11. CLL

DIFFERENTIATION OF HUMAN PRE-B CELL LYMPHOMA INDUCED BY NORADRENALINE VIA a1-ADRENOCEPTORS AND p53 EXPRESSION
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We found that hematopoiesis is regulated by neural and neuroendocrine mechanisms. Adrenergic agents can affect hematopoiesis either in vivo or in vitro via adrenoceptors present on bone marrow cells. On the other hand, bone marrow seems to contain substantial amount of noradrenaline which decreases upon chemical sympathectomy. This is consistent with a physiological sympathetic regulation of hematopoiesis. Moreover, noradrenaline administration can protect mice from a lethal dose of carboplatin. The protection seems to be mediated mainly by a1-adrénoceptors which are present in pre-B cells. We found that also the human IgM, NALM-6 pre-B cell line bears a1-adrenoceptors. Activation of these adrenoceptors by noradrenaline results in a significantly increased expression of p53 and in IgM, B cell differentiation. After noradrenaline exposure the cell line showed enhanced mortality and growth inhibition. All these effects of noradrenaline were prevented by the a1-antagonist prazosin. This finding is consistent with and might explain previous data which show that administration of the a1-antagonist prazosin in normal mice enhanced myelosuppression at the expense of lymphopoiesis. Furthermore, the fact that a human lymphoma cell line could be induced to differentiate by the sympathetic neurotransmitter noradrenaline may open new perspectives either in our understanding of lymphomas pathogenesis and progression or in the therapeutic approach.

THE INFLUENCE OF CHEMOTHERAPY ON THE PREDICTING VALUES OF PHA INDUCED LYMPHOPROLIFERATIVE RESPONSE (LPR) IN PATIENTS WITH MALIGNANT LYMPHOBLASTIC DISEASES
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The capacity of peripheral blood lymphocytes of patients with malignant lymphoproliferative diseases (before therapy n=86) to undergo mitosis in whole blood culture supplemented with phytohemagglutinin (PHA) is rather (r=0.65 for individual, or r=0.85 for raged, normal or diminished values) determined by several immune system humoral and cellular blood components. This is represented by the Backward regression analysis equation: %LPR = 83 + (0.02 x IgM) - (0.94 x IgA) - (28.72 x IC) - (0.65 x CD4+) + (7.89 x C fago) - (0.89 x YM-RFC) + (2.16 x ARFC) - (0.05 x PBL), previously reported.

We applied the same equation in predicting values of LPR in patients under chemotherapy and in patients controlled after therapeutic procedure. The predicted values were not in accordance with real ones neither in patients under chemotherapy (r=0.24, even less for raged values), nor in patients presumably cured (r=0.44). The revised Backward analysis in these patients gave almost the same results as the formerly applied equation.

These results suggest that chemotherapy induced the impairment of relationship between the LPR and cellular and humoral immune components determinative for it's value.

MALIGNANCIES IN THE FAMILIES OF 54 PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)
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Chronic lymphocytic leukemia is the commonest leukemia in the Western world (30% of all cases), but is rare in the Orient. A familial tendency has been reported, as well as concordance in several identical twins, but no pattern of inheritance has been reported.

A family history has been elicited with a prestructured questionnaire in a representative sample of 54 patients with CLL (n=proband: 34 male, 20 female; median age at diagnosis: 68 years, range: 38-88 years, 35 B-cell, 1 T-cell, 18 unknown cell type; 32% multiple malignancies). Analysis of familial clustering is performed by comparing tumor prevalence and spectrum in the families with tumor prevalence and spectrum in the population. The computer program DISEASES contains the data of the population-based Basel Cancer Registry (Head: Prof. J.Torthorst). It allows calculations with small numbers by a Markov chain Monte Carlo procedure.

15 (30%) of the probands had one, 6 (11%) had two or more first degree relatives with malignancies. 32 of the 315 first degree relatives were affected.

The following malignancies were overrepresented in first degree relatives at p<0.05: leukemia in female (n=4), breast cancer in male (n=3) and esophageal cancer in male (n=3). Breast cancer (n=4) and lung cancer (n=3) prevalence was not increased.

The leukemia excess among first degree relatives of CLL patients is confirmed. Inherited predispositions also play a role in late onset malignancies. In CLL families the immune system could be genetically deregulated.

TUMOR LYSIS SYNDROME (TLS) IN THE NINETIES
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The incidence and clinical characteristics of TLS were determined in pediatric patients treated on POG #3017, an ongoing aggressive chemotherapy protocol for stage III/IV NHL and B-cell ALL. TLS was defined as (1) need for dialysis, or (2) 20% decrease in GFR plus one or more of the following: Ca >7.5 mg/dl, PO4 >5.5 mg/dl, symptomatic fluid overload (eg respiratory distress) and hyperkalemia requiring therapy. Data was analyzed from the first 98 patients registered with sufficient information to determine TLS. 40 patients received allopurinol, hydration, and alkalinization to prevent TLS. Results: Patients with TLS had significantly higher initial uric acid levels than those without TLS (10.4±4.4 mg/dl vs. 8.1±3.4 mg/dl), however 11 patients with initial levels >10mg/dl did not have TLS. Initial LDH values were also significantly higher in the TLS group. Overall 25 patients (26%) had TLS (23/81 NHL, and 2/17 B-ALL). Fourteen were dialyzed. TLS most often began between hours 24-72 following initial chemotherapy. Clinical problems associated with TLS included: respiratory failure or distress 45%, hypotension 28%, seizures/encephalopathy 20%, lethargy 12% cardiac arrhythmias 8% and hypotension 8%. The single fatality was due to cardiac arrhythmia caused by electrolyte imbalance. We conclude (1) TLS remains a frequent problem in Stage III/IV NHL (28% on this protocol), (2) Symptomatic electrolyte abnormalities are not common, but can be severe enough to cause sudden death, (3) Fluid overload, resulting in respiratory distress/failure, hypertension and other problems is responsible for much of the morbidity associated with TLS.
Risk Factors for Disease Progression in Early Stage Chronic Lymphocytic Leukemia (CLL).

Patients with CLL Binet stage A/Rai stage 0-II represent a heterogeneous group regarding disease progression. Given the increasing number of treatment options, better risk assessment strategies are highly desired.

Therefore we evaluated risk factors in 122 previously untreated patients from 7 institutions. Diagnosis of disease progression was made according to the NCI CLL working group criteria. A multivariate stepwise forward regression analysis (Cox model) was performed to determine the relevant parameters for disease progression.

Median time to disease progression was 31 months. 63 patients had disease progression. The following parameters which were of significant value in a univariate model were tested: serum thymidine kinase (S-TK), β₂-microglobulin, LDH, presence of enlarged lymph node (LN), Rai stage, time from diagnosis to study entry, leucocyte (LEU), lymphocytes and platelet count, lymphocyte doubling time and hemoglobin. The Cox analysis demonstrated that three parameters contained all relevant prognostic information (p < 0.0001): 1. S-TK levels ≥ 7.1 U/L, 2. LN, 3. LEU ≥ 75 100/μl. S-TK levels ≥ 7.1 U/L identified a patient group which was likely to progress within nine months.

Within CLL/Binet Stage A factors like serum thymidine kinase, presence of enlarged lymph nodes and leucocyte counts may predict early disease progression.

Analysis by fluorescence in situ hybridisation (FISH) of a partial duplication of chromosome 12 in chronic lymphocytic leukemia

Trisomy 12 is the most common cytogenetic abnormality in chronic lymphocytic leukemia (CLL) and it is found in about one-third of cases with normal metaphases on cytogenetic analysis. Trisomy 12 is associated with a poor prognosis and with atypical CLL morphology. The mechanism for the biological effect of trisomy 12 in lymphoproliferative disease is still not clear.

We describe a patient with CLL (according to the Kiel classification a polymorphic immunocytoma) where trisomy of chromosome 12 was shown by Southern blot analysis at diagnosis. Cytogenetic analysis showed a complex karyotype but trisomy 12 was not found. Complete remission was achieved after intensive chemotherapy and autologous bone marrow transplant but the patient soon had an aggressive relapse. Cytogenetic analysis after relapse revealed that the malignant clone now included a partial duplication of chromosome 12.

Metaphases after relapse were analysed by fluorescence in situ hybridisation (FISH). FISH with whole painting chromosome 12 probe confirmed that the duplicated segment was made up of material from this chromosome. Analysis with cosmids clones covering different regions along chromosome 12 showed that three cosmids from q13.1 to q14.3 were repeated three times on the duplicated segment giving rise to 5 copies of this chromosome segment in the leukemic cells. These data indicate that 12(q13.1-1q4.3) harbours a gene of importance for leukemia development.
GLYOSAMINOGLYCANS (GAGS) OF LYMPHOCYTES IN B-CLL

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GAGs of lymphoid cells are known to play important roles in immunity by taking part in antigen presentation, B- and T-cell cooperation, their homing and proliferation, storage of substances with cytotoxic activity. GAGs in lymphoproliferative disorders are poorly investigated. We studied the content and composition of GAGs in lymphocytes of 60 patients with CLL. GAGs were isolated from acetic-dried cells after deproteination by papain and TCA treatment and were analysed using electrophoresis on cellulose acetate, enzimatic and HNO2 treatment. In most patients they were represented by very homogenous, high charge chondroitin sulphate (CS), its undersulfated forms were practically absent. In 25% of patients traces of heparin substances were revealed too. In addition to this fractions, a major unidentified polydispersed glycoconjugate and a minor component, susceptible to chondroitinase ABC treatment were found. Comparison of GAGs electrophoretic patterns of leukemic cells with those of lymphocytes from normal peripheral blood, thymus, spleen and tonsils revealed some similarities with the latter. In 15% of patients, lymphocytes displayed another electrophoretic patterns (polydispersed CS, presence of its low charge fraction etc.), which as a rule were associated with a severe course of the disease and poor response to therapy. GAG content of lymphocytes in CLL was usually no more than 10 g uronic acid/100 mg of dried cells.

11. CLL

RISK OF HEPATITIS C VIRUS INFECTION, WALDENSTROM’S MACROGLOBULINEMIA AND MONOCLONAL GAMMAPATHIES.

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We have recently determined the prevalence of hepatitis C virus (HCV) infection among patients with lymphoproliferative disorders and showed that the relative risk (RR) of being infected is increased only in a subgroup of B-cell non-Hodgkin’s lymphomas (NHL), the Immunocytomas, which correspond to the pathologic subset of the so called Essential Mixed Cryoglobulinemia. The nature of the risk remains unknown, as the same population including in this new analysis only the cases with a Monoclonal Gammapathy (MG) (70 NHL and 81 Multiple Myelomas), and extended our study to 180 cases of MG of unknown significance (MGUS) observed at our Institution in the last 2 years. HCV infection was investigated through determination of anti-HCV antibodies (Ab) (by EIA and RIBA) and HCV-RNA (by RT-PCR). Cryoglobulins (cryoglob) were sought in all as previously described. The risk of being infected by HCV was compared to that of the general population of our area (prevalence of 2.87%). Overall, 24 (7%) cases of HCV infection were detected out of 331 cases of MG: 2/13 (1.6%) G, 2/7 (2.9%) G, 1/16 (6%) A, 1/4 (4%) MK, 1/2 (50%) MK type I cryoglob and 17/17 (100%) MK type II cryoglob. The RR of infection was increased only in the group of MK type II cryoglob (RR: 17.88; P < 0.0001). The pathogenic subtypes of HCV-positive cases were: 3 MGUS (2 G and 1 MK); 3 Multiple Myelomas (2 G and 1 A); 1 Centroblastic/Centrocytic follicular lymphoma (1 MK type II cryoglob); 4 Centroblastic lymphomas (4 MK type II cryoglob); and 13 Immunocytomas (1 MK type I and 12 MK type II cryoglob). This study shows that in MG without cryoglobulinemia activity the prevalence of HCV infection is low, comparable to that of the general population. On the contrary, if a cryoglob is detected, the prevalence of HCV infection approaches the 100% (with 100% of our patients of this group being HCV-RNA positive). This is true also for patients with Waldenstrom’s Macroglobulinemia: 2/20 HCV-positive if bearing a cryoglob; 18/20 HCV- negative (both Ab and RNA) if bearing a non-cry-cry MK or MA component. Our overall data confirm the association between HCV infection and MG with cryoglobulinemia activity. This relation does not seem to exist with the MG without cryoglobulinemia activity, such as MGUS, Multiple Myeloma and Waldenstrom’s Macroglobulinemia.
A comparison between two hour i.v. infusion of 2-chlorodeoxyadenosine (2-CDA) for 5 days and continuous infusion for seven days in the treatment of hairy-cell leukemia showed the same result and no significant difference in efficacy and toxicity in a study carried out by the Italian Cooperative Group for the study of HCL (ICGCHL).


Since March 1994 we have been treating two groups of patients with probel HCL.

One group of 21 pts. have been treated with a single cycle of 2-CDA given as a 2-hours i.v. infusion on 5 consecutive days in a dosage of 0.15 mg/kg/day while a second group of 19 pts. has been treated with continuous infusion of 0.10 mg/kg/day for 7 consecutive days. The first group consisted of 17 males and 4 females, median age 51 yr (range 23-86yrs.). Sixteen pts. were pre-treated (1 splenectomy, 6 splenectomy + IFN, 8 IFN, 1 IFN + DCF) and five were not previously treated. The second group consists of 17 males and 2 females, median age 49 yrs. (range 33-74 yrs.). Thirteen pts. were pre-treated (3 splenectomy + IFN, 10 IFN) and six were not previously treated. Response criteria were those proposed by the NCI (CR, GPR, PR, SD e DP).

In the first group 17 p were evaluable at 3 months (4 CR, 5 GPR, 4 PR, 1 SD, 1 DP) and 16 at 6 months (7 CR, 3 GPR, 4 PR, 1 SD, 1 Severe aplastic anemia). Patient performance status (ECOG) was 0-1 in 16 pts and 2-3 in 5 pts. According to WHO criteria, toxicity was 0 in 16 patients, 1 in 1 patient (nausea) and 2 in 4 pts (1 general fatigue, 2 infection, 1 respiratory distress). In the second group 15 pts. were evaluable at 3 months (6 CR, 5 PR, 4 SD) and 15 at 6 months (4 CR, 5 GPR, 1 PR, 4 SD, 1 DP) and the performance status was 0-1 in all patients. Toxicity was 0 in 14 pts. 1 in 1 patient (fever), 2 in 1 patient (nausea). From a comparison of the two responses in both treatment groups it appears that the response rate improves from 39% in the first two treatment schedules Obviously the number of pts. studied is inadequate and a more precise evaluation will require a longer follow up period. However, a 3 day schedule would be less expensive and provide the possibility of one-patient treatment.

FLUDARABINE AND EPIRubicin in the Treatment of CLL as First Line Therapy or In First Relapse. PREDILMINary Results of a Phase-II STUDY L. Bergman (1), M. Rummel (1), A. Knoth (2), H. Riedke (3), D. Hoeft (1), P. S. Mitrov (1), J. W. Goethe-University Hospital, Medical Clinic III, Hematology, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany; (2) Nordwest Hospital Frankfurt; (3) Universital Hospital Wurzburg

Fludarabine has been reported to be an effective treatment in previously treated chronic lymphocytic leukemia (CLL). Based on in vitro synergism of fludarabine with anthracyclines and on recently reported results showing a higher efficacy of CHOIP against COP it seems to be advisable to try a combination of fludarabine and an anthracycline to improve response rate as well as long-term results. Aim of the multicenter-study is to evaluate the rate and duration of response and to assess toxicity and immunological effects of fludarabine and epirubicin in treatment of CLL in stages Binet B and C as a first line therapy or in first relapse.

Treatment schedule: fludarabine 25 mg/m² day 1-5, epirubicin 25 mg/m² day 4-5, for a maximum of six cycles every 6 weeks. 22 patients entered the study. 10 pts. are evaluable for response, 12 pts still under treatment. All 10 evaluable pts. responded to fludarabine/epirubicin.

The results so far show, that the combination of fludarabine and epirubicin is highly effective in the treatment of CLL. Due to the addition of epirubicin to fludarabine it seems to be possible to reach a higher response rate and a more rapid response especially of nodal manifestations of the CLL. The immunoglobulin levels increased significantly with the following median values (mg/dl) after and after therapy: IgG before: 887 after: 1138, IgM: 107 after: 143, IgA: 54 after therapy: Nodularity grade 3 occurred in 10 of 12 evaluable cycles, grade 4 occurred in 5 cycles. Grade 3 or 4 of thrombocytopenia or anemia did not occur. CD4-lymphocytes decreased in every case with a median of 135/μl before treatment to 292/μl after cessation of therapy. infections: 2 respiratory infections. Other side effects were not observed. The first cycle should be performed in the ward to monitor an eventual tumour lysis syndrome. Summary: Because of its mild toxicity the presented regimen can be administered in an outpatient facility with the exception of the first cycle. It is effective in untreated pts. or in first relapse. From the preliminary results the combination of fludarabine and epirubicin appears to be a highly effective treatment of CLL. The long-term immunosuppressive effect and its consequences are not evaluable so far and nor is remission duration.

FLUDARABINE, MITOXANTRONE AND DEXAMETHASONE (FND) IN REFRACTORY LYMPHOPROLIFERATIVE DISORDERS

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15 patients with refractory lymphoproliferative disorders, 8 with low grade non Hodgkin lymphoma (LGLNH) and 6 with polyclonid lymphocytic leukemia (PL), were treated with a combination chemotherapy regimen consisting of fludarabine (25 mg/m² i.v. day 1 to 3), mitoxantrone 10 mg/m² L.v. day 1 and dexamethasone (20 mg i.m. day 1 to 5). The planning was to administer 6 cycles with interval of 21 days. There were 8 males and 7 females. The median age was 54 (range 39-63) and all patients have been pretreated with 2 lines of chemotherapy at least. All were enroled in the setting of refractory disease. Among patients with LGLNH, 6 had bone marrow involvement, 6 had bulky disease; extranodal disease was observed in 3 cases. All patients with PL were in stage 4 according to Rai staging system and all had massive splenomegaly. Median LDH value was 560 (range 235-875), median serum PCR was 15.3 (range 2.7-29.5). 13 patients are evaluable at the time of writing. The median number of cycles administered was 4 (3-5) and in all cases the treatment was administered in an outpatient setting. Complete remission (CR) was achieved in 5 cases (38 %), while 4 patients (31%) achieved partial response (PR) for an overall response rate of 69 %. Among responders 5 patients had LGLNH and 3 PL.There was one death due to infection in a non responding patient in the setting of refractory disease. Toxicity was low and mainly hematologic; in particular, 4 patients experienced WHO grade 3 neutropenia and received G-CSF and in 3 cases (all with bone marrow involvement and anemia at the beginning of the treatment) packed red cells support was needed. In 4 cases a delay in the administration of the cycles was necessary because of neutropenia. Extranodal toxicity was virtually absent (in no patient we observed grade 4 or 5 toxicity). The median duration of response was 7 months (range 4-11). We conclude that the FND combination is an effective treatment for refractory lymphoproliferative disorders with low toxicity also in cases of patients heavily pretreated and should be probably investigated as frontline therapy in advanced stages of low grade lymphoproliferative disorders.

Conclusion: The present data show that the ...sbe evaluated the two models of administration have similar therapeutic efficacy.
COMPLETE REMISSION OF SINGLE-DOSE CLADRIBINE THERAPY OF HAIRY CELL LEUKEMIA. Gunnar Julisson, Anders Räflund, Carl-Magnus Stöltz, and Jan Lillemark. Department of Hematology, University Hospital Linköping; and Medicine, Borås Hospital; Oncology and Pharmacology, Karolinska Hospital, Stockholm, Sweden.

We have previously shown that cladribine (2-CDA) 2 mg/m² daily for 7 days is an effective therapy as standard dose (3.4 mg/m²/day for 7 days) for symptomatic hairy cell leukemia, whereas 1 mg/m²/day for 7 days was ineffective. We have also shown a prolonged retention of phosphorylated active metabolites within leukemic cells in vivo, with a half-life of 30 hours. It seemed thus possible to achieve the required therapeutic plasma AUC of cladribine with a single dose. We chose to evaluate the clinical response to the total dose of the 2 mg/m²/day x 7 schedule, i.e., 14 mg/m², given as a single 2-hour intravenous infusion to four previously untreated patients with hairy cell leukemia. AUC of cladribine in plasma was evaluated and compared to calculated total AUC per course from studies of other regimens.

Two of four patients achieved ongoing complete remission with durations of 18 and 10 months. Flow cytometry identified 0.2% and 1.3% residual CD103-positive bone marrow cells, respectively. One patient had minor response with normalized platelets and improved granulocytes, and achieved full response from another course of cladribine at standard dose. The fourth patient had a reduction of bone marrow hairy cells from 47% to 12%, but no improvement of cytopenia. A second course (2 mg/m²/day x 7) resulted in a minor response. No patient had fever or signs of infection. AUC per course was 167 ± 265 μmol/L/hr (14 mg/m², n = 4), 233 ± 28 μmol/L/hr (2 mg/m², n = 7), and 414 ± 163 μmol/L/hr (3.4 mg/m², n = 6).

Single-dose cladribine therapy of HCL seems feasible, but a somewhat higher dose might improve the therapeutic results with acceptable toxicity.


Series of MM including very old pts are rarely reported. Little is known about the specific management of these populations. We report herein clinical and biological profiles and our management policy about 15 pts older than 80 at diagnosis of symptomatic stages I, and stage II or III of MM. Asymptomatic stage I and MGUS were excluded. They were 8 men and 7 women. The mean age was 85.2 years (range: 80-92). Circumstances of diagnosis were: bone pain (especially of the lumbar region); 7 pts, general status deterioration; 3 pts, anemia; 2, acute renal insufficiency; 1, pneumonia; 1, visual symptoms. 1 important comorbidity was noted in 8 cases including severe cardiovascular problems (3 cases), past medical history of malignancy (2) and gastric ulcers plus uremic psychiatric disorder (1). Three pts were in stage I with severe bone pain, one in stage II, 5 in stage IIIA and 6 in IIIB. The type of monoclonal component was: Ig G: 10 pts, Ig A: 3, or light chains: 2. Bm was elevated in 10 cases as was CRP in 5 pts. Management of the disease included chemotherapy (CT) with Alexanian's regimen at least one day i.v. melphalan + steroids for 9 pts or VMCPer, VRBP for 3 pts both distributed in the out-patient unit. CT was still given at the time of plateau achievement but cycles periodicity was increased with variable frequency with the aim to promote a regular activity on the malignant clone. Clinical or X-ray bone symptomatic pts received bisphosphonates (mainly pamidronate) at each cycle of CT. Use of antibiotics was systematic for febrile or respiratory episodes. In spite of these low aggressive regimens, chemotherapy design was difficult to apply in a significant subset of pts. Bone events as fractures, hypercalcemia or pain were extremely less frequent than in our historical controls treated before bisphosphonates era. In addition, prolonged hospitalizations were rare preserving a good quality of life (QOL). Six pts have died at (1 shock), 6 (sepsis), 18 (7), 22 (9) (sepsis), 19 (cardiac rupture) and 71 months (probable alkylating-related AML/MDS) from diagnosis. The other pts are alive and well after a mean follow-up of 26.6 months (range: 4-53).

These results are very satisfactory considering high age, and clinical and biological data at diagnosis. In our opinion, regular pressure on the disease represents the main key of MM management in very old pts preventing or differing symptoms development which is synergistic with QOL deterioration, hospitalization, morbidity or mortality. The leukemic risk induced by prolonged alkylating exposure does not represent here a crucial issue as in younger pts. Role of bisphosphonates appears fundamental as shown by some recent reports. More extensive studies are of course necessary to confirm these preliminary data.


The median survival of ATL patients (pts) of acute and lymphoma types is only 8 months by current combination chemotherapies. New agents are thus needed for the treatment of this disease. Cladribine (2-chlorodeoxyadenosine; 2-CDA) is a purine analogue with definitive clinical activity against hairy cell leukemia (HCL), B- chronic lymphocytic leukemia (B-CLL), cutaneous T-cell lymphoma (CTCL) and indolent lymphomas. To establish a new effective treatment of ATL, we initiated a clinical trial of 2-CDA in Japan. A phase I and pharmacological study was conducted with a schedule of 7-day continuous IV infusion every 28 days up to a maximum of 3 cycles. We defined dose-limiting toxicity (DLT) as grade 4 hematologic and/or grade 3 or more non-hematologic toxicities. Between May and October in 1995, we enrolled 16 previously untreated pts (6 males and 4 females; 45-73 years old) with follicular small cleaved cell lymphoma (1), follicular mixed lymphoma (3), mantle cell lymphoma (MCL) (2), B-CLL (1), ATL (1) and CTCL (2). No DLT was observed in 3 pts who received 0.06 mg/kg (Level 1). In 7 pts receiving 0.09 mg/kg (Level 2), 1 pt developed grade 4 pulmonary toxicity and grade 4 thrombocytopenia at the third cycle, and another developed grade 4 neutropenia after the first cycle. Neurotoxicity and serious infectious complications were not observed. Of the 7 pts who were treated at Level 2, 1 CTCL attained complete remission, 1 MCL and 1 B-CLL partial remission (PR), and 1 ATL of acute type showed marked reduction of leukemic cells and lymph nodes (PR). Dose of 2-CDA was not escalated further. Plasma concentrations of 2-CDA were measured by a newly-developed method of liquid chromatography-mass spectrometry (LCMS). A pharmacokinetic analysis in 7 pts without leukemic cells showed that their area under the concentration versus time curve (AUC) of plasma 2-CDA at Level 1 (n=3) and Level 2 (n=4) were 2660 ± 3075 nmol x h and 3418 ± 3395 nmol x h, respectively, suggesting a dose-dependent increase of AUC. In conclusion, the recommended phase II dose of 2-CDA (0.09 mg/kg) as a 7-day continuous IV in US pts can be safely administered to Japanese pts. The encouraging result in an ATL patient prompted us to plan a subsequent phase II study, in addition to those for HCL and indolent lymphomas.


Between June 1991 and December 1993 a total of 72 consecutive patients with untreated Multiple Myeloma stage III Durie - Salmon (D.S.) were treated with melphalan 0.25 mg/kg and prednison 100 mg/day (M.P.) on days 1-4 at 6 weeks intervals during induction (minimum 8 courses) and after relapse. Interferon-Alpha2a was added in a dose of 9 MU x 3 for week from the start of treatment through response, plateau phase and response relapse. The response rate was 45 % and the response duration (for patients with at least a PR) was of 21 months. Toxicity was not important. This management did not reveal any advantage in response rate or survival by the use of IFN concomitant with M.P. However, the results show a prolongation of relapse-free survival after achievement of response or plateau phase.
FLUDARABINE FOR THE TREATMENT OF ESSENTIAL MIXED CRYOGLYCOSAEMIA
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The new purine analogue Fludarabine monophosphate (Fluda) has offered in the last years a new important tool for the treatment of chronic lymphatic leukemia and low-grade non-
Hodgkin lymphomas (NHL), including Waldenstrom cryoglobulinaemia, but up to today no studies on Fluda for the treatment of essential cryoglobulinaemia (MC) have been reported. We have treated with Fluda 4 patients with typical clinical and laboratoristic features of MC and with a documented low-grade NHL infiltration in the bone marrow biopsy. Table 1 summarizes patients data.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Monoclonal component</th>
<th>Type II cryo</th>
<th>HCV genotype</th>
<th>BM NHL infiltration</th>
<th>Organ involvement</th>
</tr>
</thead>
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<tr>
<td>D.P.</td>
<td>M</td>
<td>40</td>
<td>IgM K</td>
<td>700 mg/dl</td>
<td>1 b</td>
<td>+</td>
<td>MPMG</td>
</tr>
<tr>
<td>R.G.</td>
<td>M</td>
<td>47</td>
<td>IgM K</td>
<td>670 mg/dl</td>
<td>2 b</td>
<td>+</td>
<td>MPMG</td>
</tr>
<tr>
<td>D.M.</td>
<td>M</td>
<td>59</td>
<td>IgM K</td>
<td>270 mg/dl</td>
<td>1 b</td>
<td>+</td>
<td>CH</td>
</tr>
<tr>
<td>M.B.</td>
<td>M</td>
<td>69</td>
<td>IgM K</td>
<td>+ (not quantified)</td>
<td>1 b</td>
<td>+</td>
<td>CH</td>
</tr>
</tbody>
</table>

MPMG: membranoproliferative glomerulonephritis; CH: chronic hepatitis

All of them were previously treated with Interferon-α-2b (IFN) for 6 to 10 months, being resistant; two of them had also received treatment with alkylating agents, without any improvement. In each patient were documented: a cryoprecipitable monoclonal component of IgM K type with reitumid factor activity (Type II cryo); HCV Ab (by EIA and RIBA) and RNA (by RT-PCR); the presence of a low grade lymphoid proliferation (immunocytoma) in the bone marrow (BM); Fluda, 25 mg/m² daily, was administered for 5 consecutive days every 28 days for 2 cycles (two patients), 4 cycles (one patient) and 6 cycles (one patient). Clinical and laboratory (liver and renal function tests, total immunoglobulins and cryoglobulins) parameters of response were evaluated during Fluda therapy with monthly physical examination and blood sampling. In no patients any clinical or laboratoristic improvement of MC during and after Fluda therapy was observed. This data, even if preliminary and on a small sample, seem to indicate that Fluda is not effective in the treatment of MC, at least in the cases previously resistant to IFN and alkylating agents. Since Fluda has already been shown to be more effective in previously untreated low-grade NHL patients, a trial should be undertaken to test Fluda in untreated MC.

A PHASE-I/II STUDY OF IDARUBICIN, DEXAMETHASONE AND INTERFERON-α2a IN PATIENTS WITH ADVANCED MULTIPLE MYELOMA

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Idarubicin (Ida) is a new anthracycline with high activity against multiple myeloma (MM) in experimental systems. In this ongoing phase-I/II study we are evaluating the maximal tolerated dose (MTD), efficacy, and toxicity of Ida in combination with Dexamethasone (1 - Dexa) in patients with relapsed or refractory MM. Here we report our results of the first 20 patients with histologically confirmed advanced MM. There were 11 males and 9 females. The mean age was 62 years (range 49-75). All patients had failed to respond to first line therapy with Melphalan/Prednisone. Treatment consisted of up to six cycles of Ida (Day 1; i.v.) and Dexamethasone (20 mg; p.o.; days 2-5 and 11-14). Ida doses were 5 mg/m² (4 pts) and 7.5 mg/m² (16 pts). In total, 87 courses were administered. Toxicity was generally mild with WHO grade III and IV thrombocytopenia in 4 courses (5%), grade IV anemia in 2 courses (2%), and grade III leukopenia in 1 course (1%), respectively. One patient had a treatment-related pneumonia requiring i.v. antibiotics, one patient died because of relapsed pneumonia and cardiomegaly. 6/17 evaluable pts. achieved a partial response (PR) after 4-6 cycles of 1 - Dexa; 6 pts. had no changes, 5 pts. progressed. All pts. with PR received IFN-maintenance (3x10⁶IU/day s.c., three times weekly), 4 pts. relapsed after 3-16 months (mean 8.8 months). The MTD for Ida was estimated with 7.5 mg/m². I - Dexa might be an effective new regimen for the treatment of relapsed MM and enrollment continues.

EXTRAEMULDIARY PLASMACYTOMA: PRESENTING FEATURES, RESPONSE TO THERAPY, AND SURVIVAL IN A SERIES OF 46 CASES.


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Extramedullary Plasmacytoma (EMP) is an uncommon plasmacellular dyscrasia, which constitutes less than 5% of all plasma cell malignancies. Forty-six patients with EMP diagnosed between August 1968 and June 1993 were carefully evaluated. Average observation time was 84 months (range 12-280). The average age at diagnosis was 55 (range 16-80) years; in 14 cases (30%) it was less than 50. The disorder was about twice more common in males than females. Ten (21%) patients presented a monoclonal component. The disease mostly involved the upper air passages (37/46, 80%), and 8 (17%) demonstrated dissemination of disease to contiguous sites. Other localizations were lymphnodes, thyroid, skin, stomach, and brain. The clinical symptoms were lymphnodes, thyroid, skin, stomach, and brain. The therapeutic strategy applied varied in the different institutions: surgery, radiotherapy, chemotherapy, or an association of the three. However, the most frequent form of treatment was local irradiation. The median dose of radiotherapy was 45 Gy (range 30-60). The classical Melphalan + Steroid regime was given to those patients (11/21) treated with chemotherapy. Thirty-nine patients (85%) achieved complete remission (CR), partial remission (PR) was obtained in 5 (11%) cases, and 2 (4%) did not respond to therapy (NR). Local recurrence (LR) or recurrence at other sites (ROS) occurred in 8.5 and 3 cases, respectively. Frequently, in these patients a second CR was obtained by radiotherapy. Seventen patients (15%) developed widespread disease, characterized by "metastatic" diffusion, in the absence of bone marrow plasmacytosis and urinary or plasma M-component. Long term survival at 15 years was observed in 80%. The data obtained from this review of a relatively large series of patients, confirm the good prognosis and curability of EMP through the use of an adequate local therapy, irradiation and surgical treatment of the treatment of essential mixed cryoglobulinaemia. In view of the absence of bone marrow plasmacytosis and relative young age, patients could benefit from autologous bone marrow transplant.