HIGH RISK POST-TRANSPLANT LYMPHOPOLERATIVE DISORDER (PTLD) CAN BE CURED BY "QUINTUPLE APPROACH"  
Departments of Hematology, *Gastroenterology, Pathology, Leiden University Medical Center, Nki Amsterdam and Dental Rotterdam, The Netherlands*.  
PTLD represents an EBV-related B-cell proliferation ranging from mononucleosis infections to lymphoma. The prognosis of the latter is extremely poor with survival usually < 1 year. Since 1993 we used a combined approach for PTLD consisting of 5 interventions: 1) reduction of immunosuppression; 2) antiviral drugs; 3) interferon-α 3 MIU daily for 1 week; 4) high dose gamma globulin 0.4 g/kg/day 1-3; 5) anti-CD19 monoclonal antibody 50 mg day 1-5. Six consecutive patients were treated, 24, 46, age 26-51 yr. They had undergone a bone/renal (n=2), liver (n=2), heart (n=1), or kidney (n=1) transplantation. Staging showed cavo pelvic disease in 2 (n=2), cholecodochus (n=1). Six patients received the full quadruplet approach and all rapidly obtained a continuous CR with a duration of >90 days. Two patients did not receive rituximab for fear of loss of the transplant. One had a secondary NHL 96 months after kidney transplantation and obtained a CR 7 months after the initial therapy without any further intervention except for a permanent reduction in immunosuppression. The other one (heart transplant) a CR following a relapse at months 4 followed. The three patients with a liver or heart transplant could keep their grafts. In both pancreas-kidney recipients, the grafts were intentionally removed. The patient with a kidney transplant lost it after one year.  
In conclusion, this combination approach resulted in a favorable outcome in the majority of patients with high risk monoclonal PTLD after solid organ transplantation.

UMDNJ- New Jersey Medical School, Newark, New Jersey.  
Post-transplant lymphoproliferative disorders (PTLD) occur in 2-10% of the solid-organ transplant population. Reduction of immunosuppressants, treatment with anti-virals (acyclovir) and interferon have all been recommended prior to chemotherapy, but are usually ineffective in aggressive lymphomas. Despite chemotherapy, monoclonal grade lymphomas are associated with a high mortality. We report the first successful treatment of a monoclonal high-grade lymphoma following liver transplant with Rituximab. The patient developed cryogenic cirrhosis and required a liver transplant in December 1997. Her post-transplant course was unremarkable until May 1998, when she developed a sore throat, cough and back pain. She was found to have a grossly enlarged right tonsil on laryngoscopy, right lower lobe lung mass and retroperitoneal adenopathy on CT scan. Biopsy of the tonsil and open biopsy of the right lung mass demonstrated atypical, large lymphoid cells which were virtually all CD20+. Flow cytometry within the large cell gate co-expressed CD19 and kappa light chains. In situ hybridization was positive for Epstein-Barr (EBER) RNA. The patient had withdrawal of her immunosuppressants and acyclovir was added without response. She was treated for four consecutive weeks with Rituximab 375 mg/m² IV in June 1998. She experienced no side effects. The patient underwent repeat laryngoscopy with biopsy and repeat CT scan after eight weeks following therapy which demonstrated no evidence of disease. She has been maintained on low dose cyclosporine and prednisone for graft rejection, since June 1998. Six month (January 1999) follow-up scans continue to reveal no active disease. Rituximab warrants further investigation as an effective, non-toxic therapy for the treatment of PTLD.
HISTOPATHOLOGY AND CLINICAL CHARACTERISTICS OF POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLDs) IN ALLOGRAFT RECIPIENTS: REPORT OF 19 CASES FROM A SINGLE CENTER


Department of Hematology and "Pathology, Niguarda Ca' Granda, Milan, Italy.

During the years 1973-1998, 2,053 transplant (tx) were performed: 493 heart, 49 lung, 420 liver and 1,091 kidney tx. Standard immunosuppressive protocols - consisting of ATG, cyclosporin A, prednisone and azathioprine - were administered; OKT3 was never used. PTLD was diagnosed in 19 pts (0.935%, 14 M, 5 F); heart 9/493 (1.8%), lung 14/420 (3.3%), liver 3/420 (0.7%), kidney 6/1091 (0.6%). Data on PTLDs are shown in the table:

<table>
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<th>PH/M</th>
<th>Histo</th>
<th>Polyclonal</th>
<th>Monoclonal</th>
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<tr>
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<table>
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<th>N Patient</th>
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<tr>
<td>Median age at PTLD-diagnosis (range)</td>
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<tr>
<td>Median time to PTLD-diagnosis (range)</td>
<td>2/4 to 6/6 months (1-11/4 months)</td>
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<td>Stage at diagnosis: (KS)</td>
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<tr>
<td>Monoclonal</td>
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</table>

**PH** = plasmocytosis hyperplasia; **MA/MM** = malignant lymphoma/multiple myelomas

**Clinical course and outcome:** 10/19 received Acyclovir (Acv) followed by Ganciclovir for chronic EBV disease with recurrent monoclonal-cell activations. At 22 mos from dx of PTLD, histologic shift to polymorphic PTLD was observed and chemotherapy (CHT) was started. The pt is alive at 24 mos follow-up (dx) (P). Polyclonal PTLD was followed by 1pr. 

**EBER positivity:** 1/2 (7/2) 1/1 (11/5) n.d.

**CONCLUSIONS:**
- Acyclovir and Ganciclovir are effective in managing PTLD.
- Early identification and treatment of PTLD are crucial.
- Further studies are needed to evaluate the long-term outcomes of these treatments.

**REFERENCES:**

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9.2-1TC-Tositumomab imaging of lymphoma: correlation with histological type and treatment response.


Radiation Medicine Center, BARC, Tata Memorial Hospital, Mumbai, India.

Introduction: 90Y-Te-Tositumomab is one of the lyophilic radiotracers that has been used to target lymphoma cells. However, the specific radiolabel on the antibody is not known. The aim of this study was to evaluate the efficacy of 90Y-Te-Tositumomab in the treatment of lymphoma.

Methods: A total of 20 patients with lymphoma were enrolled in the study. The patients were divided into two groups: Group A with a diagnosis of lymphoma, and Group B with a diagnosis of leukemia. The patients were treated with 90Y-Te-Tositumomab and the response was evaluated using standard imaging techniques.

Results: The overall response rate was 85% in Group A and 70% in Group B. The median time to response was 4.5 months in Group A and 6 months in Group B. The median duration of response was 12 months in both groups.

Conclusion: 90Y-Te-Tositumomab is an effective treatment for lymphoma and leukemia. Further studies are needed to evaluate the long-term outcomes of these treatments.

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COMPARISON OF THE PHARMACOKINETICS AND BIO AVAILABILITY OF ORAL FLUDARIABINE PROPHYLAXIS ADMINISTERED EITHER FASTING OR AFTER FOOD.

D. G. Osier, J. A. Orchard, D. Collfard, D. Cunningham, S. Johnson, A. Parker, S. Thorpe, H. Guoexpress, Haematology Department Royal Bournemouth Hospital, Royal London Hospital, St Thomas and Somerset Hospitals, Western General Hospital, Edinburgh, UK, Schering Health Care, Schering AG, Berlin, Germany.

Oral fludarabine phosphate has a bioavailability of approximately 60% when administered after an overnight fast. To determine whether the bioavailability is affected by food, a prospective randomised two way crossover study was performed on 16 previously treated patients with either chronic lymphocytic leukaemia or low grade B cell non Hodgkin's lymphoma. On day 1 of the first cycle of the treatment patients randomly assigned to receive 90 mg of oral fludarabine phosphate after either an overnight fast or following a standard breakfast containing approximately 1,000 calories. Each patient received treatment under both feeding regimens. Intravenous fludarabine phosphate (25 mg/m² over 30 minutes) was administered on days 3 - 6 of the first two cycles. All patients were eligible to receive a further four cycles of fludarabine by the standard iv regimen. The pharmacokinetics of 2-F-Ara-c (the primary plasma metabolite of fludarabine phosphate) were evaluated 48 hours post-administration in each case. The pharmacokinetic data on the 16 patients who completed both cycles of treatment is given below.

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**Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(0-24h) [g*haval/0.1]/ng m/min</th>
<th>AUC(0-48h) [g*haval/0.1]/ng m/min</th>
<th>Cmax [ng/mL]</th>
<th>Tmax [h]</th>
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<tr>
<td>Fasted mean ± s.d.</td>
<td>3.25 ± 1.56 (n=16)</td>
<td>3.91 ± 2.77 (n=15)</td>
<td>488 ± 270 (n=16)</td>
<td>1.3 ± 0.74 (n=16)</td>
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<tr>
<td>Non-fasted mean ± s.d.</td>
<td>3.28 ± 1.48 (n=15)</td>
<td>4.23 ± 2.76 (n=16)</td>
<td>442 ± 181 (n=16)</td>
<td>2.2 ± 1.0 (n=16)</td>
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</table>

AUC: area under the curve; Cmax: maximum plasma level, Tmax: time of peak of maximum plasma level

**Conclusion:** Oral fludarabine with food resulted in a slight increase of total systemic availability and a delayed occurrence of a slightly reduced peak plasma level of 2-F-Ara-c. However, these differences are clinically irrelevant and in therapeutic regimens oral fludarabine phosphate can be taken either on an empty stomach or together with food.
PHASE-I STUDY OF BBR2778, A NEW AZA-ANTHRACENEDIONE, IN ADVANCED OR REFRACTORY NON-HODGKIN LYMPHOMAS

P. Borghmann, R. Knippertz, R. Schnell, G. Cambron, V. Diehl, A. Engert
1Klinik I für Innere Medizin der Universität Köln, Josef-Stellmann Strasse 9, 50924 Köln,
2Clinical Research Boehringer Ingelheim Italia

Introduction: BBR2778 is a new azanthracycline with superior toxicity profile and antitumor activity against leukemias compared to Doxorubicin or Mitoxantrone in animal models. Here, we report on the first results of BBR2778 in a phase-I study in patients with relapsed/refractory lymphoma or chronic lymphocytic leukemia, in which established chemotherapy has failed.

Methods: Primary objective of this phase-I study was to determine the Maximum Tolerated Dose (MTD) of BBR2778 for a 4/6 x 3 treatment schedule weekly administration on days 1, 7 and 14, repeated on day 28 on the basis of the Fibonacci dose escalation method. BBR2778 was diluted in 500 ml normal saline and administered by an 1 hour infusion. Secondary objectives included the dose limiting toxicity (DLT), clinical pharmacokinetics and any antitumor activity.

Results: 26 pts have been enrolled and are evaluable. 7 dose escalation groups have been completed at a dosage of 5, 10, 15, 25, 34, 36 and 84mg/m² respectively in these 26 pts. On the 7th dose level (84mg/m²) 6 pts had to be included, since DLT has been observed with neutropenia WHO grade III (>7 days) in 3/6 pts, neutropenia grade IV in 2/6 pts and thrombopenia grade IV in 1 pt. Apart from vomiting, nausea and alopecia no other serious drug related side effects could be observed.

Tumor response has been as follows: complete remission (1), partial remission (3), stable disease (9), progressive disease (13). Pharmacokinetic analysis showed a large volume of distribution, a high plasma clearance and a long elimination half-life.

Conclusions: These results indicate that the DLT of BBR2778 is neutropenia and that this new drug seems to be effective even in heavily pretreated pts with NHL. Since the main toxicity of BBR2778 is myelosuppression that may be overestimated in these pts with markedly reduced hematopoietic capacity, we would recommend a dosage of 64 mg/m² for a clinical phase II study.

MURINE AND HUMAN ANTI-CD30 SINGLE-CHAIN Fv SELECTED BY PHAGE DISPLAY AND FUSED TO PSEUDOMONAS EXOTOXIN A SHOW HIGH TOXICITY AGAINST HODGKIN-DERIVED CELLS

B. Matthey1, S. Barth1, A. Klimka1, M. Huhm2, V. Diehl1, H. Hoogenboom1, A. Engert1
1Laboratory of Immunotherapy, University Hospital of Cologne, Cologne, Germany;
2CEASEM at the University Hospital Maastricht, the Netherlands

Introduction: Since the CD30 receptor is highly overexpressed on the surface of Hodgkin- Reed/Sternberg and other lymphoma cells, we constructed a new recombinant anti-CD30 immunotoxin fusing a high-affinity binding moiety to a potent bacterial toxin (Pseudomonas Exotoxin A).

Methods: We first synthesized a single chain variable fragment (scFv) from the murine anti-CD30 antibody Ki-4. To retrieve a functional high affinity scFv we then cloned a cDNAs assembling VH- and VL- genes into a phagemid vector. Plasmidous phages displaying scFv on their surface and their genes within the phage particle were produced, purified and selected for binding on the Hodgkin cell line L540Cy. Two rounds of selection on the Hodgkin cells with scFv-phages derived from a mini-repertoire of 100,000 different clones were necessary to retrieve a binding Ki-4-scFv clone. To reduce the immunogenicity we subsequently created a human anti-CD30 scFv antibody using guided selection. Binding clones were characterized by sequencing, ELISA, FACS analysis, competition assays and immunohistochemical staining, showing their specificity for the original Ki-4 epitope within the CD30 receptor. The recombinant murine and human anti-CD30 scFv antibodies were genetically fused in a deletion mutant of Pseudomonas exotoxin (ETA) using an improved new PET-derived expression vector (gBM1.1). Results: The results of anti-CD30(scFv)ETA’ imunotoxins were expressed in E.coli and binding properties of anti-CD30(scFv)ETA’ were assessed on CD30+ and CD30- cell lines by FACS. The cytotoxic potency was determined by MTT-assay. Murine Ki-4(scFv)ETA’ inhibits the protein synthesis of L540Cy cells by 50% at concentrations of 3 μg/ml. The IC50 of the human construct was slightly higher.

Conclusions: These recombinant immunotoxins are currently being investigated in vitro for their value as new immunotherapeutic agents in the treatment of Hodgkin’s lymphoma and other CD30-positive malignancies.

9. Miscellaneous

A MURINE ANIMAL MODEL OF HUMAN ANAPLASTIC LARGE CELL LYMPHOMA

C. Bissett1, H. van Steenis1, H. Wagner1, G. Wiedemann2, M. Mert1, A.C. Feller1
1Institute of Pathology, University of Luebeck
2Ludwig Institute, Brussels

Introduction: As there is still a high rate of mortality (15-50%) of patients suffering from anaplastic large cell lymphoma (ALCL) or Hodgkin’s disease (HD) treated with standard adjuvant chemotherapy, there is a need for an animal model to study ALCL and HD in vivo.

We were able to establish a murine animal model of ALCL with the typical features of the disease in humans in order to create new immunotherapeutic strategies.

Methods: A murine IL-9 dependent T-cell line was transfected with CD40-DNA. By injecting the transfecants subcutaneously into syngeneic mice (C57/B6) tumors with all morphological and immunophenotypical features of ALCL were induced. These tumors couldn’t be cured by adjuvant high dose chemotherapy.

Different immunotherapeutic approaches were used. Vaccination of mice was performed by intraperitoneal injection of irradiated tumor cells prior to, in combination with, and after application of vital tumor cells. Additionally, immunostimulatory CpG-DNA oligonucleotides (ODNs) were injected with or without irradiated tumor cells at various timepoints. As tumorinjections were proven to express a Th2 cytokine profile we treated mice with variable combinations of Th1 cytokines or Th2-anticytokine antibodies.

Results: The IL-9 transfected cell line is tumorigenic after injecting into immunocompetent syngeneic mice with striking parallels to ALCL in humans.

Vaccination with irradiated tumor cells prior to injection of vital tumor cells successfully prevented or led to significant delay of tumor growth in all animals. Vaccination in combination with or after injection of vital tumor cells caused a delay of tumor growth in some of the mice tested. While vaccination in combination with CpG-ODNs significantly delayed or prevented tumor growth. The treatment with CpG-ODNs alone led to a delay of tumor growth in 40% of the mice. At least a delay or some experiments a complete abrogation of tumor growth was caused by subcutaneous injection of cytokines. Depending on the combination of cytokines used as well as on the tumor stage when therapy was initiated Conclusion: These mouse models reveal many parallels to ALCL in humans. As a useful experimental in vivo system for testing new therapeutic approaches, specific immunotherapeutic techniques could be established. Vaccination of irradiated tumor cells is a potent target of a specific immune response against ALCL, which can be supported by CpG-ODNs as adjuvant. Specific cytokines or anti-cytokine antibodies can significantly modify or suppress tumor growth. In summary, immunomodulatory agents seem to be new promising tools in the therapy of malignant lymphoma.

Fourth Dept. of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

Introduction α-Galactosylsaccharide(α-Gal) has been reported to induce marked proliferative response of Var™NK T cells and augmentation of the in vivo NK activity of syngeneic mice. It also showed significant antitumor activity in mice model with lung and liver metastasis of solid cell tumor line. However, it has not been clear whether α-Gal has antitumor activity against lymphoma. Aim of this study was to investigate whether α-Gal has strong antitumor activity against lymphoma cells that were inoculated in mice and explore the mechanism of the antitumor activity.

Methods: Kirin Brewery Co. Ltd provided α-Gal. BW5147 murine T-cell lymphoma cell line was ATCC and syngeneic AKRJ mice were from Crea Japan Co. Ltd. Intraperitoneal administration of BW5147 were s.c. transplanted into the back of AKRJ mice. α-Gal (100μg/kg, i.p.) was administered on the day after tumor inoculation and conducted every other day total 4 times. NK cytolytic activity was assayed using standard 51Cr-release assay with YAC-1 cells as target. Serum IL-12 and INF-γ were assayed by ELISA.

Results: α-Gal administration produced 50% reduction of tumor growth. Survival in α-Gal treated mice was 32.4days, significantly longer(p<0.01) than 21 days in control mice. One of seven α-Gal treated mice showed disappearence of inoculated tumor and later rejected second challenge of BW5147 inoculation. NK activity in α-Gal treated mice was 30%, significantly stronger than 3% in control mice. Serum IL-12 was 232pg/ml in α-Gal treated mice, while 38pg/ml in control mice. Serum INF-γ was 935pg/ml in α-Gal treated mice, while less than detectable level in control mouse.

Conclusions: These data suggested α-Gal would be a new and potent therapeutic agent against lymphoma. It was also demonstrated that the mechanism of its action was through marked activation of NK activity accompanied with elevated IL-12 and INF-γ.
ENHANCED SENSITIVITY OF LYMPHOMA CELLS TO DOXORUBICIN WITH THE BUTYRIC ACID DERIVATIVE AN9

N. Nurse1, T. Kusakabe, M. Imeda, Y. Honna2
1. 1st Dept Int Med, Toho Univ Sch Med, Tokyo, Japan
2. Saitama Cancer Ctr Res Inst, Saitama, Japan

Introduction: Pivaloxymethyl butyrate (AN9) is an anticancer derivative of butyric acid. AN9 and antineoplastic drugs synergistically inhibit the growth of lymphoma and leukemia cells in vitro and in vivo. The present study was undertaken to examine the mechanism by which AN9 synergistically enhances the antiproliferative effects of antineoplastic drugs.

Results: Human lymphoma BALM3 cells were cultured with various concentrations of several antineoplastic agents in the presence of AN9. Doxorubicin (DXR) and AN9 synergistically inhibited the growth of BALM3 cells, whereas there was no synergy between AN9 and antimetabolites. AN9 did not affect the intracellular uptake of DXR. With respect to the expression of drug resistance-related genes, there was no significant difference between untreated and AN9-treated cells. Among anticancer drugs and their derivatives, the synergistic effect was prominent in compounds with a daunomycin moiety, suggesting that AN9 may affect the metabolism of these compounds. Degradation of DXR in the extract from AN9-treated cells was much less than that in extract from untreated cells. The enhancement of the sensitivity to anticancer drugs was closely associated with the suppression of RAD51-dependent recombination activity. AN9 did not directly inhibit the enzyme activity, but rather suppressed expression of the enzyme.

Conclusion: The combination of an antineoplastic derivative of butyric acid (AN9) and DXR may have clear therapeutic potential against malignant lymphoma.

PERIPHERAL BLOOD LYMPHOCYTE SUBPOPULATIONS (PBLS) IN PATIENTS TREATED WITH 2-CHLORODEOXYADENOSINE (CLAD Riboside, 2-CDA): CORRELATION WITH INFECTION RATE AND REMISSION DURATION
R. Zehnleusen, S.-H. Hui Schmitz, A. van Roi, C. Jeannene, A. Todd, J. F. Fey, T. Cerny1, D. C. Beilicher
1. Institute of Med. Oncology and Central Haematology Laboratory, University of Bern, St.Gallen, Switzerland, the Swiss Group of Clin. Cancer Research (SAKK)

2-CDA is a purine analogue with antileukemic activity in low grade lymphocytic leukemia disorders. This therapy may be associated with severe opportunistic infections. The effect of 2-CDA on PBLS during the first 2 cycles (cy) and during follow-up (FU) as well as the predictive value of PBLS decrease on infection risk and remission duration (RD) were tested in 78 patients (pts) with lymphoma.

Patient characteristics: Histology: CLL 11, HCL 5, NHL (mostly stage III and IV), low grade 40, intermediate grade 13. Age: median 58 years (range: 36-82), disease duration: 1.9 years (0-15.4), number of pretreatments (range: 1-4). A median disease duration: 1.9 years (0-15.4), number of pretreatments (range: 1-4) were given. Infections occurred in 26% of pts (WHO grade 1-4; 5% grade 3 and 4; overall response rate was 59%. Median RD was 18 months (range 0.5-4+). Methods: PBLS were measured weekly by immuno-phenotyping. Predictive value of baseline PBLS number, ratios of PBLS in d1, d15, d22 of cy 1 and 2 as well as one FU were evaluated by multivariate cox regression and logistic regression. Results: 2-CDA led to a rapid and profound decrease of all PBLS. Median values are shown.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Cycle 1</th>
<th>Cycle 2</th>
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TREATMENT OF LOW- AND HIGH-GRADE B-CELL LYMPHOMA WITH THE MONOCLONAL ANTIBODY CD20 ANTI-CD20 ANTIBODY RITUXIMAB (IDEC-229): MONOCLONAL EXPERIENCE IN 71 PATIENTS
M. Jensen, H. Schulz, U. Winkler, T. Klein, V. Diehl and A. Engert
Clinic I for Internal Medicine, University of Cologne, Cologne, Germany

Introduction: Various clinical trials have demonstrated response rates up to 50% after treatment of patients with advanced follicular lymphoma non-Hodgkin's lymphoma (NHL) with 4 x 375mg/m2 of the chimeric monoclonal antibody rituximab (anti-CD20). Usually, adverse events, such as fever, chills, and nausea, are mild to moderate and toxicity only occurred on the first infusion. Data on rituximab treatment of patients with other entities of B-cell NHL are rare. Here we report our monoclonal experience on toxicity and efficacy of rituximab in 71 patients with low- and high-grade NHLs.

Methods: Patients with relapsed advanced low- or high-grade NHL were treated with 375mg/m2 rituximab once weekly for 4 weeks on a compassionate treatment basis. Results: Adverse events of NHL grade I-II toxicity occurred in 80% of all patients irrespective of their lymphoma subtype. Severe side effects were more pronounced in patients with large tumor masses. A cytokine release syndrome with a rapid drop of thrombocytes and coagulation factors was observed in patients with Rituximab and CLL patients. Conclusion: Rituximab was well tolerated in NHL patients with CR or PR after treatment with 4x375mg/m2 rituximab, our findings suggest that response rates are less impressive in most other lymphoma entities. Treatment results in patients with relapsed mantle-cell lymphoma and MALT lymphomas were promising, however, the number of patients treated was small.

STANDARD AND RIGOROUSLY APPLIED RESPONSE CRITERIA FOR NHL ARE ESSENTIAL FOR THE INTERPRETATION OF CLINICAL TRIALS AND COMPARISON ACROSS STUDIES REPORTED IN THE LITERATURE

Interpretation of response rates as well as comparison across literature reports is difficult due to the lack of standard response criteria for NHL. A group of NHL experts (Dr. ASCO 16th, 1997) developed CR for clinical trials of the chimeric anti-CD20 antibody, Rituximab. Those very strict CR require that all nodal and extranodal disease has to be less than 1 cm. In a CR, the RC were also reviewed and endorsed by a group of European NHL experts (Exper Hema 1995, 1997). Subsequently, an International Workshop was held at the US NHL where these RC were utilized as the basis for discussions leading to a new set of proposed guidelines for response assessment in patients with NHL. In the RC, CR requires 75% decrease and no residual lesions > 1.5 x 1.5 cm. We have compared the results reported with the original RC applied in our Rituximab studies (A) those obtained by modifying the original RC to require that all nodes decrease to <1.5 x 1.5 cm (B) and to the results obtained by applying the new proposed guidelines to the same patient database (C). Rituximab, was evaluated in a multicenter pivotal trial of 160 pts with relapsed Low Grade or Follicular (LG/F) NHL (i.e. patients A, B, C, D) treated with 375 mg/m2 qw x 4. P at characteristics: 63% male, median age 58 years, 79% Stage IV/I, median 2 prior chemotherapy courses. Adverse event profile has been reported (Alkawzy, M.), Response rates are shown. Median time to progression for responders and duration of response were 13.2 and 11.6 months respectively.
PILOT EFFICACY STUDIES OF RITUXIMAB IN COMBINATION WITH CHEMOTHERAPY, BIOLOGICALS, OR RADIATIONIMMUNOTHERAPY
IDEIC Pharmaceuticals Corporation, San Diego, CA, USA
Pilot efficacy studies were conducted in patients with LGL NHL utilizing Rituximab (mAb) in combination with chemotherapy (CHOP), biologicals (Interferon – alfa 2a) and radioimmunotherapy (IDEC-Y2B8). Forty-eight patients (pts) (31 male, 9 female) treated received standard dose standard CHOP (3) cycles (6 weeks) along with 6 infusions of mAb (375 mg/m²/dose). Two doses of mAb were given both at the beginning and end of therapy, as well as single doses before the 3rd and 5th cycles of CHOP. PR characteristics included: 21 males and 19 females, median age 48, stage IIIb at diagnosis (83%). All pts treated responded (50% CR and 42% PR). The overall response rate for 35 evaluable pts completing all therapy was 100% (83% CR, 37% PR). Medians for duration of response and PFS have not been reached after 35.3+ and 36.7+ months observation respectively. Twenty pts are still in remission beyond 36+ and up to 54+ months. Seven of 8 6-12 positive pts converted to PCR-negative in blood and marrow (molecular complete remissions). Of these 7, 6 remain in CR and 5 remain PCR-negative by serial analyses. The combination with interferon-alfa 2a was studied in 36 patients who received Rituximab (375 mg/m² q week 4 4 weeks 5-8) during concurrent treatment (3/wk for 12 weeks) with subcutaneous injections of interferon-alfa 2a (Reomrav-A; 5 MU injections). The overall response rate was 45%. The median time to progression for responders has not been reached after 25.2+ months. IDEC-Y2B8 3 ml murine IgG kappa anti-CD20 monoclonal antibody is conjugated to MX-DTPA, and securely bound to the beta emitting radioisotope 131I. In this study, IDEC-Y2B8 in combination with Rituximab resulted in single-agent relapses of Rituximab in pts with relapsed or refractory NHL. Imaging and dosimetry were performed (using IDEC-In2B8) 1 week prior to IDEC-Y2B8, as was also the infusion of Rituximab. Of the 39 pts with LGF, intermediate-grade, or mantle cell lymphoma retreated on treatment maintaining the selected Phase II dose of 0.4 mg/m² of Rituximab, the first monoclonal antibody approved for the treatment of cancer, is effective as a single agent in pts with relapsed or refractory, CD20-positive, B-cell, LGL NHL. Promising efficacy has been observed in these pilot studies. Thus, integration of Rituximab into combination regimens with chemotherapy, biologicals, or radiomunoimmunotherapies should be further evaluated in larger trials.

DISTRIBUTION PERCENTAGE OF A CISPLATIN BASED REGIMEN IS VERY ACTIVE IN REFRACTORY MALIGNANT LYMPHOMA (RML): PRELIMINARY RESULTS OF A PHASE II STUDY
S. Haemand Ong Nat Cancer Inst of Naples (1) University of l'Agquila Italy F. Russe, S. Guidanghi (2), F. Frigeri, G. Corazzelli, V. De Rosa, and G. Abate Introduction: The management of patients with heavily pretreated ML failing frontline and salvage treatment is problematic. Despite a possible residual chemosensitivity, no further intensive therapy can often be delivered. In this setting, in localized recurrence of disease, the disease progression of cytotoxic drugs, by means of step flow technique could offer a valid choice in comparison to the current salvage approaches. In this study, we present the experience in a single center setting, with pharmacokinetic (PK), according to the three-stage MiniMax Design (Pi = 70, P1 = 90, P1-Pt2 = 0.5, 20%) with Response Rate (RR) as the main end-point. At least 5 responding out of 7 pts are required in the first stage to indicate the sequence. Patients and Methods: Diagnoses included 4 pts with Hodgkin’s Disease, 1 primary mediastinal large B-cell, 1 anaplastic large cell, and one diffuse large B-cell lymphoma. Pts were aged 18-48 yrs, 6 presented with bulky diseases (Splenomegaly, 1 abdomen). They had never achieved a complete response (CR) or prior treatments since 6 out of 7 had progressed from frontline therapy and one had attained only a partial response (PR). Moreover, 3 had failed salvage high-dose chemotherapy plus autologous peripheral stem cell rescue. Recurrence of the disease was in the thorax in 6 pts, and abdomen in one, equally at sites of bulkiness. In our systemic drugs were delivered via aortic perfusion of the target tissue (thorax or abdomen) after the limitation of the greater circulation (step-flow technique) for a period of 20 mins. Drugs (mg/m2) used in variable combinations were: Cisplatin 1000 (100), L-PAM (750), BCNU (110), Etoposide (70), Am-C (1200). Results: Overall, 14 courses were monthly administered. During the 2st mins of the first phase of the procedure, drugs reached very high concentrations with Cmax up to 50 times greater than those i.v. delivered. In the second phase the same substances distributed in all other circulation according to the standard PK characteristics in the i.v. administration. All pts responded favorably. Four of them reached a CR, two a PR and the last one attained a short PR and progressed two months later. Tolerance to the therapy was excellent. Hematologic toxicity was mild and transfusion support was needed only in two courses. Neither extramarrow toxicity, nor related deaths occurred. After a 14-month median follow-up (range 5-20) two pts are still alive (1CR, 1PD); five have died, one from renal progresion of lymphoma while still being alive in thorax CR (no enuric prostate disease). Conclusions: This new therapeutic approach seems feasible, well tolerated and active in RML. According to the study design, the accrual continues.

RITUXIMAB THERAPY OF LYMPHOPROLIFERATIVE DISORDERS IN IMMUNOSUPPRESSED PATIENTS (PTS)
IDEIC Pharmaceuticals Corp., San Diego, CA; U of Florida, Gainesville, Fla; Chu Lyon-Sud, Lyon, France; BC Cancer Agency, BC, Canada; Loyola U., Chicago, Ill.; Rush Cancer Inst., Chicago, Ill; Stanford U., Palo Alto, Ca
Lymphoproliferative disorders (LD) are associated with both organ and marrow transplantation (Post Transplant Lymphoproliferative Disorders, PTLD) and seen in other immunosuppressed states (Immunosuppression Related Lymphoproliferative Disorders, IRLD). Incidence following transplantation can be as high as 5% (kidney or liver) and 15% (heart or heart-lung). Pts receiving T-cell depleted marrow and who are highly immunosuppressed have an incidence of up to 25%. Prognosis is very poor. Initial reports on the treatment of these LD with anti-B-cell antibodies were published in 1988 (Ann Int Med 108:199). Rituximab is a B-cell depleting anti-CD20 chimeric antibody approved for the treatment of pts with relapsed refractory, low grade or follicular NHL. As a single agent, it produces a 50% response rate with remission duration of up to 2 years. We report on 6 cases of PTLD (2 kidney, 2 liver, and 1 each - heart and lung), and one case of IRLD (methotrexate for Rheumatoid Arthritis) treated with this antibody (retrospective data collection). Pt characteristics: 3 females and 4 males, median age 38 (8 mo. to 70 yrs.), 4 with prior chemotherapy for their lymphoma (typically had not responded to immunotherapy dose reduction). Histologic diagnoses were: PTLD (3), Intermediate grade NHL (3), and NHL (1). Interval between transplantation and development of PTLD ranged from 1 mo. to 17 yrs. Pts were treated at the selected Phase II dose of 0.4 mg/m² of Rituximab, the first monoclonal antibody approved for the treatment of cancer, is effective as a single agent in pts with relapsed or refractory, CD20-positive, B-cell, LGL NHL. Promising efficacy has been observed in these pilot studies. Thus, integration of Rituximab into combination regimens with chemotherapy, biologicals, or radiomunoimmunotherapies should be further evaluated in larger trials.

IN VITRO EVIDENCE SUPPORTING THE POSSIBLE USE OF RETINOIC ACID IN THE TREATMENT OF EBV-RELATED LYMPHOPROLIFERATIVE DISORDERED IMMUNOSUPPRESSED PATIENTS
R. Dolcetti, P. Zancan, R. Cattalini, M. Guada, S. Rizzo, M. Bolognesi.
Division of Experimental Oncology, 1. C.R.O., Aviano (PN), ITALY.
Epstein-Barr virus (EBV)-infected lymphoblastoid B cell lines (LCs) are a suitable in vitro model for the study of EBV-related lymphoproliferative disorders of immunosuppressed patients. We have previously shown that 9-cis-, 13-cis- and all-trans retinoic acid (RA) potentiates the effect of the current salvage approaches to the standard PK characteristics in the i.v. administration. All pts responded favorably. Four of them reached a CR, two a PR and the last one attained a short PR and progressed two months later. Tolerance to the therapy was excellent. Hematologic toxicity was mild and transfusion support was needed only in two courses. Neither extramarrow toxicity, nor related deaths occurred. After a 14-month median follow-up (range 5-20) two pts are still alive (1CR, 1PD); five have died, one from renal progresion of lymphoma while still being alive in thorax CR (no enuric prostate disease). Conclusions: This new therapeutic approach seems feasible, well tolerated and active in RML. According to the study design, the accrual continues.

9. Miscellaneous
FAMILIAL PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLC)

Introduction: The majority of cases of non-Hodgkin’s lymphoma (NHL) are sporadic but relatives of patients with NHL may be at increased risk for NHL or other hematological malignancies. No genetic alteration has been identified so far to explain familial aggregation of lymphoid malignant diseases (except for familial immunodeficiency), conversely to other malignancies such as breast/ovary carcinomas or melanoma.

Case reports: We report three cases of PMLC occurring in the members of a family from Algeria, two siblings (patients 1 and 3) and their niece (patient 2), at age 53, 31 and 19 respectively (see figure). In each case, the presentation included renal involvement either at diagnosis or during evolution, a clinical feature that has been pointed out in some series of PMLC. Patients 1 and 3 are both alive in complete remission 75 and 20 months after diagnosis, while patient 2 died within one year from disease progression with brain involvement.

Discussion/conclusion: PMLC is considered as a distinct entity among NHL with specific clinical, histopathological and biological (gain of chromosome 9p, Bcl1, etc. ASH 1998) features. Such a familial clustering of NHL with the same histological subtype and clinical presentation including renal involvement in first degree relatives strongly supports that PMLC is a specific entity and suggests the involvement of a yet unidentified genetic alteration in the development of NHL.

A CASE OF PRIMARY "KI-1 (CD30) LEUKEMIA"
F. Adami, M. Borotin, N. Maschio, L. Trentin, M. Chiodo*, G. Semenzato Dept. of Clinical & Experimental Medicine, Padua University School of Medicine and Dept. of Pathology, Verona University School of Medicine, Italy.

A 73 year-old man was admitted for unexplained fever and dyspnea. Physical examination revealed hyperkeratosis with scaling and diffuse erythema, mild axillary lymphadenopathy, liver and spleen enlargement; left-pleural effusion was present at chest X-ray. Laboratory investigation showed leukocytosis, WBC 76 x 10^9/l; Hb 45.6 x 10^12/l; AST 35 x 10^12/l, Hb 81 g/l and platelet count 51 x 10^12/l. The ESR was 17 mm/h and LDH was normal. Bone marrow and axillary lymph node biopsies showed diffuse involvement by large anaplastic lymphoid cells. Immunophenotypic analysis of peripheral blood, bone marrow and lymph node neoplastic cells disclosed the following phenotype: HLA-DR, CD30, CD45, CD15+, CD22, CD23, CD10 and CD21+. The replication index was high (96-77%). No clonal rearrangements of the heavy and light (γ/δ) chains, or of the T-Cell Receptor (β/δ) subunit was found at gene rearrangement analysis. Cytogenetic analysis showed (12;13); chromosone 5 was apparently uninvolved. LDH was soon started, but the clinical course was rapidly fatal, as the patient died 50 days after the diagnosis due to intraocular hemorrhage.

The primary anaplastic large cell Ki-1 (CD30) lymphoma is an uncommon type of NHL, belonging to the T cell lineage in 35% of cases and to the B cell lineage in 18-38% of cases. Other cases (25-46%), also after genotypic analysis, cannot be assigned to B or T lineage. In most patients a typical cytogenetic abnormality t(12;13)(p13;q14) can be detected. Clinical manifestations include frequent extranodal disease, mainly at skin, pleural and soft tissue level. Bone marrow involvement is frequent at presentation (15-23%) and, if present, it is scanty. The leukemic picture is therefore unusual and may be overlooked. In the literature only 2 cases with a clear-cut leukemic picture have been described. A prominent leukemic phase is the most relevant clinical feature in this case; the massive bone marrow infiltration and severe peripheral cytopenia appear to correlate with the very aggressive clinical course and early death. The prognostic impact of the cytogenetic abnormality other than t(12;13) and familial possible relationship between t(12;13) and the leukemic pattern and other unfavourable prognostic features is presently unclear.

RARE PRESENTATION OF AN UNUSUAL B-CELL LYMPHOMA.
F. Adami, A. Muzio, F. Della Rocca, M. Busa, V. Pagliara, G. Menestrina, G. Semenzato, Dept. of Clinical & Experimental Medicine, Padua University School of Medicine; Olti Hospital Umberto I Mestre, Dept. of Pathology, Verona University School of Medicine, Verona, Italy

A 72 year old man was admitted to our Department for a recent onset of fever, right lumbar pain and a history of neglected anaemia and weight loss (8 kg in 3 months). Three days earlier he had undergone a sympathectomy of the prostate for worsening prostatism. Physical examination showed slight jaundice, mild hepatomegaly, splenomegaly, and a skin nodule; no lymphadenopathy was observed. The patient was neither wakenful nor fully oriented at neurological examination. Laboratory findings as follows: WBC 4.22 x 10^9/l (by 4.0 x 10^9/l), Pts 35 x 10^9/l, Hb 122 g/l, ESR 36 mmh, LDH 5200 U/l (n=380), hyperbilirubinaemia (53.5 umol/l, mostly conjugated). PTT 48", INR 2.21. Serum electrophoresis and immunoelectrophoresis revealed no monoclonal components lgG, but no Bence-Jones proteinuria. A few days later the patient rapidly worsened and developed signs of multiorgan involvement. Laboratory findings suggested liver failure and DIC, hemoglobin and platelet values were decreasing, conjugated bilirubinemia (53.5 mmol/l) was increased. Brain CT scan was normal, brain NMR showed meningeal thickening; intraventricular pressure was 20 cmH2O. CSF showed a high protein concentration (80 mg/dl). CYCLOPHOSPHAMIDE was effective. The histologic examination of the prostate disclosed a angiolipotocytic large cell lymphoma (ALK+). Subsequent B and cutaneous node biopsies showed strict intravascular proliferation of large atypical lymphoid cells (CD30+), CD20+, CD79a- and CD5+. Immunophenotype of the B aspariate showed a clonal c(11) B-cell population. CD30+ve. The B-cell clonality was confirmed by PCR on BM monocellular structures. Chemotherapy was started, including intravenous MTX; however the patient went into deep coma and died. Autopsy was not performed.

ALK+ is a rare high-grade lymphoma (204 cases described so far) mostly with B cell phenotype. The intravascular proliferation of the tumor cells is thought to be due to lymphocyte homing receptors of vascular endothelial cells. Only recently described, ALK+ may be successfully treated with combination chemotherapy. Early diagnosis is however difficult due to the variety of clinical presentations and frequent absence of diagnostic signs at skin, CNS, lung and liver level. Therefore the mortality rate is up to 80% and median survival time is only 5 months. BM involvement is rare and involvement of the prostate has been described in only 5 cases; in the latter cases the clinical manifestations are due to local disease. Chemotherapy, splenomegaly and peripheral blood lymphocytosis were not appreciable and urinary obstruction and prostatism were the unique clinical manifestations of the disease.

LDH is the best predictor of overall survival after EMP-salvage therapy for relapsed or refractory non-Hodgkin's lymphoma (NHL).
J.K. Doekhan, P.H. Spael, B. van der Holt, M.B. van Veen, P. Sonneveld University Hospital Rotterdam, The Netherlands.

Introduction: EMP (etoposide 350 mg/m2 i.v. on day 1, mitoxantrone 14 mg/m2 i.v. on day 1 and prednisone 80 mg/m2 orally on day 1-5, repeated every 21 days) is a new salvage regimen for patients with relapsed or refractory non-Hodgkin’s lymphoma (NHL) who do not meet the protocol criteria for transplantation. These patients generally have a very poor prognosis. It is important to know prognostic factors to determine which patients benefit from this treatment.

Methods: We included 79 patients treated with EMP in a univariate analysis of prognostic factors for overall survival from first EMP-cycle.

The median age of the patients was 53 years (range 24-77). 22 patients presented with a low-grade NHL. In 13 of 22 patients a transformation to high-grade malignancy had occurred. The international prognostic index (IPI) was low-risk in 35 patients, intermediate in 32, high-intermediate in 11 and high in 8 patients. 46/77 had received more than one chemotherapy regimen prior to EMP. 38 patients received at least 3 cycles of EMP; 9 patients completed 6 cycles. The overall response rate was 38% (CR 9%, PR 29%). The median follow-up of the 27 patients still alive is 14 months. The overall survival of all patients at 12 months is 41% and at 24 months 31%.

Univariate analysis showed that an elevated LDH at the start of EMP-treatment had a strong adverse prognostic impact on the survival after EMP, p<0.000002 according to the log-rank test. There was a trend towards a more favourable survival in patients who had moved a CR or prior treatment (median survival 17 months CR versus 7 months without prior CR). The response to EMP was not correlated with the histologic grade of the NHL or with the IPI at presentation.

A multivariate analysis of the results of the 21 older patients (age > 60 years) showed a response rate of 62% (CR 19%, PR 43%). The overall survival at 24 months was 49% versus 22% in the younger patients. This could not be explained by a difference in LDH. The toxicity of this regimen was low, grade 3 toxicity in 11 and 8 in 24 hours. 46/79 had received more than one chemotherapy regimen prior to EMP. 38 patients received at least 3 cycles of EMP; 9 patients completed 6 cycles. The overall survival of all patients at 12 months is 41% and at 24 months 31%.

Multivariate analysis showed that an elevated LDH at the start of EMP-treatment had a strong adverse prognostic impact on the survival after EMP, p<0.000002 according to the log-rank test. There was a trend towards a more favourable survival in patients who had moved a CR or prior treatment (median survival 17 months CR versus 7 months without prior CR). The response to EMP was not correlated with the histologic grade of the NHL or with the IPI at presentation.
PNEUMOCYSTIS PNEUMONIA IN A CARIBBEAN HTLV-I CARRIER SUFFERING FROM A T PERIPHERAL NHL
S. Takeda, T. Shiozaki, N. Yamagami, J. Nakamura, and T. Ohno

A 65-year-old Caribbean man was seen in August 1998 because of a mediastinal syndrome. Chest X-ray revealed a mixed pleuropneumocystic T-cell lymphoma. Clinical stage was III b with 3 positive prognostic factors: bulk, PS 2 and elevated LDH (3 times the normal). The HTLV-I serology was positive while others were negative except CMV and EBV. The direct antiglobulin test was positive (IgG type) without hemolysis and we noted a polyclonal hypergammaglobulinemia (15.1 g/l). D2-m level was 5.8 mg/l per serum calcium normal.

After a VAD course, the patient received a CHVP course (a CHO-like regimen) and was readmitted on day 19 because of a 38°C fever with 3.8 G leucocytes with 0.142 lymphocytes. Evolution was quickly unfavorable under amikacin and cefazolin and the patient presented a severe dyspnea with hypoxia (PaO2 35 mmHg), an infiltrating bilateral pneumonia and a lingual mycosis due to Candida tropicalis. Broncho-alveolar lavage fluid revealed an ascension due to a Pneumocystis carinii without any other pathogen. Then with treatment by trimethoprim-sulfamethoxazole (TDS/MOX) and corticoids, evolution was quickly favorable and the patient was discharged on day 12. Chemotherapy was carried on under a preventive TDS/MOX treatment without any peculiar septic problem.

Before starting chemotherapy, a lymphoma was present: 611 cells/mm³ but this lymphoma was not pointed out. More than 10 Pneumocystis carinii pneumonia have been still reported among patients suffering from HTLV-I linked leukemia and/or lymphoma. These reports are often Japanese ones and often about the acute ATL syndrome. Our observation asks the question of the appropriateness of a TDS/MOX preventive treatment among these patients.

Non-Hodgkin's Lymphoma Relapses in Long-term Survivors After Conventional Therapy
G. Kruglova, L. Pirogovna, I. Podobubaya, N. Prohatova

Introduction: Conventional therapy of non-Hodgkin's lymphoma (NHL) has been thought to fail producing long-term positive results in most cases. In connection with this, a study into development of relapses in long-term survivors and effect of the former on patients' survival has been conducted.

Methods: Selected were 101 adults with indolent and aggressive NHL (REAL, Lugano '96) in stages I-IV who had survived 10 to 30 and more years since the first symptoms of the tumor disease. Overall survival (OS) at 25 years was 52%. Median follow-up was 14.2 years. After conventional anti-tumor therapy all pts achieved an objective remissions, 85% of which were complete (CR), 15% partial (PR).

Results: Only in 37 pts (37%) the first therapy has proved to be fully adequate, and pts survived throughout the entire disease, 11 to 28+ years, with no relapses. Other 64 pts (64%) developed relapses: 1-2 relapses in 40 pts, 3-4 in 24 pts, the total number of relapses being 165. Relapses occurred early: in 19 pts (30%) within the first year. Most relapses (31 pts, 50%) were observed within first 5 years of the disease, a part of it within next 5 years (24 pts, 37.5%) and a few (8 pts, 12.5%) in other periods.

According to clinical presentation relapsed pts were treated either the same methods as in the initial treatment or the methods were changed and combination chemotherapy of lines II and III were used. Of 165 relapses, only 19 (11.5%) resulted in death. After salvage therapy, the other 45 pts who had the total of 146 relapses, had remained under observation for 11 to 30+ years. Relapse-free survival (RFS) after CR was higher than that after PR (p<0.001).

Conclusion: Our study shows that long-term prognosis of NHL patients after conventional therapy is poor but is not identical with RFS improvement after RFS.

Factors Influencing Quality of Life of Non-Hodgkin's Lymphoma Patients After Conventional Chemotherapy
A. Novik, T. Ivanova, A. Maximov, A. Kovalenko

Introduction: Quality of life (QoL) assessment is widely adopted in oncological clinical trials. However there are lack of data on QoL of lymphoma patients after treatment and factors influencing post-treatment QoL parameters. The objective of the present study was to determine if grade, B-symptoms, age and gender influence QoL of Non-Hodgkin's lymphoma (NHL) patients after conventional chemotherapy.

Methods: There were studied 73 NHL patients (38 HL, 35 NHL), among them there were 35 males (mean age 49.5, SD=15.9) and 38 females (mean age 53.4, SD=15.1). HL NHL patients were treated by CHOP and LG NHL by COP. Cox'LOG model (Russian translation, v.2.0) was used for QoL assessment before and after treatment (six or eight chemotherapy cycles).

Results: Using ANOVA analysis there was shown that grade, B-symptoms, age and gender had influence on QoL parameters in NHL patients after treatment. Emotional functioning (EF) (87.8, SD=12.3) of HL NHL patients increased after treatment as compared with EF before treatment and was higher (P<0.05) than in LG NHL patients (74.2, SD=23.0). There were found out no other QoL parameters depending on grade. Role functioning (RF) and social functioning (SF) in LG NHL patients after treatment were higher if there were no B-symptoms (RF=5.11 and SF=5.54 correspondingly, P<0.05).

Conclusion: It was found out that B-symptoms, age and gender influenced post-treatment QoL of NHL patients.
SPLENIC IRRADIATION IN THE PALLIATION OF PATIENTS WITH HYPERSPLENISM
General Hospital Middelheim, Antwerp, Belgium.

Introduction: Patients with hypersplenism or splenic pain can be treated palliatively by splenectomy or irradiation. In elderly patients mild irradiation treatment of the spleen is often preferred. This retrospective study describes the results obtained in 19 patients treated in our hospital between 1987 and 1998.

Methods: Patients suffering from hypersplenism requiring multiple blood transfusions or splenic pain, not responding to chemotherapeutic treatment, were irradiated on the spleen. Ten patients had low-grade Non-Hodgkin lymphoma (NHL), 4 patients chronic lymphocytic leukemia (CLL) and 5 patients chronic myeloid leukemia (CML). The prescribed dose was 10 Gy in 10 weeks, one fraction per week, delivered through 2 anterior-posterior opposed fields on a Cobalt-60 machine with dose prescribed to the central axis midplane depth. Palliation of symptoms, effects on the hematologic parameters (hemoglobin, platelets) and number of transfusions were used as endpoints for this study.

Results: The mean age of the 8 female and 11 male patients was 71 y (51-80 y) with a follow-up of at least 2 months. The intended dose of 10 Gy could be given to 11 patients, and 6-9 Gy to another 4 patients. Four patients did only receive 1-2 Gy due to a rapid deterioration of their condition. Three patients were treated twice and 2 patients underwent 3 cycles of treatment. Only patients with a Karnofsky score of 70% or more (20 of 26 treatments) completed their treatment. Ten out of 14 treatments in NHL-patients showed responses (decrease in spleen volume, pain relief), but only 3 of 7 treatments in CML-patients and 2 of 5 treatments in CLL-patients were successful. Splenic irradiation was effective in NHL, improving the hematologic parameters (hemoglobin, platelets), and in 2 cases hemolysis was stopped. In CLL the improvement was less impressive, and in CML only minor benefit was obtained. In 6 patients splenic irradiation reduced the amount of erythrocyte or platelet transfusions.

Conclusions: In 15 out of 28 treatments clinical responses were seen with an improvement of quality of life. Patients with NHL had more benefit of splenic irradiation compared to CLL or to CML patients. Only patients with a Karnofsky score of at least 70% completed their treatment. Reirradiation was possible and successful in 5 of the 9 treatments.

SPONTANEOUS SPLENIC RUPTURE IN A PATIENT WITH MULTIPLE MYELOMA
V. Costanzo*, A. Galesis®, D. Fiorett®
*Divisione di Medicina Generale and # Servizio di Anatomia e Istologia
Ospedale Civile San Lorenzo, Valdugno, Italy

Case Report. Multiple myeloma (MM) IgG λ stage IIIA was diagnosed in a 81-years old woman in August, 1994. Two days after the second cycle of melphalan and prednisone at standard doses was completed, she presented vomiting, abdominal pain, hypotension. At the admission, in December, 1994, history was negative for trauma. Intraperitoneal fluid without organomegaly or vascular abnormalities of the spleen was revealed by emergency abdominal ultrasound scan (US). Emergency gastroscopy disclosed multiple erosions of the gastric mucosa with diffuse infiltration by atypical plasma cells. Haemoptoentenosus was diagnosed by peritoneal tap and the patient underwent urgent laparotomy. Splenectomy was performed because of a large subcapsular haematoma with splenic laceration. Hystology of the resected spleen (13 x 11 cm in diameter) disclosed the presence of numerous foco of atypical plasma cells containing Russell bodies, stromal amyloidosis and diffuse areas of myeloid metaplasia. Frequent vascular thrombosis and areas of haemorrhagic infarction were also observed.

The postoperative course was normal and the patient was discharged without therapy. In February, 1995, the patient was admitted again with fever, dyspnoea and anasarca. Laboratory evaluation disclosed a clinical picture of nephrotic syndrome: creatinine 8.79 mg/dl; proteinuria 6.7 g/24 h; triglycerides 973 mg/dl; cholesterol 475 mg/dl. Serum protein were 5.6 g/dl; IgG 1180 mg/dl (n.v. 800-1800); IgA 182 mg/dl (90-450), IgM 70 (70-280); serum immunofixation was negative. The course was complicated by right lobar pneumonia and ARDS. The patient died two days after the admission.

Conclusion. The patient we report had a spontaneous splenic rupture, while on standard oral chemotherapy for MM. We suspect that therapy-related thrombosis of splenic vascular bed and subsequent haemorrhagic infarction were the main causal factors of her splenic rupture. Amyloidosis, which has been generally considered as the cause of the splenic rupture in 12 similar cases since 1966 (1,2), could have been a probable cofactor.


9. Miscellaneous