4. Pediatric Lymphomas

Experience in Venezuela with the LMB-89 Protocol (French Pediatric Oncology Society) in Childhood B Cell Lymphoma.


Introduction: From 1995 to 1998 we treated 31 pts with the LMB-89 Protocol. We included only B-cell malignancies (small cleaved and non cleaved types and B-large cell lymphoma).

Material and Methods: Mean age was 16 years (range 2 to 16). 25 were male. Pts classification was: small cell non-Burkitt (20 pts, 65%), B large cell lymphoma (5 pts, 25%), Burkitt type (3 pts, 9%). Among pts, disease-free status (DFS) was present in 9 pts (29%). LDH levels < 500 u/l were found in 14 yrs (44%), of whom had bulky disease. Treatment was related to the risk group. Group A: 2 pts (6%) (consisted of restated Group I st and abdominal ST II) received only 2 chemotherapy courses (COPAD) without CNS prophylaxis. Group B: 25 pts (81%) (included other ST II--II), received 5 courses (COPADIM 1-2, CYM 2-1, maintenance 1-4) during 4 months. None had bone marrow involvement in this group. Group C: 4 pts (13%) with bone involvement, and CNS infiltration were treated similarly as group B, but consolidation included 2 CYVE cycles performed with HA-Dara and VP16. CNS treatment was performed with HD MTX (Bg/m^2), HA Dara-C, and triple intrathecal injections. No cranial irradiation was given. Maintenance cycles were performed later 7 months. Results: Mean follow-up was 25 months (range 1-63). Four group B pts had treatment failures: 1 died due to inesoviol perforation after COP, 2 pts disease progression during consolidation (1 died, 1 switched to Group C treatment, having complete remission), and 1 pt relapsed and died 4 months after finishing the whole protocol. In addition, 1 group C pt relapsed and died at 8 months. Over-all survival was 85%, and event-free survival 79% at 16 months for the whole series. Conclusions: In our initial experience with LMB-89 protocol we obtained moderate toxicity and almost similar results as previously reported.

MANGANESE SUPEROXIDE DISMUTASE LEVELS IN PAEDIATRIC MALIGNANCIES

E. Unal, S. Gülaboğlu, E. Babacan, G. Yarav, N. Tagyıldız, S. Aksel, S. Cin, A.O. Çavdar

Dept of Paediatrics, Division of Paediatric Oncology, Haematology and Immunology, School of Medicine, University of Ankara, Ankara-TURKEY

Superoxide dismutases (SODs) are currently of interest in oncology and immunology, as they perform the essential defense against oxygen toxicity. Strong evidence has been presented that many of the cell alterations in cancer are due to oxidative damage from active oxygen species. Human cells contain two forms of SOD with different immunological specificities. One is a manganese containing SOD (Mn-SOD), which is principally present in mitochondria. Regulation of mitochondrial and/or cytosolic oxygen intermediates in mammalian cells might be modulated by the Mn-2 gene product. It has been suggested that the Mn-2 gene product inhibits apoptosis by interacting with mitochondrial SOD. Serum Mn-SOD levels were determined in 21 biopsy proven metastatic Hodgkin's patients and in 25 newly diagnosed acute leukemia cases, both in active disease and in remission. The Hodgkin's Lymphoma group consisted of 14 males and 7 females with an age range of 3.5-16 years (median 8 yrs), while the newly diagnosed acute leukemia group (30 ALL, 5 AML), including 14 males and 11 females with an age range of 1.5-12 years (median 6 yrs). Twenty-two age matched healthy children were used as controls. A sandwich enzyme immunoassay was used for enzyme measurements. Serum Mn-SOD levels in Hodgkin's patients with active disease (340±94 ng/ml) were significantly high compared to remission (165±65.5 ng/ml) and control groups (76±130.1 ng/ml) (p<0.001). In leukemia group serum Mn-SOD levels were found to be significantly high (322±118.4 ng/ml) in newly diagnosed patients as compared to remission (182±143.1 ng/ml) and controls (76±130.1 ng/ml) (p<0.001). Disease activity was accompanied by an increase of the enzyme level and regression of the disease by a decrease in the serum level of Mn-SOD. The role of Mn-SOD in the pathogenesis of malignancies is not known although serum levels of the enzyme were found to correlate with malignant potential of some leukemias. Increased expression of mitochondrial SOD has been found to play a central role in protecting various cell types, including tumor cells from the lethal effects of IFN and TNF, modifying immune responses, certain anticancer drugs and ionizing radiation. Measurement of serum manganese containing SOD levels seems to be promising as a prognostic tool and assessment of changes of the tissue enzyme expressions will likely provide insight into the biochemical process involved in carcinogenesis

This study was supported by Turkish Research Council (TUBITAK).

MEDIASTINAL NON-HODGKIN'S LYMPHOMAS (NHL) IN CHILDREN OF KYRGYZSTAN

D.O. Baitzakova

Kyrgyz Research Institute of Oncology & Radiobiology, Bishkek, Kyrgyzstan

Introduction: In Kyrgyzstan, the majority of non-Hodgkin lymphoma involve the mediastinum (30.1%). The purpose of our research was to study the clinical course of mediastinal NHL in children and evaluation of treatment outcomes.

Materials and methods: We observed the mediastinal involvement in 43 (30.1%) NHL patients: 32 boys and 11 girls. An average age of patients was 9 years 6 months. Histology findings showed a lymphoblastic type, cytomorphoscopy - L1 - 18%, L2 - 25%, T-phenotype of tumor cells was diagnosed in 93.7%, and B-phenotype in 6.3%. All the patients received the intensive therapy: Group I - COPA, COPAD (25 patients) and Group II - HDM-90 (18). According to S. Murphy, in 21 (48.8%) patients had Stage III and in 22 (51.2%) Stage IV.

Results: The evidence of intensive symptoms was observed in 92.8%, "biological activity" in 91%. The mediastinal diameter in 30 patients (69.8%) exceeded more than 10 cm, (39.5%) patients demonstrated symptoms of anterior stem lymph nodes enlargement, involvement of lung roots in 11 (25.6%), that of pleura, in 24 (55.8%), bone marrow, in 22 (55%), and central nervous system, in 6 (10%). Thirty-two (74.4%) patients achieved a complete remission 11 (25.6%) did not achieve an effect.

Conclusion: Intensive chemotherapy protocols significantly improve the achievement of the complete remission and survival even in Stage III or IV mediastinal non-Hodgkin's lymphomas - the largest childhood NHL group in Kyrgyzstan.

The Profile Of Pediatric Intestinal Non Hodgkin'S Lymphoma NHL in NEMROCK, EGYPT A Single Institute Experience (1985-1997)

L, Sedky

Kasr El Einy Center of Clinical Oncology, Pediatric Oncology Unit, Cairo University Hospitals, (NEMROCK)

Objective: Between 1985 and 1997, 210 children with non hodgkin's lymphoma (NHL) were referred to (NEMROCK). Abdomen was the primary site in 74 patients (34%). This retrospective study reviewed the clinical profile and the therapeutic outcome in 51 evaluable cases, as well as analysis of the problems and obstacles in recruiting patients.

Materials: The group included 55 males and 19 females, aged 2.5 to 18 years (mean 6.6). According to the classification, stage II was recorded in 35 patients, (47%), stage III : 31 patients (42%) and stage IV : 9 patients (11%). Histologically 50% of the cases had small non cleaved (SNC) subtype, 29% had diffuse large (DL) type, and 29% had both diffuse small (DS) and diffuse mixed (DM) type. The small intestine especially the ileum was the main site of involvement in 70% of patients, Bone marrow (BM) was invaded in 6 cases and CNS in 3 patients. Complete gross resection was performed in 35 (45%) cases. During the study period 2 different dose levels of the COMP regimen were used: Standard low dose regimes (1985-1989) and short duration high dose regimen (1990-1997).

Results: Fifty one cases were evaluable, complete remission (CR) was achieved in 39 patients (76.4%), in favor of the high dose regimen (P=0.05). Relapses (n=10) during the first year. At a median follow up period of 64 months (range 12 - 120 months), the actuarial 10y survival and event- free survival rates were calculated by the Kaplan Meier method. The major events were: loss to follow up (28%) especially during the early phase of the study and lack of compliance because of the parents.

Conclusion: High dose COMP is an effective modality in the treatment of abdominal NHL. The significantly poor prognostic factors were: bulky disease (P<0.0001), stage (p=0.01) and initial CNS involvement (p=0.05).
4. Pediatric Lymphomas

T-CELL-RICH LARGE B-CELL LYMPHOMA (TCRBLCL) IN CHILDREN: REPORT OF FOUR CASES FROM THE CHILDREN'S CANCER GROUP STUDY CCG-5961

M. Longo, M. Cairo, R. Spósito, S. Perkins. Children's Cancer Group, Arcadia, CA

Introduction: TCRBLCL is recognized as a subtype of Diffuse Large B-cell Lymphoma (DLBCL) characterized by neoplastic large B-cells accompanied by an extensive infiltrate of reactive T-cells. TCRBLCL has been reported in adult cases, but rarely in children. The 4 cases in this report were identified as part of an international cooperative protocol for treatment of mature B-cell lymphoma/leukemia (FAB LMB 96 Treatment of Mature B-Cell Lymphoma/Leukemia: A SFOP LMB 96/CCG-5661/UKCCSG NHL 9600 Cooperative Study).

Methods: Cases in this report were derived from the CCG arm of the study. This protocol required a diagnosis of B-lineage lymphoma by the Revised European-American Lymphoma Classification and a history of Burkitt's lymphoma (including ALL-L3; high-grade non-Hodgkin lymphoma, Burkitt-like; and DLBCL [excluding anaplastic large cell lymphoma]). Patients underwent standard clinical examinations, staging procedures (radiology exams), bone marrow (BM) and cerebrospinal fluid (CSF) exams, and lab tests - including lactate dehydrogenase (LDH). Cases underwent central pathology review including immunophenotypic studies.

Results: Of 84 cases reviewed to date on the CCG arm, 18 were classified as DLBCL including 4 as TCRBLCL. Three TCRBLCL cases were initially favorably as mixed cellularity Hodgkin's disease (MCHD). Clinical features included: age range 12-16 years, males (4), B symptoms (3), I. LDH (0), Murphy Stage III (3), BM (0), CSF (0). Histologic features: CD20+, negative for CD5, CD10, CD23, 23%, while negative for CD3, CD8, HMB-45, and LMP-1.

Conclusions: In this protocol, pathology review identified 4 cases of TCRBLCL representing 22% of DLBCL's. Clinical features of TCRBLCL include frequent high Murphy stage disease without BM or CSF involvement, similar to other childhood large cell lymphomas. Immunophenotypic features of TCRBLCL may frequently be confused with MCHD, and immunophenotyping in paraffin sections is essential to identify TCRBLCL. TCRBLCL may be an underrecognized type of DLBCL in children.

HIGH-GRADE B LYMPHOLASTIC LYMPHOMA IN HUMAN IMMUNODEFICIENCY VIRUS (HIV)-INFECTED CHILDREN: TWO CASE REPORTS


Istituto Nazionale Tumori Milano, *Clinica Pediatrica IV Milano University.

Introduction: The increasing number of HIV-infected related malignancies in children poses a serious issue of treatment and clinical outcome as well. We describe our experience with two pediatric cases.

Methods and Results. Case 1: A 12-year-old boy, HIV-infected when aged 7 (AIDS stage A3) and with normal blood transfusions during the course of B-homopemia; in June 1990 diagnosis of B lympholastic lymphoma (stage IA) by St. Jude's staging System, with blood markers documenting acute EBV infection. He was started on the induction-phase of chemotherapy (CT) with VCR, CTX, PRED, HD-MTX and ADR, followed by maintenance with 6MP/MTX, 2G/ARA-C, and reinductions with VCR/CTX/ADR. Throughout CT he received AZT for HIV infection, antibiotic prophylaxis for Pneumocystis carinii pneumonia (Pneumocystis because less myelosuppressive) and mycotic infections. CT acute side effects were: WHO grade 4 anemia and granulocytopenia, grade 3 stomatitis, widespread genital HS-2 infection responsive to acyclovir. CD4/CD8 lymphocyte ratio didn't change during CT. Four yrs after the diagnosis of lymphoma in continuous complete remission (CCR) he died of Mycobacterium tuberculosis sepsis. Case 2: A 9-year-old boy developed AIDS (CT) at the age of 7 because of vertically acquired HIV infection. In October 1997 a diagnosis of B immunoblastic lymphoma was made, WF: II, stage IV. EBV-DNA was detected in tumor cells chromosomes. After diagnostic laparotomy he started sequential intensive CT with CTX, HD-MTX, PF16, ADR, VCR, CDDP, ARA-C, and CDX. He was referred for diagnosis to the American Society of Hematopathology (Gasparro M et al in Eur J Cancer 1993:29A:692-8). The spectrum of toxicities was similar to that of HIV-negative children (4 grade thrombocytopenia and granulocytopenia, SIADH due to VCR, grade 2 mucositis). No infectious complications were observed. The ongoing anti-retrovirus therapy with protease and reverse-transcriptase inhibitors was stopped because of liver dysfunction. A 50% dose-reduction of myeloablative CT with Ara-c/CDP is necessary because of myelotoxicity. The patient remains in CCR 1 year after ending treatment.

Conclusion: Feasibility of an intensive chemotherapy regimen for HIV-related infection cancers is suggested by these two cases. The toxicity spectrum - including infections - was similar to that of HIV-negative children. The clinical outcome in $b$ of these patients is related to AIDS rather than lymphoma.

GASTRIC B-CELL LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) IN CHILDREN

M. Malamino, R. Giardino

Istituto Nazionale Tumori, Milan, Italy

Introduction: Of 366 consecutive pediatric pts less than 18 years old with NHL, treated from 1976 to 1998 at this Institute, 109 had exclusive or concomitant lesion within the gastro-intestinal tract. The stomach was primarily involved in 10/109.

Methods: In 3/10, according to the REAL classification, a diagnosis of extranodal marginal-zone lymphoma (B cell lymphoma of MALT type) was made.

Results: There were one male aged 17 years and two females aged 15 years, each. Previous history was characterized by persistent gastric discomfort and anorexia with weight loss and episodes of melena over a period ranging from 2 to 4 years. Treatment with anti-HB, because of a diagnosis of gastritis, had produced only transient relief. Biopsies performed during gastroscopy were diagnostic. Except for a mild anemia and hyposideremia in two pts, biochemistry was normal. Partial gastrectomy and total gastrectomy were carried out in one and two pts, respectively. The pathologic diagnosis of MALT lymphoma was based on a combination of histologic and immunophenotypic findings; immunocytochemical detection of Helicobacter pylori infection was negative. The neoplasms were in all cases limited to submucosa. Microscopic examination of locoregional lymph nodes showed a lesser curvature nodes involvement. According to Masshoffs's system, the stage was III E each pt. They all were given a 7-month post-operative chemotherapy, according to the program in use for children with localized NHL. All three were alive and disease-free from more than 6 years after surgery.

Conclusions: As in adults, MALToma was characterized by symptoms of long duration simulating gastritis and had no tendency to disseminate. To the best of our knowledge, this is the first report of gastric MALToma in a pediatric population. This entity should be considered even in children in the case of persistent gastralgia.


From 1977 to 1995, CCG conducted 5 non-Hodgkin's lymphoma (NHL) clinical trials: 67 patients (pts) with localized (L) LCL and 212 pts with disseminated (D) LCL were treated on CCG-551, 501, 552, and 5911. 467 pts with D-SNCLL were treated on CCG-551, 501, 552, and 5911. On CCG-551, 73 D-LCL pts and 131 D-SNCLL pts were randomized to receive COMP or LSA-L, for 18 months (maunders). 56 pts with L-LCL were randomized to receive COMP for 6 or 18 mos on CCG-551. On CCG-503, 117 D-LCL pts and 238 D-SNCLL pts were randomized to receive COMP or without discontinuation for 18 months (maunders). On CCG-552, on which 13 D-LCL and 52 D-SNCLL pts were treated, was a single-arm pilot study employing 10 mos of CHOP plus Ara-C, 6-TG, and VP-16. 18 D-LCL and 46 D-SNCLL pts on CCG-5911 were randomized to one or two short, intensive regimens (a CCG hybrid regimen [Orange] or LMB-89 therapy) for 6 or 9 months, depending on risk group. The male female ratio was 1.8:1 for LCL pts and 4:1 for SNCLL pts. The incidence of bone marrow (BM) and CNS disease was lower for D-LCL pts (3% M3, 2% CNS) than for D-SNCLL pts (17% M3, 12% CNS). Seven LNH was ≥ 500 U/L in 50% of D-SNCLL pts and 19% of D-LCL pts. 5-year EFS for pts with L- and D-LCL was 92% and 524% respectively. 4-year EFS for pts with D-SNCLL treated on those studies was 583%. D-LCL pts 5 yrs of age had a 5-yr EFS of 55% vs. 35% for older pts (p<0.05) while older age (23 yrs) was a poor prognostic factor for D-SNCLL pts (5-yr EFS 312% vs. 572%, p<0.01). BM disease (M3) and LDH ≥ 500 U/L predicted a poor prognosis in D-SNCLL (5-yr EFS 38% for M3 BM vs. 623% for MI (p=0.001) and 424% for LDH ≥ 500 U/L vs. 714% for LDH<500 U/L (p=0.001). Pts in both histologic groups had a significantly improved EFS when treated with short, intensive therapy (CGG-5911) compared to those treated on earlier protocols employing longer and less intensive therapy (86% vs. 523-3-yr EFS for D-LCL, p<0.02; 82% vs. 583% 3-yr EFS for D-SNCLL, p<0.05). In summary, age at diagnosis is a significant prognostic factor for children with different NHL histologies and shorter, intensive therapy offers significantly improved survival for pts with D-LCL and D-SNCLL.
A CASE OF ATAXIA-TELANGIECTASIA WITH PERSISTENT MASSIVE LYPHOPROLIFERATION.
A.Kambounakis, E.Stiakaki, I.Bouzouka, L.Notarangelo, D.Schindler, K.Stefanaki, M.Kalimani. Department of Pediatric Hematology/Oncology, University Hospital of Heraklion, Crete, Greece.

A 9 year old boy was first admitted for evaluation of neutropenia and cervical lymphadenopathy. A low serum IgG with non detectable IgA, IgE, and IgM, and increased IgM were found, findings consistent with the diagnosis of Hyper-IgM syndrome. Chest X-ray and cell mediated immunity evaluation were normal. At that time lymph node biopsy showed reactive hyperplasia. The child was doing well on supportive therapy with IVIG every 21 days and G-CSF during neutropenic periods. Mild episodes of recurrent upper respiratory tract infections, wheezing and mild diarrhea were the consequences of his immunodeficiency. Three years following initial admission, the boy presented with a rapid progression of his organomegaly (spleen 12cm, liver 8cm below margins), cervical, mediastinal, axillary, abdominal and inguinal lymphadenopathy with a concomitant polyclonal increase in IgM serum levels (as high as 4500mg/dl) and increased serum alpha-fetoprotein. Extensive investigation for infectious agents as cause of the lymphoproliferation did not yield positive results. Biopsies obtained from liver, spleen, abdominal and inguinal lymph nodes showed a polyclonal B-cell hyperplasia with intact secondary follicles and presence of germinal centers. Analysis of the expression of CD40L in peripheral blood lymphocytes was normal, most likely excluding the diagnosis of Hyper-IgM syndrome. At the age of four, he developed cerebellar ataxia and ocular telangiectasias, symptoms and findings, which were progressively more prominent. At that time an MRI showed cortical cerebellar degeneration, while karyotype with bleomycin for evaluation of chromosomal instability and radiosensitivity test, by flow-cytometric analysis, performed in peripheral blood lymphocytes, were consistent with Ataxia-Telangiectasia. The case represents a typical AT with massive persistent lymphoproliferation and high polyclonal IgM serum levels.

FAVORABLE RESULTS OF AN INTENSIVE PROTOCOL FOR ADVANCED-STAGE T-CELL LYPHОBLASTIC LYMPHOMA AND ACUTE LYMPHОBLASTIC LEUKEMIA IN CHILDHOOD

Introduction: Patients (pts) with advanced-stage T-cell lymphoblastic lymphoma (LL) and acute lymphoblastic leukemia (T-ALL) are at a relatively high risk of treatment (Tx) failure. We evaluated the effectiveness and toxicity of an intensive regimen for such pts.

Methods: Tx consisted of 10 weeks of induction therapy which included prednisone (PDN), vincristine (VCR), doxorubicin (DOX), cyclophosphamide, cytarabine (Ara-C), and etoposide. This was followed by 20 weeks of intensive consolidation which included rotating courses of high-dose methotrexate (MTX), high-dose Ara-C, and pulses of VCR/DOX/PDN, and 6-mercaptopurine (6-MP). These were given in conjunction with weekly high-dose E. coli asparaginase. Consolidation was followed by 7 pulses of VCR/DOX/PDN/6-MP, identical to those given during consolidation, given every 3 weeks. The second year of Tx consisted of weekly IM MTX, daily 6-MP given 2 out of 3 weeks, and VCR given every 3 weeks. Triple intrathecal Tx was given for CNS prophylaxis. G-CSF support was used only following high dose Ara-C courses. Cranial irradiation was given at the end of consolidation for those patients with presenting WBC >50,000/mm³ or with initial CNS involvement. The planned duration of Tx was 2 years.

Results: Twenty consecutive pts (10 with Murphy stage III or IV LL and 10 with T-ALL) were enrolled from 8/93-9/95. With a median follow-up of 19 mos, eight of ten pts each with LL and T-ALL remain in CR. Seven pts have completed Tx. Toxicity has been primarily hematologic. Most pts have tolerated therapy well, but neurologic toxicity requiring Tx modification was required for a teenager with transient weakness and slurred speech. Another child developed severe neurologic sequelae with ascending paralysis; he was subsequently found to have a chromosomal fragility syndrome.

Conclusion: Preliminary results of our pilot protocol suggest it has promise as an effective, tolerable Tx for pts with advanced-stage LL and T-ALL.

CHEMOTHERAPY COMBINED WITH INVOLVED-FIELD RADIOTHERAPY FOR 88 CHILDREN WITH HODGKIN’S DISEASE (HD) TREATED IN 1971-97: COMPARATIVE EFFECTIVENESS IN FOUR CONSECUTIVE PERIODS

Introduction: Controversy still exists regarding the optimal therapy for HD in children.

Methods: From 1971 to 1997, 88 children with HD were treated at seven oncologic centers: Children were treated with chemotherapy combined with involved-field radiotherapy (first, 30-45 Gy, since 1988: 20-30 GY). Year by year intensity of therapy was gradually adjusted to the stage of the disease and to other significant factors. Along with a modified therapy protocol, four consecutive periods of time (I: 1971-82, II: 1983-87, III: 1988-93, IV: 1994-97) were analyzed. In the first period the basic chemotherapy was MPP (methotrexate, vinblastine, prednisone), while later B-DOPA (bleomycin, dacarbazine, vinblastin, prednisone, Adriamycin) was gradually introduced alone or alternately with MPP. The observations were completed on December 31, 1998.

Results: Results of treatment in the 4 periods are presented in table:

<table>
<thead>
<tr>
<th>Time period</th>
<th>Number of pts</th>
<th>% of pts with death</th>
<th>Probability of 5-years survival (%)</th>
<th>Probability of 10-years survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>203</td>
<td>10.5</td>
<td>92</td>
<td>87</td>
</tr>
<tr>
<td>II</td>
<td>177</td>
<td>1.7</td>
<td>97</td>
<td>91</td>
</tr>
<tr>
<td>III</td>
<td>271</td>
<td>2.6</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>IV</td>
<td>177</td>
<td>3.0</td>
<td>98</td>
<td>95.5</td>
</tr>
</tbody>
</table>

Improvement of our therapeutic results was revealed by an increase in the level of both survival (OS) and relapse free survival (RFS), and decreasing rate of serious complications.

Conclusions: Alternate multidrug chemotherapy combined with low-dose involved-field radiotherapy may cure more than 90% children and it seems now to be the optimal method of treatment for Hodgkin’s disease. Intensity of therapy should be tailored to the stage of the disease and to other significant risk factors. There is still a need to determine new risk groups which require more effective treatment. Further modifications of treatment should improve the cure rate, while minimizing the complications.

CYTOTOGENIC CHARACTERIZATION OF CHILDHOOD LYMPHOMA
F.K. Niggli, D.R. Betts
Department of Oncology, University Children's Hospital, Zurich, Switzerland.

The cytogenetic characterization of lymphoma is dominated by the study of the disease in adults and has resulted in a number of described biological and clinical implications. However, whether the same implications hold true for childhood lymphoma still requires further investigation. We report the cytogenetic investigation of 40 biopsies of non-Hodgkin lymphomas (NHL) and 13 Hodgkin disease (HD). The NHL comprised of 13 B-NHL, 9 T-cell NHL, and 5 various, of which 20 had a detected abnormal clone. In the NHL group as a whole the clones were characterized by structural rather than numerical aberrations with the chromosome arms 1q, 6q, 14q and 5q the most frequently involved. In the B-NHL group 8/9 abnormal cases contained the expected t(8;14) or t(14;22) translocation. One further feature of this group was the frequent cell death in transport, resulting in a failure to obtain a result on 3 occasions. The T-cell NHL group (6/9 abnormal) contained two surprises with the finding of a 5q33 or 14q32 breakpoint in two tumours. The finding of an abnormal clone in the HD group was less frequent (5/13 cases), but when found were typically very complex and comprised only a small percentage of metaphases. Structural rearrangements of the chromosome arms 1q, 7q, 21p and 22q were seen in 2 or more tumours. The results indicate that the cytogenetic features of childhood lymphoma do not differ significantly from a like lymphoma occurring in an adult, although if the clinical implications are similar requires further studies.
PARENCHYMAL LUNG INVOLVEMENT IN CHILDREN WITH ADVANCED HODGKIN’S DISEASE (HD).


Introduction: Lung involvement, isolated or in conjunction with other organs, is not uncommon in children with advanced HD. Chemotherapy with or without lung irradiation is the standard treatment. We reviewed all children with Stage IV HD and isolated parenchymal lung involvement to study the outcome and compare this to that of patients with involvement of other extra-lymphatic organ(s).

Methods: Between February 1982 and May 1998, 39 children aged less than 16 years with stage IV HD and isolated lung involvement, were treated according to the UKCCSG/HD protocol with 6-8 cycles of chemotherapy. Eighteen (46%) had B-symptoms. The predominant histological subtype was nodular sclerosing (n=33). All patients received 6-8 cycles of chemotherapy according to the speed of response; CHVPP (n=32), alternating CHVPP/ABVD (n=6) and VEEP (n=1). Six had radiotherapy to sites of bulky disease and 2 had whole lung irradiation (12Gy).

Results: With a median follow up of 32 months, the overall and DFS are 88% and 63%. Three patients died of HD and one survives in relapse on palliative treatment.

Conclusions: Isolated parenchymal lung involvement doesn’t carry an adverse prognostic significance compared to other organ involvement. Systemic chemotherapy is an effective modality and avoidance of lung irradiation may help to avoid long-term morbidity.

TREATMENT OF CHILDHOOD B-LYMPHOMA. RESULTS OF THE POLISH PEDIATRIC LEUKEMIA/LYMPHOMA STUDY GROUP.


The prognosis for children with B-cell lymphomas has gradually improved in the past 15 years. The efficacy of a LMB-89 protocol for children with B-NHL has been investigated. The patients (pts) were treated in 9 oncological centers of Polish Leukemia/Lymphoma Study Group during the years 1993-1998. In this study 99 (M/F: 2.91) from 115 registered patients were analyzed. Median age of children was 8.9 months and median time of observation was 29 months. The diagnosis was based on histomorphological investigation and supplemented with immunophenotyping. The staging system of S. Murphy was used for prognostic stratification. Treatment intensity was adapted to 3-risk group acc. to K. Patte. The majority pts were in advanced st. on admission: 47 (47.5%) in st. III, 34 (34.3%) in st. IV and only 5 (5.1%) in st. I and 13 (13.1%) in st. II. Twenty-six (26.3%) associated to BM involvement. Primary sites were: abdomen in 45 (45.4%), peripheral lymph nodes in 19 (19.2%), head-neck in 20 (20.2%), Elsewhere in 15 (15.1%). Seven (7.1%) pts were treated in gr. A, 67 (67.7%) in gr. B, 25 (25.2%) in gr. C.

Complete remission was achieved in 92 from 99 pts (92.9%). There were 4% non responder pts (all with extensive tumor, high LDH and delayed diagnosis), 2% early death (tumor lysis syndrome; circulatory insufficiency), 1% deaths before CR due to therapy toxicity and 1% deaths in CR due to infection. Eleven pts relapsed (11.9%). EFS is 0.8 for all pts, 0.1 in group A, 0.88 in group B and 0.76 in group C; 0.94 in st. I+II, 0.88 in st. III and 0.86 in st. IV with a median follow up of 29 months. EFS was 0.58 for st. III and only 0.38 for st. IV by contrast, with the previous protocol. Severe marrow suppression and neutropenic infections were the major complications of this intensive protocol.

This study shows a significant improvement in overall survival and EFS of B-NHL in comparison with previous study. However the relapses rate is high (11.9%) and the EFS in st. IV is still unsatisfactory. In our series, advanced st. NHL with extensive tumor at presentation still have a high mortality (4.2%).

4. Pediatric Lymphomas
5. CLL/Indolent Lymphomas

THE INFLUENCE OF LOW DOSE INTERLEUKIN-2 (IL-2) ON CLADRIBINE (2-CDa) INDUCED CD4-LYMPHOPENIA IN PATIENTS WITH LOW GRADE NON-HODGKIN'S LYMPHOMA (NHL)

Michael A. Fridlak, Richard Great, Gerhard Jäger, Heinz R. Kienzer, Hubert Hauenstein, Angelika Erhardgruber, Andreas Chott, Werner Linkesch
Working Party of Medical Tumor Therapy
1st Dept. of Medicine, AOK-Linth, Linz, Austria, Europe

Introduction: In an earlier study we achieved a remission rate of 88% with 2-CDa in previously untreated, advanced low grade non-Hodgkin's lymphoma. However 2-CDa produced a long-lasting and substantial lymphopenia. Median CD4 counts remained below 0.3 x 10^9/L for more than 12 months, IL-2 acts as a growth factor for T-lymphocytes. In the recent trial we evaluate the effect of low dose IL-2 treatment on 2-CDa induced CD4-lymphopenia.

Methods: Previously untreated low grade NHL stage 3 or 4 were eligible to the trial. From May 96 to August 99 49 patients gave informed consent and were entered to the trial. 2-CDa, 0.12 mg/kg body weight was given in an 2-h i.v. infusion on day 1-4 of an 28 day cycle. Four cycles were given. In responding patients a maintenance therapy with IL-2 alternating with interferon a-2c (IF) was given for 9 cycles, starting in week 17. IL-2 was given s.c. 4.5 x 10^6 IU daily on Monday to Thursday in 2 consecutive weeks. IF was given 15 mg daily on Monday, Wednesday and Friday in 2 consecutive weeks following IL-2. After 2 weeks of rest, the next IL-2-IF cycle was started. Two to nine of the 49 patients are evaluable to date. Mean age is 58 years. Ninety-six (1-2) cycles are evaluable.

Results: During IL-2IF maintenance therapy mean CD4 count was 0.97 x 10^9/L. The CD4 count in the previous study with 2-CDa induction and IF maintenance was 0.19 x 10^9/L. This difference is significant in the Mann Whitney test with a P < 0.001. Allergic reactions, hematological toxicity, Flu-like syndrome and gastrointestinal toxicity are the most common reactions. Toxicity only occasionally exceeded WHO grade 2, no grade 4 toxicities were observed. Four patients stopped IL-2 therapy because of toxicity. One patient progressed and 2 patients of 5 who have finished all 9 IL-2IF cycles converted from PR to CR while on IL-2IF.

Conclusions: IL-2 is able to improve 2-CDa induced CD4-lymphopenia. We do not have enough data to confirm a sustained normal CD4-lymphocyte count. Because of the low infection rate in first line cladribine treatment, more patients are needed to demonstrate a possible reduction of infections.

EFFICACY AND TOXICITY OF BENDAMUSTIN IN PATIENTS WITH RELAPSED LOW GRADE NON HODGKIN LYMPHOMA

A. Heider, T. Gauler and N. Niederle
Dept. of Hematology and Oncology, Klinikum Leverkusen, Germany

Introduction: High response rates could be induced in patients with low grade NHL by using cytostatic treatment regimens. Relapse rates, however, remain even after aggressive cytostatic combinations in first line therapy. Therefore, an effective and well-tolerated salvage therapy is very important. In this monoclinical institution trial, the efficacy and toxicity of Bendamustin in the treatment of relapsed low grade NHL was investigated.

Methods: Forty-seven patients (pts) with low grade NHL (lymphocytic 24, centroblastic centrocytic 15, centrocytic 5, immunocytic 3) were included. Pts were pretreated with 1-6 (median, 2) cytostatic regimens including cyclophosphamide, ifosfamide, anthracyclines, chlorambucil, etoposide, vinca-alkaloides and corticosteroids. All pts received Bendamustin 120 mg/m^2 as an one-hour infusion on two consecutive days. The treatment was repeated every three weeks and continued, until a complete remission (CR), a partial remission (PR) or a stable disease (NC) was confirmed on two consecutive evaluations. In case of further progression (PD), treatment was immediately stopped.

Results: So far, 40 patients are evaluable for response and toxicity. Five patients (12.5 %) showed a CR, 22 patients (55 %) a PR, and 5 patients (12.5 %) a NC status. Another 8 patients (20 %) had PD. The median remission duration is 10+ months (2-27). Side-effects were generally mild and restricted to myelosuppression, gastrointestinal toxicity and allergic reactions (mostly WHO grade 1 or 2).

Conclusions: Bendamustin has proven to be very effective and well tolerated in pretreated pts with low grade NHL. Further investigations in prospective randomized trials are warranted.

PROGNOSTIC FACTORS AND SURVIVAL IN LOW-GRADE NON-HODGKIN'S LYMPHOMA (NHL) -- ANALYSIS OF 329 CASES

J. Zahner, Main-Spessart-Klinik, D - 97737 Gemünden a. M.

Introduction: The majority of low-grade NHL show a chronic, indolent clinical course without cure. Assessment of survival probability under conventional treatment by pretherapeutic prognostic factors is an obligatory prerequisite for dose-intensified treatment.

Method: 329 patients with low-grade NHL, conventionally treated over a period of 13 years at Heinrich-Heine-Universität Düsseldorf, were analyzed for survival. Results were demonstrated according to the method of Kaplan-Meier and prognostic factors were developed by univariate analysis to predict clinical outcome.

Results: There was no statistical difference in survival between the most frequent variants of low-grade NHL, i.e. 160 chronic lymphocytic leukemias (CLL), 64 follicle center lymphomas and 65 lymphoplasmacytic lymphomas (p = 0.30). Overall median survival of all 329 low-grade NHL amounted to 95 months and was significantly longer than overall median survival of 110 patients with multiple myeloma treated in the same period (p = 0.01). Elevation of serum LDH (p = 0.002), Hb < 10 g/dl (p = 0.003) and failure of complete remission (p = 0.005) indicated shorter survival for the entire group of all low-grade NHL. In CLL elevated serum LDH (p = 0.004), the modified Rai classification dividing in Rai 0, Rai I, Rai III/IV (p = 0.005) and Hb < 10 g/dl (p = 0.01) are significant prognostic parameters. In follicle center lymphoma distribution in Ann-Arbor stage I-II and Ann-Arbor III/IV was the most powerful prognostic parameter. For lymphoplasmacytic lymphoma the classification of Rai was of no prognostic importance.

Conclusion: The clinical course of the most frequent types of low-grade NHL showed no statistical difference in survival. However, survival in low-grade lymphoma was significantly longer than in multiple myeloma. Elevated serum LDH value, decreased hemoglobin level and failure of complete remission are prognostic factors for the whole of all low-grade lymphomas.

Predictive Value of International Prognostic Index for Chemotherapy Responsive/Resistant Immunocompetent Low-Grade Non-Hodgkin's Lymphoma (NHL) Patients Treated with Iodine-131 Anti-B1 Antibody

M. Kaminska, University of Michigan, Ann Arbor, MS; JM Vosen, University of Nebraska Cancer Center, Omaha, NE; SM Koll, RJ Stag, and GF Tiderman, Coulter Pharmaceutical, Inc., Palo Alto, CA.

The International Prognostic Index (IPI) was originally devised for patients with newly diagnosed aggressive lymphoma and has been shown to be predictive for response, duration of response, relapse-free survival and overall survival following chemotherapy treatment. Subsequent studies have shown that the IPI is also prognostically valid for previously untreated indolent lymphoma. For patients with indolent lymphoma who have failed chemotherapy, the most important IPI prognostic variables currently employed are the number of prior therapies and the duration of response to the previous chemotherapy. However, little has been published about the prognostic value of the IPI for chemotherapy relapsed and refractory indolent lymphoma patients. We examined the prognostic value of the IPI for 167 patients with low-grade and transformed low-grade NHL patients treated with Iodine-131 Anti-B1 Antibody for 5 separate clinical trials. All patients were originally diagnosed with low-grade NHL and subsequently received chemotherapy. The IPI for these patients at the time of initial diagnosis is not available. The mean IPI prior to therapy was 2.4. At the time of study entry, the median age was 54 yrs, 58% were male, 33% had bulky tumors, and 43% had elevated LDH. These patients had been treated with a median of 4 prior chemotherapies and 53% were not responsive to their last prior chemotherapy. The response outcome on Iodine-131 Anti-B1 Antibody for these 167 patients stratified by IPI at the time of treatment was as follows:

---

5. CLL/Indolent Lymphomas
449

BP VERUS COP IN ADVANCED LOW GRADE NON-HODGKIN'S LYMPHOMAS—RESULTS OF A RANDOMIZED MULTICENTER STUDY


Introduction: The results of a phase III study conducted by the EHSO comparing the effectiveness and toxicity of the standard COP-program (cyclophosphamide 400 mg/m2 d 1-5, vincristine 2 mg d 1), prednisolone 100mg/m2 d 1-5) and a combination containing bendamustine, an alkylating benzoimidazole derivative, instead of cyclophosphamide (bendamustine 60 mg/ m2 d 1-5, vincristine 2 mg d 1, prednisolone 100mg/m2 d 1-5) are reported.

Methods: From 12/93 to 4/96 164 previously untreated patients with advanced, treatment demanding (CLL and LP2), as well as HD, in stages III and IV entered the study. Randomization was stratified according to the histologic entities. 182 patients are evaluable concerning response, follow-up, and toxicities. The patient's characteristics in the respective treatment arms are well balanced.

Results: The response rates in the either treatment arms are: COP 33%, CR 23%, PR 46%, CRF 7%, CR 23%, PR 58%; the differences are not statistically significant (p<0.10). After a median follow-up of 20 months (5-64 months) EFS is 58% (BOP) and 55% (COP); overall survival 73% (BOP) and 64% (COP) without statistical significance. Concerning toxicity BOP is significantly superior in respect of alopecia (3,8% vs.48,3% WHO 3, p=0.01), leukopenia (19,2% vs. 31,1% WHO 3-4, p=0.001), and thrombocytopenia (0,8% vs. 4,0 WHO 3-4, p=0.001). Leucopenia did not result in an increased rate of severe infections(p=0.03). BOP caused more allergic skin reactions of moderate intensity (29,8% vs.4,4% max. WHO 2, p=0.02).

Conclusions: The BOP program is not superior to the standard COP regimen concerning remission induction. But it is significantly less toxic in respect of myelotoxicity and hair loss. Secondary neoplasms have not yet been observed in the two treatment groups.

451

COA REGIMEN FOR TREATMENT OF LOW GRADE MALIGNANT LYMPHOMAS

M. Badea, T. Ciurea, D. Badea, A. Tanase
Hematology Clinic, University of Medicine and Pharmacy, Craiova, Romania

Introduction: Despite a high initial response rate, recurrence or progression make death from low-grade lymphoma almost inevitable and the shape of the survival curve is unchanged since 20 years. The objective of low-grade lymphoma treatment is to maintain a convenient biological status with a low interfer of the usual habitude.

Methods: Our study contains 38 patients with low-grade lymphoma in stages III and IV. All the patients received COA regimen (Chlorambucil, Vincristine, Cytarabine) for obtain complete remission or good partial response (average 8 cycles / patient).

Results: Median age was 58.3 years and sex ratio (M/F) 1:1.23. The response rate was 76.31%, 57.69% of this was complete remission. The percentage of death at 40 month was 29.95% from which 5.26% died unrelieved with lymphoma. The patients included in high-risk group (with four negative prognostic factors by International Prognostic Index) have a worse prognosis and 66.66% of them died. The evaluation of 5 years survival was 80%. The medullar toxicity of forth degree was found at 7.89% cases. We have not notice any death chemotherapy-related.

Conclusions: The COA regimen represent a very good alternative of treatment for patients with low grade lymphoma in stages III and IV, because the medullar toxicity is low and the 5 years survival is important (60%). The patients included in high-risk group (by International Prognostic Index) have probably a serious prognostic and require another type of therapy (tot was too small).

452

ANALYSIS OF CLINICO-PATHOLOGIC CHARACTERISTICS AND PROGNOSTIC FACTORS OF 117 LOW-GRADE NON-HODGKIN'S LYMPHOMAS (NHL) FROM A SINGLE CENTER


Objective: To analyze the prognostic significance of the main clinical and biological features of 117 patients with low-grade NHL from a single center recategorized according to the REAL classification.

Patients and methods: Between 1983 and 1997, 117 cases of low-grade NHL according to the WF were diagnosed and treated in a single institution. After reclassification by REAL criteria, the main clinical and laboratory features, histological subtypes and International Prognostic Factor (IPF) score were evaluated for prognosis. Uni and multivariate analysis for overall survival (OS) and disease-free survival (DFS) were performed.

Results: Mean age (SD) was 59 (14) yr, sex ratio M 65/F 52. Histologic subtypes included: 13 small lymphocytic, 7 lymphoplasmacytoid, 44 follicular, 24 mantle cell, 2 plasmic, 25 MALT, and 2 no classified. Median OS and DFS were 34 and 13 months respectively. In the univariate analysis, the following variables had negative influence on OS: age >55 yr., creatinine >1.2 mg/dL, albumin <33g/L, serum LDH level >400 U/L, serum β2-microglobulin>4 mg/dL, B symptoms and intermediate and high IPF scores. By multivariate analysis, increased β2-microglobulin, poor performance status, and B symptoms were the only parameters with negative influence for OS (p=0.04, p=0.03, and p=0.01, respectively). In both uni and multivariate analysis intermediate and high IPF score was the only bad prognostic factor for DFS (p=0.05).

Conclusions: 1) Most of the low grade lymphomas can be reclassified according to the REAL criteria. 2) IPF score is the most important unfavorable prognostic factor for DFS, and, together with high β2-microglobulin, poor performance status and B symptoms has a negative impact on OS.

Supported by grants FI3-98-1332 and FUC-PIEF-98.

THERAPY OF LOW GRADE NON-HODGKIN'S LYMPHOMA (NHL) WITH BENDAMUSTINE AND ORAL ETOPSIDE

K. Ruffert.
Practice for Hematology and Oncology, Iena, Germany.

Introduction: Bendamustine hydrochloride is a well tolerable multivalent antagonist combining a purine-like benzenimidazole nucleus and a bifunctionally alkylating nitrogen mustard group with high activity in lymphoma. In previous studies combinations with vincristine and prodisolone (BOP) as well as with methotrexate, etoposide and prodisolone (BMEP) were investigated in Iena. In a phase III study BOP vs. COP was equal for response rate in low-grade lymphoma. N Engl. J. Med. 339 (1998) 997-1003. In a phase III study bendamustine was effective in low-grade lymphoma and in combination with rituximab in patients with relapsed or refractory low-grade lymphoma. Blood 2004;103:375-380.

Methods: In an ongoing study, the efficacy, tolerability and convenience for delivery in an outpatient setting of a combination with oral etoposide in low grade NHL is taken under investigation. Up to now 38 outpatients (15 female and 23 male) with low grade NHL (n=22) and B-CLL (n=16) were prospectively treated. Mean age was 64.2 years (range 46-83). 12 pts were pretreated. Therapy consisted of 100 mg/m2 bendamustine i.v. on day 1 and 50 mg etoposide p.o. on days 1-5. Treatment was repeated every 21 days and continued in pts achieving an objective response for a total of 8 courses.

Results: Objective responses were seen in 32/33 evaluable pts. (RR=97%, CR= 67%, PR= 10%). No patient showed stable disease under the treatment, only one patient progressed. Median duration of remissions is 15,4+ months for pts with CR and 15,4+ months for pts with PR. In the B-CLL subgroup 9 CRs and 2 PRs could be induced. Toxicity was very mild and consisted of hematological toxicity (WHO grade 1: 6 pts., grade 2: 5 pts., grade 3: 1 patient), gastrointestinal toxicity grade 1 (4 pts.), allergy grade 1 in one patient and grade 1-hypotension in 4 pts. None of the pts. experienced alopecia or infections. The CD4/CD8-ratio was not significantly influenced by the treatment.

Conclusions: Bendamustine and oral etoposide represent a highly active combination in NHL and CLL with very good tolerability which makes this regimen convenient for an outpatient setting.

5. CLL/Indolent Lymphomas 125
MULTICENTRIC PROSPECTIVE RANDOMISED TRIAL OF BENDAMUSTINE/PREDNISONE VERSUS MELPHALANE/PREDNISONE IN 136 PREVIOUSLY UNTREATED PATIENTS WITH MULTIPLE MYELOMA.
Univ. of Leipzig, Univ. of Frankfurt/Main, Hospital Erfurt, Hospital Riesa, Hospital Plauen, Hospital Wernigerode, Hospital Nordhausen, Hospital Zella-Mehlis, Hospital Schwein, Univ. of Rostock, Germany

Patients and methods: Previously untreated patients with multiple myeloma (MM) were randomized in a prospective multicenter study to receive bendamustine/prednisone (BP) or melphalan/prednisone (MP). Between May 1994 and October 1998, 136 MM patients (stage II in 2 patients, stage III in 125) were recruited at 31 hospitals in Germany. 69 patients received BP (bendamustine 150 mg/m² day 1-2, prednisone 60 mg/m² day 1-4) and 67 patients MP (melphalan 15 mg/m² day 1, prednisone 60 mg/m² day 1-4). Response was assessed by SWOG criteria. Changes of the individual tumor cell mass (TCM) were determined by myeloma protein concentrations. TCM reduction of more than 25% was defined as complete and between 25% and 74% as partial remission. Minor variations (±24%) of the TCM were designated as no change. In responding patients, chemotherapy cycles were repeated until no further TCM reduction was observed during the therapy.

Results: Analysis was performed after a median follow-up of 24 months in 100 patients.

<table>
<thead>
<tr>
<th>Maximal response</th>
<th>BP (n=50)</th>
<th>MP (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission</td>
<td>13 (26%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>23 (46%)</td>
<td>31 (62%)</td>
</tr>
<tr>
<td>No change</td>
<td>14 (28%)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

In responding patients remission was reached after 5.7 cycles in the BP arm compared to 7.1 cycles in the MP arm. The median time to progress was 14 months in both groups. Minimal increased toxicity (leukopenia, gastrointestinal complaints) was observed with BP therapy.

Conclusion: The preliminary results suggest that BP provides a well tolerated regimen for first treatment of multiple myeloma.

FLURADARINE VERSUS FLURADARINE PLUS EPIRubicin in the treatment of chronic lymphocytic leukemia - PRELIMINARY RESULTS OF A RANDOMIZED PHASE-III MULTICENTER STUDY


In our previous phase-II study using the combination of fluradarine plus epirubicin in previously untreated patients with CLL we reached an overall response rate of 92% with a high rate of complete remissions of 40%. Based on these results we initiated a randomized phase-III study to compare efficacy and toxicity of the combination fluradine plus epirubicin versus monotherapy with fluradine as first-line therapy or therapy of first relapse. In addition, cytogenetic aberrations will be investigated in all patients to evaluate, if special chromosomal abnormalities are associated with prognosis and response to fluradine. Treatment schedule: Fluradine 25 mg/m² day 1-5, epirubicin 25 mg/m² day 6-5 for a maximum of 6 cycles every 4 weeks. 80 patients entered the study, 34 are evaluable for response so far, 24 patients out of these are previously untreated. CR was achieved in 11 cases (33%) and PR in 16 cases (47%). The overall response rate is 80%. One bacterial sepsis and 2 AIHa have been observed so far. From our preliminary results so far we can corroborate the high activity of fluradine in the treatment of CLL. It is of particular interest if a higher response rate and a longer duration of achieved remissions will be observed for the combination therapy in this ongoing study.

2-CDA (CLADOBINE) PLUS MITOXANTRONE IN THE TREATMENT OF LOW-GRADE NON-HODGKIN’S LYMPHOMAS - PRELIMINARY RESULTS OF A PHASE-II STUDY

M. J. Rummel, K. U. Chow, D. Hoelzer, P. S. Mitrou, J.W.-Goethe Universität, Frankfurt, for the 2-CDA study group: T. Karakas, Ulm; E. Jäger, Frankfurt; G. Käfer, Mannheim; J. Merger, Karlsruhe; M. Westerhausen, Düsseldorf; K. Schäkel, Limburg; R. Hoelzer, Groß-Gerau; M. Fischer, Frankfurt; L. Bergmann, Ulm – GERMANY

In our previous phase-II study using 2-CDA as single-agent therapy in previously untreated low-grade lymphomas we reached an overall response rate of 85% with a high rate of complete remissions of 42%. Based on these promising results and on our preclinical evaluation of 2-CDA induced apoptosis in vitro, showing a supranaductive effect of 2-CDA with mitoxantrone, we initiated a phase-II study to examine efficacy and toxicity of dose-reduced 2-CDA combined with mitoxantrone as first-line therapy or therapy of first relapse. Treatment schedule: 2-CDA 5 mg/m² as intermittent 2-hour infusion day 1-3, mitoxantrone 8 mg/m² day 1+2 for untreated patients or mitoxantrone 12 mg/m² day 1 for first relapse for a maximum of six cycles every four weeks. Included entities: immunocytoma, mantle cell, follicular center, and other low-grade B-cell lymphomas. 65 patients entered the study; 48 are evaluable for response, out of these 33 are previously untreated.

<table>
<thead>
<tr>
<th>Entity</th>
<th>n</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>NC</th>
<th>CR+PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular center</td>
<td>26</td>
<td>7 (27)</td>
<td>13 (50)</td>
<td>6</td>
<td>20 (77)</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>10</td>
<td>5 (50)</td>
<td>5 (50)</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>Immunocytoma</td>
<td>8</td>
<td>2 (25)</td>
<td>6 (75)</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Other low grade B-cell</td>
<td>4</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>17 (35)</td>
<td>25 (52)</td>
<td>6</td>
<td>42 (88)</td>
</tr>
</tbody>
</table>

So far, it appears that the combination of 2-CDA plus mitoxantrone seems to be very effective in the treatment of low-grade lymphomas reaching an overall response rate of 88%. The presented combination induced up to 5 days (median) lasting granulocytopenia grade 4 and is therefore more myelotoxic compared to 2-CDA as single-agent therapy. One bacterial pneumonia and 4 herpes zoster have been observed so far. This pilot-study is the basis for a prospective randomized trial, which has been already initiated to compare the effectiveness of 2-CDA plus mitoxantrone (CDM) versus chlorambucil, mitoxantrone plus prednisone (MCP).

PROGNOSTIC SIGNIFICANCE OF DEGREE OF CD23 POSITIVITY IN B-CELL CHRONIC LYMPHOCYTIC LEUKAEMIA AND SMALL LYMHPHOCYTIC LYMPHOMA

M. Coločić, A. Bogdanović, N. Kragnjić, Š. Janković, M. Dončić, N. Đinđić, V. Cemernik-Martinić, V. Jovanović, M. Petrović, D. Bobović, G. Janković

Institute of Hematology, 1. Department of Pathology, 2. Clinical Center of Serbia, Beograd, Yugoslavia

Introduction: It is necessary to perform adequate immunophenotyping with all cases of B-CLL/SLL to separate it from other B-chronic lymphoproliferative disorders. As defined in REAL classification B-CLL/SLL are CD5 and CD23+. The aim of our study is to evaluate prognostic significance of the degree of CD23+ in patients with B-CLL/SLL.

Methods: We analyzed 77 patients with B-CLL/SLL. There was 43% of stage I (63±10±4 years). Diagnosis was made on FAB and REAL proposal and included patients with cytologically and trephine proved CLL/SLL. Immunophenotyping was performed by indirect immunofluorescent flow cytometry (FACS, Coulter Inc.). 33 of 77 pts had extensive disease according to Rai (III-IV), while 44 had lower clinical stage. Lymphadenopathy was present in 75% and hepatitis in 34% and splenomegaly in 25%. Patients were treated with Clb (pred) not more than 24 pts, with combined CT (no antmyelodri) 17 pts and with antmyelodri based regimen 7 pts.

Results: All patients (100%) had positivity of HLA-DR, CD19, CD20, CD45 ranging from 73-98% of cells. SmIg was positive in 75.2% of pts in low density (36%), cdCD22 in 40.3% of pts (23% of cells) and CD52 in 45.5% of pts (23%). CD23 was positive in 97.4% of patients, with high density (70±23% of cells). In univariate and multivariate analysis CD23, CD22, CD23 and SmIg have no influence on survival (p>0.05). Quantifying positivity of class II molecules (cut-off at 50% as 1; 50-75% as 2; >75% as 3) we have found that pts with higher percentage of CD23+ cells have better survival (p<0.05). We have found that also pts with low and high SmIg positivity have better survival (20 and 22 vs 14 months for intermediate).

Conclusions: In patients with typical B-CLL/SLL degree of positivity of CD22 and SmIg, and to certain extent CD23 have prognostic influence to survival of these patients, representing some biological features of B-CLL/SLL.

In our institution we have enrolled 298 patients among 5 trials of the French national study group on CLL, the LCC, 80, 85, and 92 trials. Forty-two patients were received at any time of their treatment FAMP (FAMP+) group and the 256 others never received this drug (FAMP- group). Comparison between these 2 groups shows minor differences according to age, median lymphocytosis and some LDH level but allocations of patients according to the CRIT and Rai's classifications are similar.

We have noted 14 RS among the FAMP+ group and in opposite 6 RS among the FAMP- group, i.e. 5.9% versus 14.3% (p=0.03). Diagnostic was done between the 21st and the 120th month of survey (median 37) among FAMP+ group and between the first and the 121st month (median 41) among FAMP- group. The actuarial risk of occurrence of a RS is statistically higher among the FAMP group: 39.5% versus 11.9% (p=0.03).

Furthermore, the diagnosis of RS were distinguish among the FAMP+ group:
- 2 cases were recognized during nodal RS after the second cure for a relapse of CLL and splenic RS after a severe tracheal stenosis also after a second cure in a front line treatment.
- The 4 other RS were noted quickly after initiation of FAMP - from 7 to 16 months - while the control of CLL was excellent. 3 patients were in clinical CR and the fourth in a very good PR. Clinical and biological data were "explosive and massive" with 2 medullary and blood involvement. These 4 patients died in less than 3 months.

If American authors have recognized the risk of occurrence of RS after ASHMT for CLL and have emphasized the increased risk of NHL among heavy cell leukaemia treated by purine analogs, the risk of RS among U-CLL treated by FAMP is not well established. In opposite, immunosuppressive effects of FAMP are well recognized and as mentioned by Poock, Czerven and col. (ASH 98 - Abst 1774), this drug may "give a bit of a boost" towards the emergence of a de novo lymphoid clone.

5. CLL/Indolent Lymphomas

FLUDARABINE - MITOXANTRONE COMBINATION : PRELIMINARY RESULTS OF A RANDOMIZED TRIAL VERSUS M-CHOP AS FIRST LINE TREATMENT IN PATIENTS WITH ADVANCED LOW-GRADE NON- HODGKIN LYMPHOMA BY GOELAS GROUPS .


Introduction: Although a high initial response rate, the prognosis of patients with indolent lymphomas is rather poor. Encouraging results have been obtained with a combination of Fludarabine and Mitoxantrone (FM) (JCO 1994, 12: 376). The purpose of our study was to compare the clinical activity and safety of two arms treatment: M-CHOP versus fludarabine-Mitoxantrone, in patients with advanced low-grade lymphoma, non previously treated .

Methods: Patients age 55 to 70 y with newly diagnosed stage II bulky or III or IV NL/HL, and with at least one adverse prognostic factor were included in the GOELAS 052 protocol. After randomization patients were allocated to FM arm, or CHEP arm . In FM arm, patients received fludarabine 20 mg/m²/day (d) intravenously (IV) on d 1 and 5 and mitoxantrone 10 mg/m² IV d 1. In CHEP arm, patients received dexamethasone 25 mg/m² IV d 1, cyclophosphamide 750 mg/m² IV d 1, vincristine 3 mg/m² N d 1 and d 2. Prednisone 50 mg/m² orally. In both arms, patients were to undergo 6 months courses of treatment, then every other month for 6 months i.e. 9 courses for 1 year. Response was defined according to 3 categories: CR, PR and failure . Any response less than a PR was considered a treatment failure for this analysis .

Results: From 118 patients registered, 76 were evaluable for response at 6 months, 58 for response at 1 year and for toxicity. At each end-point, the two groups were balanced, especially for age, sex, histologic feature (follicular or not), stage, B symptoms, LDH level, performance status. At 6 months CR, PR and failure were respectively for FM: 42%, 45%, 13% versus 83%, 42%, 15% for CHEP arm (p=0.0007). At 1 year CR, PR and failure were respectively for FM arm: 55%, 31%, 14% versus 11%, 38%, 5% for CHEP arm (p=0.002). Myelosuppression was the most frequent side effects observed in the two arms. 6 local herpes zoster were observed. No PCP occurred. Almost all patients experienced severe lymphopenia in FM arm. There was no toxicity-related death.

Conclusions: These results confirm efficacy of FM combination for untreated patients with NL-HL, and seems a promising regimen .
CYTOTOXIC EFFECT OF FLUDARABINE IN COMBINATION WITH CYCLOPHOSPHAMIDE AND MITOXANTRONE IN B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA

B. Relisson1,2, N. Villarroya2, D. Colomer2, G. Pons1, E. Montserrat1, J. Gil1
1Dept. de Ciències Fisiològiques II, Campus de Bellvitge, Univ. Barcelona, 2Unitat d’Hematologia, Servei d’Hematologia, IDIBAPS, Hospital Clinic, Barcelona, Spain.

Introduction: B-cell chronic lymphocytic leukemia (B-CLL) is characterized by the accumulation of long-lived CD5+ B lymphocytes. Fludarabine is a purine analogue which has shown high efficacy in the treatment of this form of leukemia and there is an increasing interest in assessing whether the results obtained with fludarabine alone could be improved by combining it with other drugs.

Objective: To analyze the in vitro effect of fludarabine in combination with cyclophosphamide and/or mitoxantrone on B-CLL cells.

Methods: Cells from 20 B-CLL patients were incubated with pharmacological concentrations of fludarabine (1 μg/ml), cyclophosphamide (0.5 μg/ml) and mitoxantrone (1 μg/ml), the active form of cyclophosphamide in vitro. The cytotoxic effect was determined by the MTT assay. Apoptosis was determined by DNA staining with propidium iodide and analysis of phosphatidylserine exposure with Annexin V.

Results: Fludarabine and mitoxantrone produced a significant cytotoxic effect in all the patients studied and the combination of the two drugs produced an additive effect (p<0.005). Mitoxantrone, increased the cytotoxicity of fludarabine in all the patients studied and produced a significant synergistic effect (p<0.01) after 48 hours of incubation. The addition of mitoxantrone to this combination increased the cytotoxic effect in cells from 8 patients, but in the remaining 12 patients no significant increase was observed. The effect of fludarabine and mitoxantrone was dose-dependent. Mitoxantrone significantly increased the apoptosis induced by fludarabine on CD19+ cells (p=0.007), but not on CD5+ cells (p=0.314). Mitoxantrone and fludarabine had a synergistic effect in inducing apoptosis of B-CLL cells.

Conclusion: These results support that fludarabine in combination with cyclophosphamide and/or mitoxantrone can be highly effective in the treatment of B-CLL.

LOW-GRADE NON HODGKIN LYMPHOMAS (LG-NHL) IN THE ELDERLY: IMPACT OF A NEW LOW-DOSE FLUDARABINE BASED COMBINATION REGIMEN (FLEC)

M. Bocciola, C. Bigazzi, S. Marconcelli, F. Forconi, G. Marotta, R. Algeri * and F. Laura. Department of Hematology, University of Siena, Italy and * Oncology Service, Grosseto, Italy.

Introduction: Conventional doses of Fludarabine (FLU) alone or in combination with other drugs have been reported to be effective in the treatment of LG-NHL. Particularly, FLU and Cyclophosphamide (CY) or FLU and Mitoxantrone or Idarubicin combined regimens have shown considerable therapeutic activity both as first line and salvage therapy. Nevertheless, severe neutropenia and infective complications have been reported in a significant number of patients (pts), especially if elderly. The aim of this study was to evaluate the efficacy and Toxicity of a new regimen combining low-dose of FLU Epirubicin (EPI) and CY (FLEC) in a group of advanced elderly LG-NHL pts.

Methods: Eighteen consecutive de novo or relapsed LG-NHL pts >= 65 years old entered the study. FLEC regimen was as follows: EPI 50mg/m² i.v. on day one, plus FLU 15mg/m²/day i.v. (max 25mg) and CY 250mg/m²/day i.v. for four days. Courses were repeated monthly for a maximum of 5 cycles.

Results: Response rate according to pts characteristics is reported in Table 1. All pts who achieved complete remission (CR) had never relapsed after 4 to 22 months with a median duration of 11 months. Four out of 7 partial responders have so far progressed after 4, 5, 7 and 8 months respectively. Median overall survival was 11 months. Therapy-related toxicity was mild and mainly consisted of grade IV neutropenia (27% of pts), fever of undetermined origin (30% of pts) with no documented infections.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>CR+PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>6 (44)</td>
<td>7 (59)</td>
<td>13 (83)</td>
</tr>
<tr>
<td>Stage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>3 (100)</td>
<td>/</td>
<td>3 (100)</td>
</tr>
<tr>
<td>III/IV</td>
<td>15 (53)</td>
<td>7 (27)</td>
<td>22 (79)</td>
</tr>
<tr>
<td>Prior Therapy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>13 (66)</td>
<td>5 (28)</td>
<td>18 (88)</td>
</tr>
<tr>
<td>&gt;1 regimen</td>
<td>5 (25)</td>
<td>2 (10)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>LDH level:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>11 (55)</td>
<td>6 (29)</td>
<td>17 (81)</td>
</tr>
<tr>
<td>Elevated</td>
<td>7 (33)</td>
<td>4 (18)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>*BM involvement</td>
<td>15 (75)</td>
<td>6 (25)</td>
<td>21 (89)</td>
</tr>
<tr>
<td>**PB involvement</td>
<td>6 (23)</td>
<td>3 (13)</td>
<td>9 (38)</td>
</tr>
</tbody>
</table>

Bone Marrow: **Peripheral Blood

Conclusions: FLEC regimen appears to be an effective treatment for elderly LG-NHL pts producing an overall response rate (83%) in the range of other published FLU-based combinations without exposing the pts to infectious complications.

INTENSIVE THERAPY FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) IN RICHER'S TRANSFORMATION (RT)

J. Rodriguez, I.F. Khouri, M. Keating, and R. Champlin.
U.T. M.D. Anderson Cancer Center, Houston, Texas, U.S.A.

Introduction: RT is associated with dismal prognosis. When treated with conventional chemotherapy, <5% of patients achieve a durable remission. Autologous (ABMT) and allogeneic (AlloBMT) marrow transplantation has been effective in various lymphoid malignancies. This is the first report to address the role of ABMT and AlloBMT in a group of patients with RT who were heavily pretreated.

Methods: We retrospectively analyzed the outcome of 12 patients who had CLL in RT who received intensive therapy and transplantation at our institution. Eight were males. The median age was 53 years (range, 38 to 65). The median number of prior chemoregimens was 4 (range, 2 to 5). Two patients failed prior ABMT for CLL. Eight received Allo BMT (two from unrelated donors) and 4 had ABMT. At transplant eight patients were in resistant and four others were in sensitive or untreated relapse. The preparative regimen was TBI-based in five patients and non-TBI in seven.

Results: Overall survival was 33%. Only 1 of 4 patients who had ABMT continues to be alive and in remission 60 months post BMT. This patient had disease limited to the axilla at the time RT was documented. Three of 8 patients (36.2%) who received Allo BMT are alive and in remission at 7, 40, 60 months respectively. Two of these 3 had nonmyeloablative preparative regimen including one with unrelated donor transplant after failing prior ABMT. These data suggest that intensive therapy for RT improves outcome compared to conventional chemotherapy and that AlloBMT, especially when non ablative regimen is used, is promising therapy for this disease. A large number of patients are needed to confirm these results.
RAPID AND DURABLE DECREASE OF LEUKEMIC LYMPHOCYTOSIS FOLLOWING RITUXIMAB MONOCONAL ANTIBODY IN NON-FOLLICULAR LOW-GRADE LYMPHOMA
Introduction: Preliminary trials in relapsed low-grade lymphoma have shown that chimeric anti-CD20 monoclonal antibody Rituximab is a new therapeutic option for CD20+ B-cell lymphoma. Most studies have been performed in recurrent follicular forms; less is known on Rituximab activity in other low-grade subtypes. Here we report Rituximab efficacy in recurrent or refractory non-follicular low-grade lymphomas.
Methods: Five patients with CD20+ B-cell lymphocytic lymphoma in leukemia phase or B-chronic lymphocytic leukemia (B-CLL) received 4 weekly infusions of Rituximab (375 mg/m² i.v. over 8-hours). All pts. were either in second or more relapse or refractory to initial therapy. They had high lymphocyte counts, low gamaglobulin levels and recurrent infections; 2 pts. had immune anemia and/or thrombocytopenia.
Results: Rituximab was well tolerated: chills and fever often developed at the first infusion, but subsided following steroids. No severe complications occurred. A rapid and sustained peripheral B-cell decrease was observed in all patients, with lowest values reached within few hours after Rituximab infusion. After 4 weeks of therapy, lymphocyte counts were less than 50% of the basal value in all cases. The marked lymphocyte reduction was maintained for at least 5 months. Improvement of immune anemia and thrombocytopenia was observed as well.
Conclusions: Rituximab is safe and effective in patients with relapsed leukemic lymphocytic lymphoma and B-CLL. The rapid and maintained decrease of lymphocytes may avoid the use of aggressive cytoreduction. Rituximab seems promising to control B-CLL-linked autoimmune phenomena as well.

MONOCONAL ANTIBODY, RITUXIMAB, ADMINISTRATION FOR THE TREATMENT OF RESISTANT B-PROLIFERATIVE LYMPHOMA.
Hematology Unit, Department of Internal Medicine, University of Ioannina GREECE.

Prolymphocytic leukemia (PLL) is an uncommon type of CLL that is characterized by a rapidly progressive and aggressive course. The major clinical features of the disease is splenomegaly. We describe a woman 34 years old who was admitted to the hospital because of splenomegaly anemia and leukocytosis. The laboratory values on admission were: Hb:7.5 g/dl, WBC:56x10⁹/L, predominantly lymphocytes, Plt:123x10⁹/L. The infiltrating the bone marrow cells were DR, CD19, CD20, CD22 positive and CD5, CD10, CD23 negative. The patient received chlorambucil and prednisone, the new purine analogue fludarabine and the chemotherapeutic regimen CHOP consecutively without any improvement of her laboratory and clinical condition. We administered then the human monoclonal antibody rituximab 350 mg/m² IV in 4 cycles. The patient received the drug with noticeable side effects and appeared remarkable clinical and hematological improvement. One year after the diagnosis and six months after discontinuation of treatment stage remains in excellent general condition and full hematologic remission.

ROLE OF INTERNATIONAL PROGNOSTIC INDEX (IPI) IN LOW-GRADE NON-HODGKIN'S LYMPHOMA (LG-NHL).
National Institute of Oncology, Budapest, Hungary.

Introduction: The value of prognostic indexes in LG-NHL is rather controversial. In a retrospective study we analysed the usefulness of IPI in different risk groups of our patients.
Methods: We had 137 previously untreated LG-NHL patients between January 1992 and December 1997. The data of 112 patients were evaluable. The mean age was 56.5 years (range 19-80), 65 (58.6%) male and 47 (42%) female patients were treated. Thirty-seven (33%) patients had stage I-II, 75 (67%) stage III-IV disease. In 32 (28.5%) of patients extranodal involvement was present at more than two sites. Thirty-four (30%) patients had activity symptoms, 13 (11,5%) had increased LDH value, 42 (37.5%) patients had bulky disease. Primary treatments were involved-field radiotherapy (IFRT) (9 cases), monotherapy (23 cases), combined chemotherapy (CHP, CHOP, CHOP-like) (7 cases) depending on stage and prognostic factors. We used "watch and wait" policy in 10% of cases. Median follow-up time was 40 months (range 6-83).
Results: We divided patients in three risk groups based on the IPI.

<table>
<thead>
<tr>
<th>IPI</th>
<th>Patients</th>
<th>CR (%)</th>
<th>Relapse</th>
<th>OS (months)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>low-risk 0/1</td>
<td>52 (66.4)</td>
<td>37 (71)</td>
<td>7 (18)</td>
<td>7 (13)</td>
<td>44</td>
</tr>
<tr>
<td>intermed-risk 2/3</td>
<td>50 (44.6)</td>
<td>10 (20)</td>
<td>3 (30)</td>
<td>39</td>
<td>25 (50)</td>
</tr>
<tr>
<td>high-risk 4/5</td>
<td>10 (90)</td>
<td>0 (0)</td>
<td>21 (71)</td>
<td>7 (70)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: In the follow-up period the overall survival was similar in the low-risk and intermediate-risk groups. However, the markedly higher fatal outcome rate in the intermediate-risk group suggests that the difference will be more pronounced in the future. We think IPI is although applicable in the prognostic evaluation of LG-NHL. We plan to introduce IPI-based protocols in our department in the near future.

5. CLL/Indolent Lymphomas

129
ALPHA INTERFERON MAINTENANCE THERAPY IN PATIENTS WITH FOLLICULAR LYMPHOMAS AFTER CYCLOTHERAPY: A RANDOMIZED TRIAL

The main point of this study was to evaluate the effect of INF alpha in the relapse-free survival (RFS), progression-free survival (PFS) and overall survival (OS) in follicular lymphoma patients responding to an unscheduled-containing regimen (CEFOP) to the trial. 115 patients with advanced stage Ann Arbor IIIb-LV, low-grade follicular lymphomas (Working Formulation B and C) at the time of 1st diagnosis (90 pts) or in 1st or subsequent relapses, (25 pts were treated with CECOP (cyclophosphamide: 750 mg/m² iv on day 1, epirubicin 70 mg/m² iv on day 1, vinristine iv in bolus of 4 mg/m² on day 1, prednisone 100 mg /day of each cycle) chemotherapy for a total of 6 cycles repeated every 3 or 4 weeks according to clinical toxicity. Patients who achieved an effective response (CR or PR) at the end of the six planned cycles have been randomized to receive or not INFα-2a 3 MIU sc every 3 days per week for one year. Of the 109 evaluable patients 94 (88%) obtained an CR. Fifty-two patients (48%) achieved a complete remission (CR) and 42 (38%) a partial remission (PR) to CECOP. Seventy-six CR and PR patients were randomized, 48 to no further therapy and 44 to INFα maintenance treatment. No differences in RFS (18 vs 20 months), PFS (22 vs 24 months) and OS (43 vs 46 months) were seen between the two treatment arms. These findings are consistent with the results reported in similar trials by A. Hagerman, A. Valenti, D. Molino, Bari.


Introduction. CLL and NHL-A are characterized by a progressive resistance to therapeutic agents with a median survival time of about 5 years for patients with advanced disease. Chlorambucil or cyclophosphamide with vincristine and prednisone are active combinations and purine analogues such as cladirebine have shown impressive activity in the treatment of these disorders. Based on encouraging results of our study (SBC 1999), cladirebine together with cyclophosphamide and prednisone (CCP) was given to B-CLL Binet stages B-D and IWF NHL-A IUCC stages III-IV patients whether or not previously treated in a national multicentric study.

Methods. From Dec. 1995 to Oct. 1998, 23 patients (pts) were included. 13 pts were male. Median age was 59 years (range 40-73) and median time since diagnosis was 2.7 years (range 0.8-12). 16 pts had CLL. 8 pts were chemotherapy naive. CCP was given on a 28-day (D) cycle basis for a minimum of 6 courses: Cladirebine 0.5 mg/m² iv bolus D1 to 5, cyclophosphamide 500 mg/m² iv D1 and dexamethasone 40 mg/m² D1 to 5. At an interim analysis, cladirebine dose was reduced to 3 days for 5 courses in pretreated pts because of unexpected toxicity.

Results. 2 pts were excluded from analysis (wrong histology). 1 pt declined treatment after registration. Median number of courses was 4 (range 1-4) for a total of 75 courses of CCP. Haematological toxicity during treatment included WHO-2 anemia in 6 pts, leucopenia in 10 patients and thrombocytopenia in 5 patients. 3 infections WHO-1 occurred in non pretreated pts and 13 in pretreated pts. 7 non haematological toxicities WHO-1 occurred. Complications after treatment included 3 deaths (peripheral neuropathy, pulmonary carinii pneumonia, thrombocytopenia) 1 transient hemolytic anemia, 2 bacterial pneumonia, 1 herpes zoster, 1 herpes simplex, 1 lung tuberculosis, 1 liver reactivation and 1 ostitis media. 5 complete and 8 partial responses were achieved for a total response rate of 88% in non pretreated pts and of 50% in pretreated pts.

Discussion. CCP combination as initially given in this 3758 protocol could not be safely administered in pretreated pts. In this group, cladirebine should not be given for more than 3 days in association with cyclophosphamide and prednisone. In contrast, non pretreated pts could receive CCP with an acceptable toxicity and this combination confirmed its high level of activity. However, fatal complications have occurred in 2 pretreated pts and 1 non pretreated pt showing the necessity of close follow-up not only during but also after treatment.

Phase II trial of Ceplastrum and Etoposide (EPO) in refractory B-cell chronic lymphoid malignancies.
Institut Gustave Roussy, Villejuif, France; ** Hôpital Necker Enfants-Malades, Paris, France.

Patients and methods: 13 patients (pts); 4 with chronic lymphocytic leukemia (CLL), 4 with mantle cell lymphoma (MCL) and 5 with follicular lymphomas (FL) were included. EPO combined: VP16 100 mg/m² X 5 days and ceplastrum 20 mg/m² X 5 days every 28 days. 6 courses were planned. Pts were evaluated after each cycles. All pts had previously received at least 3 lines of chemotherapy and were refractory to inclusion (except 1 pt who was refractory to 2 lines of chemotherapy). All were evaluable for response.

Results: Five response (38%) included 2 complete responses were observed in FL which lasted over 12 months and was longer than the best response previously achieved in these pts. 2/4 responses were observed in CLL. No response was observed in MCL. Myelodysplasia occurred in all the pts treated. Transient renal toxicity occurred in 2/13 pts. No toxic related death was observed.

Conclusion: EP is active in pts with refractory CLL and FL. Further studies are required to define the role of this combination earlier in pts with FL.

Rituximab as first-line treatment of follicular lymphoma (FL) patients with a low-tumor burden. Preliminary results of a phase II trial (M39080).

Introduction: There is no standard treatment of patients (pts) with stage III-IV low tumor burden FL. Rituximab (Macbher R, F. Hoffmann. La Roche, Basel) a humanized anti-CD 20 monoclonal antibody, was demonstrated to be active in relapsing FL pts with an overall response rate (ORR) around 50% and with a good tolerance. We report the preliminary results of the first trial of Rituximab as single treatment in previously untreated FL pts.

Methods: Informed pts were included if they had CD 20 positive FL (whatever cell type) diagnosed for less than 4 months, Ann Arbor stage II-IV, age 18-75, WHO status 0-1, measurable disease, no previous treatment. They also had to have a low-tumor burden with none of the following criteria: B symptom, tumor mass > 7 cm, organ compression or severe effusion, increased serum LDH level, serum β2 microglobulin > 3 ng/mL. Patients were treated with 4 weekly IV infusions of rituximab at a dose of 375 mg/m². Response was assessed 4 weeks (D0) and 8 weeks (D8) after treatment.

Results: Out of 50 registered patients from 10/97 to 09/98, one pt was excluded after pathology review and 49 could be analyzed for response. There were 26 M/24 F with a mean age of 52 years (32-75). Other characteristics were: 92% WHO status 0-1, 4 patients with Ann Arbor Stage II (9%), 11 stage III (22%) and 3 stage IV (70%), 9% (18%) with 1 extranodal site, 33 (60%) with narrow involvement. Treatment: tolerance (200 cycles) was excellent: no WHO grade 3 or 4 event, most frequently observed (especially during first infusion) grade 1-2 events were: fever (28% of pts), hypertension (12% of pts), skin rashes (5%), nasal symptoms (4%). Two pts were hospitalized for fever and hypotension.

Responses on day D0: complete response (CR) 20%, partial response (PR) 45%, stable disease (SD) 31%, progression (PD) 4%. All responses were confirmed on D78. Among 16 pts with SD disease at day 30, the evaluation at day 78 showed 1CR, 2PR, 11SD, 2 PD.

Conclusion: 1. Tolerance of Rituximab was excellent; 2. Encouraging response rates were observed, especially when considering the severe criteria used for response assessment; 3. Most responses occur early after treatment but some pts may have delayed responses. Molecular responses are presented in an other abstract.
LONG TERM FOLLOW-UP IN PATIENTS WITH FOLLICULAR LYMPHOMAS TREATED WITH ANTRACYCLINE CONTAINING REGIMEN


Department of Haematology University and Careggi Hospital Florence, Italy on behalf of Intergroupo Italiano Linfomi.

High percentage of complete remission in follicular lymphoma are obtained with antracycline containing regimens. In our Institution since 1974 we have applied a protocol the F12 which scheduling is: Adria 40 mg/m2 day 1, VCR 1,4 mg/m2 days 2 and 9, Bleo 10 mg/m2 days 2, 3 and 9,10, CTX 300 mg/m2 days 4,5 and 11,12; Prednisone 40 mg/m2 day 1 to 12. We report the results of a retrospective analysis of 105 patients (pts) treated with F12 between 1985 and 1996. The median age was 64 years (18-65%), 61% were stage III-IV, 26% were symptomatic, 20% had bulky disease and 35% had bone marrow involvement. The percentage of pts reached complete remission and 78% of them were consolidated with two cycles of a third generation regimen. With a median follow-up of 6 years (12-123 months) we observed an OS, DFS and PFS respectively of 90%, 70% and 63%. We have collected these cases during a retrospective study in a cooperative work with the Intergroupo Italiano Linfomi and we have compared our results with those obtained in 287 pts treated in other Institutions with CHOP or CHOP-like regimens. In these pts overall survival with the same follow-up was 71% in comparison to our 90% (p 0000). In the whole group (392 pts) a multivariate analysis showed that LDH value (p 002), age (p 000) and therapy (p 004) were statistically significant for OS. We conclude that either the different scheduling with repeated infusion of drugs in a week or the consolidation therapy could allow to obtain such results with F12 protocol.


Background: Spectrexx must be frequently considered during the evolution of chronic lymphoproliferative disorders (CLPD). Objectives: To retrospectively evaluate the results of spectrexx in patients (pts) with chronic lymphoproliferative disorders, in terms of opportunity, response and morbidity-mortality related to the procedure.

Material and methods: Between February 1981 and December 1999, 54 spectrexx were performed in pts diagnosed CLPD: 20 Chronic Lymphocytic Leukemia, 3 Diffuse Lymphomatous Lymphoma, 8 Follicular, 4 Marginal zone, 4 Mantle-cell, 3 Lymphoplasmacytoid. Decisions for spectrexx were made in: autoimmune cytopenias with no response to therapy; 22/56 pts (40%), therapeutic (mechanical or non-immune cytopenias; 11/56 pts (20%), diagnostic (in the onset of the disease or during transformation); 13/56 pts (23%), others 10/56 pts (17%). Evaluation for hematological response was performed according to peripheral blood counts after 30 days of spectrexx. Complete Response (CHR): hemoglobin >11g/dl and platelets >100.000 x10/l, Partial Response (PRH): hemoglobin > 11 g/dl or platelets >100.000 x10/l, No Response (NR): none of the above. Prophylaxis for infection: Penicillin once-a-month, and anti neumococcus vaccine (until 1994, after 1994 triple vaccination).

Results: Responses: CHR: 33/56 pts (59%), PRH: 14/56 pts (25%), NR: 3/56 pts (5.3%), 5/56 pts (10.7%) died within 5 days after spectrexx, (surgery-related mortality), 4/6 pts before 1990. Responses according to long-term follow-up in 50 pts: no specific therapy was required in 21 pts (42%) after spectrexx, and 29 pts (58%) had to be treated. Thirteen pts (26%) died between 1 year and 11 after spectrexx (8 = progression, 3 = opportunistic, 2 = cardiovascuolar). The remaining 37 pts are alive (37/56 = 66%)

Conclusion: According to this retrospective analysis, spectrexx remains a useful and feasible procedure in pts with CLPD with splenomegaly and/or hypertension, surgery-related complications are reduced in adequtely previously ‘prepared’ pts; also an adequate prophylaxis significantly reduces the risk of infection in this group of pts.


Background: Despite some progress in conventional chemotherapy, Low-grade non-Hodgkin Lymphomas (LGNHL) remain still incurable. The efficacy of Purine Analogues in LGNHL was recently reported, with a 65% remission rate (RR) for Fludara alone and more than 80% when used in combination, in untreated patients (pts).

Objectives: To evaluate: a) the efficacy of Fludarabine (FAMP) + Mitoxantrone (Mtx) in untreated LGNHL pts in terms of remission rate, disease-free and overall survivals, and b) side-effects and toxicity of this regimen in this group of pts.

Material and Methods: Between October 1996 and October 1998 34 pts, age: 68 yrs - r: 44-83; stages II (5), III: 7 (20%), IV: 22 (65%), entered the study. Treatment regimen: FAMP 25 mg/m2 x 3 days and Mtx 12 mg/m2 ay 1, 30 minutes before first FAMP dose, every 28 days, number of cycles planned: 6. The total number of cycles administered was 169, (20 pts - 59% = 6 cycles each; 9 = 26% = 4 cycles; 3 = 9% = 3 cycles; 2 = 6% = 2 cycles) Thirty-two pts were evaluated for response and toxicity.

Results: complete response (CR): 22/32 pts (68.7%); partial response (PR): 4/32 pts(12.5%); progression (P): 3/32 pts (9.4%); stable disease (SD): 3/32 pts (9.4%); the response rate being 81%.

Toxicity grade II (19/47 cases) was observed in 47/169 cycles (28%). No immune cytopenias or opportunistic infections related to therapy were reported. At the moment of this interim analysis, all pts achieving CR remain in remission and alive.

Conclusion: Despite the short-term follow-up and the relatively small cohort of pts analyzed, results of FAMP-MTX regimen seem promising in terms of response rate and toxicity in LGNHL previously untreated pts. The study remains open to the enter of new pts.

FLUDARABINE AND IDARUBICIN FOLLOWED BY IL-2 IN THE TREATMENT OF PRETREATED ADVANCED INDOLENT LYMPHOMA - RESULTS OF A PHASE II STUDY.

K. Fenchel, S. Lasannen, E. Borghardi, K. Dreher, A. Gurser, H. Praele, J. Aztoppod


Introduction: Fludarabine monophosphate (Fludara) has been shown to be effective in pretreated low grade B cell lymphoma, but leads to significant CD4+ cell depletion.

Methods: In total, 30 patients (pts) with advanced and resistant indolent lymphoma, 11 with B-CLL, 3 with immunocytoytic lymphoma, 2 with MAL-T-Lymphoma, and 14 with cc-cb NHL were treated with Fludara and Idarubicin (Zavedos). Fludara was administered at a dosage of 20 mg/m2 as 5.5 infusion for 5 days per cycle, Zavedos at a dosage of 8 mg/m2 on 3 days per os. Interleukin-2 (Proleukin) was given in a dose escalating manner (group 1 without Proleukin, group 2: 0.5 Mio. IU/m2, group 3: 2.5 Mio IU/m2, and group 4: 10 Mio IU/m2 on days 8, 9, 22, and 23).

Results: 2/30 pts. are too early for evaluation, 10/28 (36%) evaluable pts. achieved CR, 13/28 (46%) pts. achieved PR, 2/28 (7%) pts. achieved stable disease, and 2/28 (7%) pts. showed progressive disease. The median remission duration was 7.6 months (2-17= months). 8 of the patients in PR relapsed between 3 and 8 months. Major toxic side effects were myelosuppression (one pt. Grade 3) and non-severe infections.

Conclusions: In all pts., Fludara led to a marked CD4+ cell depletion, but this decrease was significantly reduced in the group receiving IL-2. The addition of the thrombocytopenia in this regimen didn’t enhance the myelotoxic effect known from Fludara-monotherapy, but improves overall remission rate up to favorable 82% and Proleukin reverses CD4+ suppression due to Fludara-therapy without compromising cytotoxic efficacy.
GRADING OF FOLLICULAR LYMPHOMAS ACCORDING TO PROLIFERATION AND APOPTOSIS RELATED MARKERS.

Hedwig Truong, Harry Schouten, Marius Nap, Frerk Bot
Departments of Pathology and Internal Medicine, University Hospital Maastricht.

AIM OF STUDY: Grading of follicular lymphoma has been and still is a problem; inter- and intra-observer variation is high, while there are clinical consequences involved in assigning a patient to a low- or high-grade group. This pilot study's purpose is to establish a quantitative method of grading, and thereby reducing the current problems in this field.

MATERIALS AND METHODS: 56 paraffin embedded follicular lymphoma specimens of 35 patients, diagnosed from 1987 till 1998 were collected. Immunohistochimical stains were done using antibodies directed against bcl-2, Mib-1, p53 and M3O (a new marker for early apoptosis) and the percentage of positive cells was established per 1000 cells. The lymphomas were histologically graded according to the criteria adopted for the REAL-classification (>50% large cells in high grade). The mean values for the markers tested in the low- and high-grade groups and the bcl-2 positive and negative groups were compared.

RESULTS:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mib-1</th>
<th>M3O</th>
<th>P53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (n=25)</td>
<td>22.13 +/- 14.16</td>
<td>10.23 +/- 9.5</td>
<td>22.3 +/- 9.05</td>
</tr>
<tr>
<td>Highgrade (n=11)</td>
<td>9.67 +/- 9.5</td>
<td>22.7 +/- 11.68</td>
<td></td>
</tr>
<tr>
<td>bcl-2 positive (n=31)</td>
<td>22.87 +/- 14.7</td>
<td>10.96 +/- 9.75</td>
<td>21.64 +/- 9.15</td>
</tr>
<tr>
<td>bcl-2 negative (n=5)</td>
<td>35.16 +/- 14.2</td>
<td>4.58 +/- 5.2</td>
<td>26.36 +/- 13.11</td>
</tr>
</tbody>
</table>

*p<0.05 (t-test) Values are mean values +/- std

Mib-1 positive cell numbers were significantly higher in the bcl-2 negative group, especially in the low-grade compartment (data not shown here). Bcl-2 negativity was associated with lower apoptosis rates, defined by M3O reactivity, indicating that apoptosis in this group may be inhibited through another pathway. There was no significant difference in p53 reactivity, possibly because of staining of wild type p53.

Conclusions: The cases with high Mib-1 and negative bcl-2, which cannot be defined histologically, might represent a group with a worse prognosis. The results of the clinical analysis will be presented, the project will be extended and more apoptosis related markers will be determined.

RESPONSE OF REFRACTORY AND RELAPSED LOW GRADE NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA TO DEXA-BID, A BENDAMUSTINEHYDROCHLORIDE CONTAINING REGIMEN.

Dept. of Hematology and Oncology, University of Rostock, PO 10088, 18055 Rostock, Germany

Objective: Evaluation of the efficacy of a new treatment protocol containing bendamustinehydrochloride and idarubicin for relapsed or refractory, multiretreated low grade NHL and CLL.

Materials and methods: Dexe-BID consists of Dexamethason 8-8-4mg/m² po i.d., bendamustinehydrochloride 70mg/m² i.v. i.d.-3, idarubicin 40mg/m² i.v. i.d.-2. Cycles were repeated every 21 days or after recovery from neutropenia, G-CSF 5µg/kg sc was given until WBC recovery - starting d4. Elegibility-criteria were: CLL Rai-stage III-IV and low grade NHL relapsed within the first year of remission or refractory disease defined as no change or progressive disease under pretreatment, age >75 years, ECOG <3.

Results: 14 patients (5 male / 9 female) with CLL (5pts) and NHL (9 pts): 4 cb-cc, 3 immunocytoma, 1 MALT were treated. Median age was 65 years (range 52-73). 2pts with CLL had a transformation into a high grade NHL. Median time from first diagnosis was 48 month (range 9-118), median number of preceding treatment regimen was 3 (range 1-7). 58 courses Dexe-BID were evaluated with a median number of 4 courses per pt. (range 1-7). 13 pts achieved PR after 2 (resp. 1) courses, 1 pt. had NC at the end of treatment 4 pts had a CR, 7 pts had a PR and 3 pts had PD. The median duration of remission was 7 months (range 1-18 months). Toxicity was tolerable. In 13/58 courses leukopenia <1,0 GPT/l occurred, in 11/57 thrombocytopenia <25 GPT/l. Infections WHO grade 2-3 occurred in 12/58, grade 4 in 2/58.

Conclusion: These preliminary results show that Dexe-BID is an active therapy for remission induction in multiple pretreated pts. with low grade NHL and CLL. The efficiency in earlier disease stages should be evaluated.

BENDAMUSTIN IN INDUCTION OF APOPTOSIS IN B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA.

C. Schwaenke, T. Karakas, M. Schrader, T. Hecker, L. Bergmann
Medical Clinic III University of Ulm, 89081 Ulm

Bendamustin is a new agent in the therapy of chronic lymphocytic leukemia (CLL) which probably combines the features of alkylating agents and purin analoga. In clinical studies bendamustin has shown its efficacy for the treatment in low and high grade non Hodgkin's lymphomas. This study investigated the in vitro ability of bendamustin alone and in combination with fludarabin to induce apoptosis on freshly isolated peripheral lymphocytes in B-cell CLL.

Peripheral mononuclear cells, isolated from highly leukemic CLL patients (n = 18), were cultured in the presence of bendamustin, fludarabin or their combination. The percentage of apoptotic cells was determined with flow cytometry using the fluorescent DNA-binding agent 7-ADD at 48 h. The constitutive Bcl-2 and bax protein expression and their alterations during the incubation with bendamustin or fludarabin was determined by flow cytometry on permeabilized cells using a monoclonal bcl-2 and bax antibody. Additionally the mRNA expression of bcl-2 and bax was analysed with the RNase protection assay.

Bendamustin was shown to be efficacy in inducing apoptosis on CLL-cells in a dose dependent manner from 8 µg to 94 µg after 48 h.

In 10/12 B-CLL cells the combination of bendamustin with fludarabin leads after 48 h to 1,4-fold higher synergistic effect in inducing apoptosis than expected for the addition of apoptotic cells of bendamustin or fludarabin alone.

Preliminary, the level of initial bcl-2 and bax protein expression and mRNA expression in B-CLL cells did not changed under the incubation with bendamustin or fludarabin over a time-period of 48 h.

In conclusion, this study demonstrates for the first time the in vitro efficacy of bendamustin in inducing apoptosis in B-CLL-cells alone and in combination with fludarabin. Additionally, no change in the Bcl-2 and Bax protein- and mRNA-level could be observed.

CYCLOPHOSPHAMIDE, FLUDARABINE, MITOXANTRONE AND PREVINISOLE IN LOW GRADE NON-HODGKIN'S LYMPHOMA.

D. Matte, M. Grasse, M. Bonderoni, C. Castellino, E. Gallo and A. Gallianni
Hematology Department, S. Croce Hospital, Cuneo, Italy

Introduction: Fludarabine, Mitoxantron and Dexametason produce CR in 47% and PR in further 47% of pretreated patients (pts) with low-grade non-Hodgkin's lymphoma (LG-NHL), with molecular response in some of them. Experimental data suggest that the therapeutic efficacy of alkylators could be increased by Fludarabine, which prevents DNA-repair and induces apoptosis. Moreover, these drugs are devoid of cross-resistance.

Methods: In a phase II study, we delivered Cyclophosphamid 300 mg/m² i.v. on day 1, Fludarabine 25 mg/m² on day 1-3, Mitoxantron 10 mg/m² on day 1, Prednisolon 40 mg/m² p.o. on day 1-5 (C-FNOP), given monthly, for six cycles. Patients were staged with FABCRUIN, Co-transaminase and Acychoil were given in all pts. Grade 4 WHO neutropenia was treated with Filgrastim until recovery. Sixteen consecutive pts. have been enrolled: 6 at diagnosis and 10 pretreated. Pts. characteristics were the following: median age 46 years (34-72), >95% 13/13, hystology: follicular 10, small lymphocytic 3, splenic lymphoma with violet lymphocytes 2, discordant lymphoma (follicular/large cell lymphoma) 1. Pts. presented with stage III, 11 with stage IV, all with bone marrow (BM) as the only extranodal site involved. Pretreated pts. included 1 refractory, 1 relapsed after CHOP, 8 in progression after PR obtained after a mean of two previous cycles (range 1-4).

Results: Response was evaluated by clinical examination and whole-body TC-scan, and in pts. with BM involvement, by morphology and flow-cytometric assay. Molecular response was evaluated in 7/10 pts with follicular lymphoma with bone marrow involvement, expressing bcl-2 rearrangement by RT-PCR.

Results: 13 pts. received 4 courses and were evaluable for response; 5 pts still in treatment received <4 courses and are evaluable for toxicity. CR was obtained in 19/33 pts. (59%), and a very good PR (disappearance of all adenopathies and a minimal persisting BM infiltration) in the remaining 4 (30%). After a median follow-up of 9 months (1-14), the 9 complete responders are still in CR. Molecular response was achieved in 3/7 pts. Hematological toxicity according WHO was grade 3 for platelets in 6/16 pts and grade 4 in 3/16 pts. Grade 4 for neutropenia was recorded in all pts. Hematological toxicity was observed after the fourth course in all cases. One pt. died of pneumonia at the end of the treatment. No other extra-hematological toxicity was recorded. Conclusions: C-FNOP is an highly effective regimen in LG-NHL.
FLUDARABINE (FLU) IN COMBINATION: AN EFFECTIVE THERAPY FOR RELAPSED OR REFRACTORY LOW-GRADE NON-HODGKIN'S LYMPHOMA (LGL).


Department of Haematology, S.Martino Hospital, Genova, Italy.

Introduction: FLU, alone or in combination, reported encouraging results in LGL. Methods: We performed a phase II study to evaluate the efficacy and toxicity of FLU in relapsed or refractory LGL in two combination schedules. A) First schedule: FLU 30 mg/m²/d. 1-3, cytoxan 300 mg/m²/d. 1-3; B) Second schedule: FLU 25 mg/m²/d. 1-3, cytoxan 300 mg/m²/d. 1-3, mitoxantrone 10 mg/m²/d. 1. Treatments were repeated at 4-week intervals for a maximum of 6 courses. Pt characteristics: From June 1996, 44 adult pts with LGL of Groups A (10 pts), B (13 pts), C (16 pts), E (5 pts) / WF entered new studies. A) Patients 22; male 9, female 13; median age 50 years (range 29 to 73); Ann Arbor stage IIIIV, 6/16; Status of pts at FLU: PR1 8, relapse 11, NR 3; median previous CT lines 3 (range 1 to 5). B) Patients 22; male 13, female 9; median age 56 years (range 36 to 71); Ann Arbor stage II/IIIIV, 2/8/12; Status of pts at FLU: PR1 8, relapse 6, NR 8, median previous CT lines 3 (range 1 to 5). Results: A) CR 12 (55%), GPR 2 (9%), PR 5 (23%), NR/PD 2 (9%); B) CR 9 (41%), GPR 1 (4.5%), PR 7 (32%), NR/PD 5 (22.5%). Extra-haematological toxicity was mild and did not delay treatment. Haematological toxicity was present in both groups of patients. The most frequent was neutropenia: A) grade 1-2 = 63%, grade 3-4 = 37%; B) grade 1-2 = 54%, grade 3 = 36%. In Group A) 5 pts died: 1 of sepsis, 1 of aplasia, 3 of lymphoma. In group B) 5 pts died of lymphoma. Conclusions: The FLU combination was active in pts with relapsed or refractory LGL in both treatment groups. Overall toxicity was acceptable and, in general, restricted to haematological toxicity.

PHASE II STUDY OF A CHIMERIC ANTI-CD20 MONOCLONAL ANTIBODY (IDEC-C2B8, RITUXIMAB) IN RELAPSED INDOLENT B-CELL LYMPHOMA


Introduction: Rituximab is a chimeric monoclonal antibody binding selectively to CD20 antigen on B-cell, inducing apoptosis, and mediating CDC and ADCC [Hoff, Blood 1994; 83:435]. The U.S. clinical trial in 166 relapsed patients (pts) with low-grade or follicular B-NHL demonstrated an overall response rate (ORR) of 50 % with a median TTP of 13.2 months [McLaughlin, JCO 1998; 16:295]. This study investigated whether a high rate of clinical efficacy could also be achieved in Japanese pts.

Methods: Relapsed B-NHL pts with IWF type A - E [excluding MCL] or REAL type II-1, 2, 4, 5 and 6 histology were treated with rituximab at 375 mg/m²/weekly 4 infusions based on the results of the preceding phase I study in Japan [Tohno, Ann Oncol 1998; 9:527]. Infusion was started at 20 mg/hr, then escalated hourly up to 100 mg/hr then 200 mg/hr. The treatment pts were monitored until tumor progression. Response was evaluated by the modified WHO criteria, and adverse drug reactions (ADRs) by JCOG toxicity criteria [modified and expanded version of NCI-CTC].

Results: A total of 69 pts from 15 institutions were enrolled. Central pathology review based on HE and immunohistochemical staining was conducted in 67 pts (97.1%), and 5 were judged ineligible. Besides, one pt was excluded due to positive HBV serology. Therefore, 61 pts were evaluated for efficacy on a protocol-compatible (PO) basis. Females comprised 52.5% (32/61 cases). The median age, number of prior chemotherapy and interval since last therapy were 51 years, 3 regimens and 8.5 months, respectively. Follicular lymphomas accounted for 91.8% (56/61 cases).

The ORR was 55.7% with 10 CRs [16.4%] and 24 PRs [39.3%] as shown below:

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Number of patients</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>61</td>
<td>10</td>
<td>24</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>55.7%</td>
</tr>
<tr>
<td>CRT</td>
<td>60</td>
<td>10</td>
<td>24</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>55.7%</td>
</tr>
<tr>
<td>LD</td>
<td>60</td>
<td>10</td>
<td>24</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>55.7%</td>
</tr>
</tbody>
</table>

Mild to moderate ADRs [such as fever, chills, rash and itching] presumably caused by cytokine release were frequently seen during the 1st infusion, but decreased during the 2nd through 4th. Grade 3 non-hematologic or grade 4 hematologic ADRs occurred only in 3 pts (systemic rash, herpes zoster and neutropenia in one pt each). Quantitative HACA developed in one pt, but did not cause severe ADR.

Conclusions: Rituximab was effective for relapsed indolent B-NHL in Japanese as well as US pts, warranting further studies such as combined use with chemotherapy or other modalities.