patient 80 comparisons were performed in 55 tumors. Comparisons were done in carcinomas of the large bowel (27), lung (13), stomach (9), melanomas (8) and breast (4) and 19 in other tumors. Combination chemotherapy was more successful than single agent therapy. 21 tumors got a remission in the patient which was obtained in 19 cases in the nude mouse system, too. In 59 cases the treatment was unsuccessful in the patient and the same result was found in 57 cases in the nude mouse system. Xenografts gave a correct prediction for resistance in 96% and for tumor response in 90%. Despite great efforts to obtain a large number of comparisons only 32 test results were available before the patients needed treatment. Therefore, the xenograft system will not have practical significance in determining the treatment of the patients. Limitations are the durations of the testing, the growth rate of only 50% and the charges for nude mice. However, the highly correct prediction rates for tumor sensitivity and resistance validates human tumor xenografts as tumor models to test new drugs and combinations. Furthermore, we use xenografts as tumor material for experiments in cell culture.

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