Lym 12

INTENSIVE CHEMOTHERAPY FOR AGGRESSIVE LYMPHOMAS - CLINICAL IMPLICATIONS OF THE GOLDIE-COLDMAN HYPOTHESIS

M. Graubner, P. Klimo*, J. Connors* and J. Goldie*

The development of drug-resistant tumor cells during cancer chemotherapy is the most important reason for treatment failure. Based on the somatic mutation theory, the Goldie-Coldman-hypothesis implies an early intensive treatment with alternating noncross-resistant drugs. In Hodgkins disease (stage IIIA2, IIIAS, IIIB, IVA, IVB) the following HYBRID-schedule was used: day 1: Nitrogen Mustard 6 mg/m², Vincristin 1.4mg/m² (max. 2.0mg),day 2 - 8: Procarbazine 100 mg/m², day 2 - 12: Prednisone 40 mg /m², day 8: Adriamycin 35 mg/m², Bleomycin 10 mg/m², Vinblastine 6 mg/m². Repeat q 28 days x 6. From 54 patients treated 88 % achieved complete and 6% partial remission. 46 patients were relapse-free after a median follow up of 20 month.

In Non-Hodgkin-Lymphomas (large cleaved, large non-cleaved, immunoblastic) stage II(only mass 10 cm diameter or extranodal disease) and stage III and IV the following MACOP-B regimen was used: day 1 and 15: Adriamycin 50mg/ m², Cyclophosphamid 350 mg/m², day 8: Methotrexat 400 mg/ m² + Leucovorin rescue, Vincristin 2 mg, day 28: Vincristin 2 mg, Bleomycin 10 mg/m². Repeat q 28 days x 3. Day 1 - 84: Prednisone 75 mg, then taper, Cotrimoxazol 960 mg. 61 patients were treated and a complete remission rate of 84% was achieved with a relapse free survival of 90% after 23 month; 16% had a partial remission.

Compared to similar regimens with much longer duration these results are among the best and possibly superior. As toxicity is not increased, these results clearly show the feasability of cytotoxic drug application in weekly intervals with the advantage of a very short treatment period of 3-4 month.

Zentrum Innere Medizin, Klinikstr. 36, D-6300 Giessen
* CCABC Vancouver (Kanada)

Lym 13

PRECLINICAL AND CLINICAL STUDY OF ANAXIRONE USING AN HPLC ASSAY (NSC 332488; TGU)

R.B.Schilcher,M.R.Nowrousian,C.Doberauer,B.Hofmann,N.Niederle,K.Höffken,C.G.Schmidt,K.Donhujsen

TGU is a new triepoxide with activity in experimental and human tumor systems which is currently evaluated in Phase II studies. Because of dose - limiting toxicities such as phlebitis and bone marrow suppression a sensitive HPLC assay was needed to determine elimination behaviour. Plasma samples were obtained at selected times from nine pts. with solid tumors before and following a 1 min iv. injection of 600 mg/m² (pretreated pts.) and 800 mg/m² (untreated pts.). To one ml plasma 9 ml chloroform were added for extraction, centrifuged at 2800 rpm and supernatant removed. The organic phase was evaporated to dryness at 40°C, resolved in 100 µl methanol, and 20 µl injected. The HPLC system consisted of a manual injector, a M45 pump (Waters Assoc.) set at 1 ml/min flow rate, a C_{18} µ Bondapak column 10 µ (3.8x250 mm), an UV detector at 216 nm and a strip chart recorder. Aqueous standards were linear from 5 ng/ml to 20 mg/ml, and the recovery from plasma was 78% with a detection limit of 15 ng/ml. Preclinical studies in F_1 mice revealed sustained drug concentrations. In heart, liver, lung and kidney tissue were found 906, 815, 474 and 332 ng TGU/mg tissue on Day 7 following 108 mg TGU/kg ip. No drug was seen in muscle tissue. In pts. a plasma concentration of 23 ng/ml was measurable 22 hrs after a single iv. dose of 600 mg/m². One pt. had fatty atrophy of bone marrow following 3 courses (total dose 4500 mg TGU). Two PR and 3 NC were observed in this study. Further trials will incorporate pts. with multiple myeloma and leukemia

Innere Universitäts- und Poliklinik (Tumorforschung), West German Tumor Center, D 4300 Essen

Lym 14

CARBOPLATIN VERSUS IPROPLATIN IN SOLID TUMORS AND LYMPHOMAS - A PHASE-III-STUDY

E. Schmoll, A. Harstrick, B. Metzner, J. Anagnou, S. Le Blanc, H. Diedrich, B. Lentmann, H.-J. Schmoll

In a prospective randomized trial the platinum derivatives carboplatin (JM8) and Iproplatin (JM9) have been investigated in 40 eval. pts. with various solid tumors and lymphomas, in order to investigate the activity of both analogues in pts. without prior treatment or with prior Cisplatinum-treatment and to compare the toxicity of both drugs. The starting dose was 400 mg/m² i.v. for JM8 and 300 mg/m² for JM9 with reduction of 10% in the first cycle for pts. with heavy pretreatment and succeedingly dose escalation to 110%. Cycles were repeated day 29 with a minimum of 2 cycles. Results: There was no remission either with Carboplatin nor with Iproplatin. NC was seen in 5/19 pts. with JM8 and 5/21 pts. with JM9 with a median duration of 14 (8-20+) and 16 (8-34) weeks respectively. The NC occurred in: 1 colon-ca. (JM8; JM9), 3 bladder-ca. (JM8; JM9), 1 renal- ca. (JM9), 1 ovarian-ca. (JM8), 2 non small cell lung ca. (JM8;JM9) and 1 lymphoma (JM8). Pts. with Cisplatinum pretreatment did as poor as pts. with non Cisplatinum containing pretreatment with 1/11 and 5/23 NC respectively. Pts. without pretreatment had a greater chance for NC (4/6). The major toxicity was bone marrow depression, with a moderate granulocytopenia mainly grade I and II and moderate to severe thrombocytopenia grade II - IV (WHO). The thrombocytopenia was more pronounced with JM9 with thrombocytes less than 50.000 in 10% of the cycles versus 5% with JM8. The renal toxicity was low with 5% grade I (JM8) and 2% grade II (JM9). No severe nausea and vomiting was observed by pretreatment with dexamethason 8 mg/m² i.v. The gastrointestinal toxicity was generally well tolerated and of very short duration but cumulativ increasing. No heavy adverse reactions have been observed. Conclusions: Carboplatin and Iproblatin are well tolerated and can be managed easily on an outpatient basis, without severe renal dysfunction. The major toxicity is bone marrow toxicity and mild to moderate nausea/vomiting. However, the antitumor effect is very poor with no remission. All 3 pts. with testicular-ca. progressed on JM8 or JM9 which is a hint to a cross-resistance between Cisplatinum and the platinum analogues used in this study. From the literature JM8 seems only to be active in untreated small cell lung cancer and ovarian cancer.

Abt. Hämatologie-Onkologie Medizinische Hochschule Hannover, Konstanty-Gutschow-Straße 8, D-3000 Hannover 61

Lym 15

MITOXANTRONE ALONE AND IN COMBINATION WITH CYTOSINE ARABINOSIDE IN REFRACTORY HODGKIN'S AND NON- HODGKIN-LYMPHOMA

A.D. Ho, B. Dörken, W. Hunstein

Phase I and Phase II studies suggested that mitoxantrone might be effective in the treatment of malignant lymphoma. The studies reported here are sequential. In the initial study, patients with refractory Hodgkin's disease (HD) or Non-Hodgkin-Lymphoma (NHL) received mitoxantrone as monotherapy. Antitumor activity was seen but no complete remissions (CR) obtained. In a subsequent study, mitoxantrone was administered in combination with cytosine arabinoside (Ara-C). All the patients have stage III and IV diseases and developed resistance to at least 2 different chemotherapy regimens. In the initial study,mitoxantrone was administered at a dosage of 5-7 mg/m² daily x 3 and treatment course repeated every 3 weeks. 3 of the 6 patients with HD and 3 of the 14 patients with NHL achieved a partial remission. The clinical data of the patients are summarized in the following table:

Histology	Eval.	Median Age	Pretreatment	CR	PR	SD	Prog.
Hodgkin (HD)	6	33.4	COPP,ABVD,IMVP-16	o	3	1	2
High gr NHL	7	59.7	CHOP,IMVP-16	o	1	1	5
Low gr NHL	7	57.4	COP,IMVP-16	o	2	o	5

This monotherapy was well tolerated. Granulocyte nadirs below 1,o X 10^9/l were observed in 4/20 of the patients and platelet nadirs below 50,o X 10^9/ l in 7. Mild to moderate stomatitis was seen in 6, mild nausea and vomiting in 5, FUO or infections in 3, tachyarrhythmia in 1. In the subsequent study, the regimen consists of mitoxantrone 7 mg/m² daily x 3 and Ara-C 75 mg/m²/12 hours x 6 (s.c.) every 3 to 4 weeks. Up till now 3 patients with HD and 2 patients with NHL were evaluable. 1 CR (in HD) and 1 PR (in NHL) have been achieved. Thus, mitoxantrone has activity in patients with refractory malignant lymphoma. We are concurrently conducting a multicenter study with the combination of mitoxantrone and Ara-C.

Med.Univ.Poliklinik, Hospitalstr.3, D 6900 Heidelberg