AML 02

HIGH-DOSE CYTOSINE ARABINOSIDE AND MITOXANTRONE: A HIGHLY EFFECTIVE REGIMEN IN REFRACTORY ACUTE MYELOID LEUKEMIA
W. Hiddemann, H. Kreutzmann, K. Straif, W.D. Ludwig, R. Donhuijsen-Ant, E. Lengfelder and Th. Büchner

Based on the promising results of monotherapy trials with HD-AraC and Mitox. in refractory AML a multi-institutional study was initiated at 6 centers in Germany to assess the toxicity and antileukemic efficacy of the two drug combination. All patients were recruited from the first line multicenter trial by the German AML Cooperative Group. Refractoriness was defined by: 1. primary resistance against two TAD-9 induction courses; 2. early relapse within the first 6 months; 3. relapse after 6 months with non-response against one additional TAD-9 cycle; 4. second and subsequent relapses. Treatment consisted in HD-AraC 3g/m² every 12 hrs on days 1 - 4. Mitox. was started at 12 mg/m²/d on days 3, 4 and 5 and escalated in subsequent cases to 4 and 5 doses of 10 mg/m²/d on days 2 - 5 and 2 - 6 respectively. From 30 patients entering the trial so far, 27 are presently evaluable. 14 patients achieved a CR (52%) while a PR was obtained in 1 additional case. 9 patients died within the first 4 weeks of therapy because of infectious complications, in 3 cases the leukemic cell population persisted or recovered after the end of therapy. Except for one death possibly related to acute cardiomyopathy, toxicity was mild to moderate consisting in nausea, vomiting, mucositis and diarrhea. These data indicate a high anti-leukemic activity of HD-AraC and Mitox. in combination in refractory AML and strongly suggest to apply this regimen at earlier stages of AML therapy.

AML 03

MITOXANTRONE AND VP-16 IN REFRACTORY ACUTE MYELOGENOUS LEUKEMIA.

P.Meyer, A.D. Ho, Th.Lipp, G.Ehninger, H.Rückle, B.Steinke, W.Kaboth, W.Hunstein.

Phase I/II studies suggested that mitoxantrone is effective in the treatment of acute leukemia. (P.Meyer, A.D.Ho, G.Ehninger, I.Mjaaland, E.Heidemann, E.Seither: Mitoxantrone in the treatment of relapsed and refractory acute leukemia. Investigational New Drugs 3,203, 1985). In this study we have investigated its efficacy in combination with VP-16 in patients with acute myelogenous leukemia (FAB M1-M6) as salvage treatment. The regimen consists of mitoxantrone 10mg/m²/day i.v. days 1-5, VP-16 100mg/m²/day as 30' infusion days 1-3 with dose escalation in subsequent patients to 100mg/m² days 1-5. As of september 1985 27 patients have been entered in the study and 21 patients are evaluable for response now. Of these 21 patients, 6 have achieved complete remission (28,6 %) including 3 patients with primary refractory disease, 2 with early relapse (<6 months CR duration) and 1 patient with relapse during maintenance therapy. Two patients have attained a partial remission. One patient died within 4 weeks of treatment, other toxicity was tolerable with reversible pancytopenia, moderate gastrointestinal toxicity and alopecia. This regimen seems to be active in acute myelogenous leukemia and its incorporation in first line protocols seems warranted.

Medizinische Poliklinik der Universität.
Klinikstraße 8, D-8700 Würzburg

AML 04

ABNORMAL PRODUCTION AND RELEASE OF FERRITIN BY IMMATURE MYELOID CELLS IN LEUKEMIA.
H. Fromm, E. Aulbert

Ferritin concentration in serum and in leukemic cells was investigated in 163 adults with different types of leukemia. The results are summarized in table 1. Extremely high serum ferritin concentrations were found in patients with acute immature myeloblastic leukemia (M1) before treatment. In patients with the more differentiated forms of acute leukemia (M3-M6) serum ferritin levels were found to be significantly lower. During tumor regression high pretreatment serum ferritin levels decreased and reached normal values in complete remission. Investigation of the intracellular ferritin concentration showed a direct correlation between the levels of serum ferritin and the amount of ferritin within the leukemic cells. In patients with chronic myeloid leukemia during the chronic phase we found normal serum ferritin concentrations, whereas myeloid blast crisis was associated with highly raised serum ferritin levels. In cases of myelomonocytic type or lymphatic type of blast crisis a significantly less increment of serum ferritin concentration was seen. There was also a direct correlation between serum ferritin concentration and intracellular ferritin content of myeloid cells in the chronic phase and in myeloid blast crisis. These findings indicate that immature myeloid cells in acute myeloblastic leukemia and in blast crisis of chronic myeloid leukemia produce and release ferritin at a very high rate. Thus, in these cases serum ferritin can be used as parameter in monitoring the activity of the disease.

Table 1:	Classification	Serum ferritin concentration	Intracell. ferritin concentration
Myeloblastic L.	FAB-M1	2235 ± 870 ng/ml	72 ± 16 fg/cell
	M2	1355 ± 532 ng/ml	
Promyelocytic L.	M3	565 ± 135 ng/ml	
Myelomonocytic L.	M4	450 ± 252 ng/ml	9 ± 4 fg/cell
Monocytic L.	M5	463 ± 254 ng/ml	
Erythroleukemia	M6	598 ± 145 ng/ml	
Acute lymphatic L.		362 ± 151 ng/ml	4 ± 2 fg/cell
Chronic myeloid L.	(chron. ph.)	84 ± 51 ng/ml	3 ± 2 fg/cell
	(blast cr.)	2180 ± 867 ng/ml	52 ± 12 fg/cell

St. Barbara-Hospital, Innere Abt., 4300 Gladbeck, Barbarastr. 1, GFR

AML 05

HIGH DOSE ARA-C AND VP16 IN TREATMENT OF REFRACTORY OR RELAPSING ACUTE LEUKEMIA

M. Freund, H. Link, H. Diedrich and H. Poliwoda.

We treated 13 patients (9 m, 4 f) with AraC 3 gr/m² twice daily d 1-6 and VP16 100 mg/m² d 1-5: 1 ALL (L1), 12 AML (3 M1, 7 M2, 2 M4). Median age was 40 yrs (18 - 62). 11 courses have been administered for induction. One of these patients had primary refractory leukemia (group 1), 5 were in refractory 1st or 2nd relapse (group 2), 5 more had 1st, 2nd or 3rd relapse (group 3) with a median preceding remission of 5 mo (3-12 mo). Consolidation therapy was not constantly given.

Treatment results were 8/11 CR (4 group 2, 4 group 3), 1/11 MR (group 2), 1/11 NR (group 1), 1/11 early death (group 3). Median CR duration was 1.5+ mo. Hematotoxicity was severe in induction with mean duration of granulocytopenia below 500/cmm for 24,3 d (beginning at d 5,2; s=13,0) and thrombocytopenia below 20 000/cmm for 18,0 d (beginning at d 6,9; s=7,6). 5 courses were administered for consolidation. Hematotoxicity of consolidation therapy was severe too: Granulocytopenia lasted for 19,3 d (s=2,5) beginning at d 9,0, thrombocytopenia for 14,0 d (s=1,0) beginning at d 10,8. There were 2 treatment related deaths due to sepsis in aplasia. Moderate hepatic toxicity was observed as well as bleeding tendency, mucositis, diarrhea, erythema, other infections, conjunctivitis but no cerebellar toxicity. We conclude that combination of high dose AraC and VP16 is a powerful though toxic induction regimen.

Abteilung Hämatologie/Onkologie, Medizinische Hochschule Hannover, Konstanty Gutschowstr. 8, D-3000 Hannover 61