CLADRIBINE ALONE OR IN COMBINATION WITH CYCLOPHOSPHAMIDE AND COP IN PREVIOUSLY UNTREATED PATIENTS WITH LOW GRADE NON-HODGKIN LYMPHOMA

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Introduction: In the first interim analysis we showed that cladribine alone (C) or in combination with cyclophosphamide (CC) provided similar overall response rates (ORR), freedom from progression (FFP), and overall survival (OS) in patients (pts) with low grade B-cell non-Hodgkin lymphoma (LGNHL), and better results than COP.

Methods: Presently we show the updated results of this randomized study on 183 patients (pts), including 121 who have completed at least 6 cycles of the scheduled chemotherapy.

Results: Compared to C and CC, COP induced lower complete remission rates (45%, 68%, 10%; P<0.001) and ORR (70%, 95%, 55%; P<0.001). FFP was longer in cladribine-treated pts compared to COP (P<0.001), but no difference in OS was observed. Incidences of infections and non-hematological side effects were similar, whereas CC but not C induced more frequent cytopenias compared to COP (30% versus 11%; P=0.05). This resulted in more frequent intervals' prolongation between CC (32.5%) versus COP (11%) cycles (P<0.05), but dose reductions were comparable in studied groups.

Conclusions: In pts with LGNHL, the first-line therapy with C and CC regimens provided better response rates and similar toxicity profile as compared to COP. These updated results have proved our interim observations, which have resulted in discontinuation of the accrual in the COP arm. However, the final conclusions of the study need larger number of pts to be randomized and their longer follow-up.

CLADRIBINE IN COMBINATION WITH RITUXIMAB AND IL-2 FORUNTREATED FOLLICULAR LYMPHOMA

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We have previously reported that a short 4 months' cladribine therapy results in durable remission in 40% of patients. This study is a pilot trial of the combination of cladribine 0.12mg/kg iv on 4 consecutive days with IL-2 s.c. day 2–5 and rituximab 375mg/m² day 1. Four cycles repeated once monthly were administered. IL-2 was chosen to minimise t-cell suppression. We treated 10 symptomatic patients 49–75 years with a median of 75 years with untreated follicular lymphoma stage 3 or 4 disease. All patients achieved a complete remission and only one patient relapsed after a median observation time of 4.5 years.

A combination of cladribine with rituximab seems to be a very effective treatment for follicular lymphoma and warrants further investigation. IL-2 seems not to influence t-cell lymphopoeisis, but adds additional toxicity.

LONG TERM RESULTS FOR CLADRIBINE INDUCTION AND INTERFERON MAINTENANCE TREATMENT IN PREVIOUSLY UNTREATED INDOMENT LYMPHOMA

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Indolent lymphoma in advanced stage is an incurable disease. The main treatment goal is palliation with low treatment related toxicity. In a multicenter setting we prospectively treated 91 previous untreated indolent lymphomas with intravenous cladribine 0.12mg/kg body weight for 4 or 5 consecutive days every 4 weeks for 4 cycles. Following the cladribine induction treatment an interferon-2c maintenance therapy was started until progression. Median age was 59 years (range 25–79). All patients had stage 3 or 4 disease. Overall remission rate was 70% with 23% complete remissions. We found no significant difference in remission rate between the 4 or 5 day regimen. The remission rate was not different between follicular lymphoma, mantle-cell lymphoma, or Waldenström's disease. Neither did the international prognostic index influence the rate of remission. Median observation was 60 months for living patients. Median time to progression and survival was 22 and 69 months respectively. At 5 years 23% and 57% were progression free and alive respectively. Transformation in a high-grade lymphoma occurred in 11/91 patients. A secondary cancer was observed in 4/91 patients. Toxicity was mainly hematologic for cladribine. Interferon maintenance was poorly tolerated. 27% of patients did not complete the therapy. Four months of cladribine is a well tolerated and short therapy with longterm results computing to other single agent chemotherapies. The long term results should be improved. We recently finished a trial in combination with rituximab.
appear to achieve a plateau. Rituximab has been used effectively to treat patients with relapsed HCL. We examined whether the prolonged administration of rituximab one month after therapy with 2CDA can effectively eradicate MRD in pts with newly diagnosed HCL or those who have relapsed after one prior therapy.

**Methods:** 2CDA 5.6 mg/m² is administered over 2 hours daily for 5 days. One month later, rituximab 375 mg/m² is administered weekly for 8 weeks. MRD was assessed by flow cytometry as well as by IgH PCR assay using framework-1, -2 and -3 primer sets. MRD is evaluated in the bone marrow at one month following 2CDA and after completion of rituximab.

**Results:** Ten pts have been enrolled onto the study. Eight pts had received no prior therapy, one pt had relapsed after prior 2CDA therapy 9 years ago and one pt had received chlorambucil only. Two pts had the variant form of HCL. Eight pts have completed all therapy, 2 are continuing to receive rituximab. Results for all 10 patients will be reported. One month after therapy with 2CDA, 6 pts had persistent morphological involvement of marrow by HCL. All eight pts who have completed rituximab have achieved a CR with no morphological marrow involvement. One month after 2CDA therapy, nine pts remained positive by flow; one had no evidence of MRD by flow. All eight pts completing rituximab have become negative by flow. One month after completion of 2CDA, Five of 7 evaluable pts remained positive by PCR, only one remained positive after completion of rituximab.

**Conclusions:** Assessment and eradication of MRD by flow and PCR in HCL is feasible. Further follow-up is necessary to determine whether MRD status at completion of therapy can predict relapse.
5. Extranodal Lymphomas

A FLORAL VARIANT OF NODAL MARGINAL ZONE LYMPHOMA

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The nodal marginal zone lymphoma (NMZL) is a relatively rare low grade malignant lymphoma. Two variants are reported until now, namely, splenic marginal zone lymphoma type and MALT type. We describe here seven cases of a specific variant of nodal marginal zone lymphoma with [fetal] lymph follicles, and it may be a specific variant of NMZL.

(Cases and Methods) All seven cases were obtained from the files of the Pathology Department of Fukuoka University Hospital from 1985 to 2004. HE staining, chromosome analysis with G-band method and immunostaining were performed following the usual methods. In five cases, we performed polymerase chain reaction (PCR) for the complementarity-determining region (CDR) of immunoglobulin to detect clonality.

(Result) The age of the patients ranged from 18 to 66 years. All seven cases showed immunophenotypic features, local (n = 5) or systemic (n = 1). All cases were positive for CD5, CD10, CD23, and CD43 and negative for CD20 and BCL-2. Two cases showed monoclonality in all cases analyzed. The survival of patients was observed in one case.

(Conclusion) This variant of nodal marginal zone lymphoma should be differentiated from nodal marginal zone lymphoma because of its specific clinical and pathological features.

PRIMARY EXTRANODAL LYMPHOMAS: CLINICAL PRESENTATION AND OUTCOMES OF PATIENTS FROM CHEZ LYMPHOMA STUDY GROUP (CLSG) REGISTRY


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Introduction: The definition of primary EN lymphomas is controversial and literary data about EN NHL as a group are limited.

Methods: The data of 1579 patients reported from 14 centres to CLSG database in the period 1999–2003 are studied considering two different definitions of primary EN lymphomas. I: presentation in other than lymphatic organ or bone marrow with no or minor lymph node involvement (group I). II: more extensive disease in both EN and nodal sites (group II). Lymphatic organs include lymph nodes, spleen, thymus and Waldeyer’s ring.

Results: EN involvement was referred in 1016 (64%) of all 1971 NHL patients. Group I (strict definition) consists of 316 cases (20% from all NHL), group II of 651 (41%) patients. Clinical characteristics: the most frequent histologies in group I are DLBCL 156 (40%), MALT 60 (19%), FCL 28 (9%), T-NHL 18 (6%). For group II: DLBCL n = 324 (50%), MALT n = 78 (12%), FCL = 62 (10%), T-NHL n = 37 (6%). Median age group I is 61, group II 59 y. Men/women ratio of group I is 142/174, group II 289/62. The response rates (RR) after initial therapy in evaluated patients are 87% with 81% CRs in group I and 82% with 66% CRs for group II. After the median follow-up of 33 months, the 3-years OS and PFS are 74% and 67% for group I and 68% and 55% for group II. We compared primary EN DLBCL patient from group I with nodal DLBCL with similar characteristic (stage I, II, IPI 0,1) and with sufficient data. We found out best OS and PFS for nodal DLBCL.

Conclusion: The frequency of primary EN NHL rises twofold using more wide definition. MALT lymphomas are more often in strictly defined group. Primary EN NHL are more frequent in women. The RR after initial therapy is the same for both groups, the CR rate is higher for localised EN NHL. The outcome of DLBCL subgroup is better for localised nodal lymphomas in our series, but result is necessary to confirm with larger number of evaluable patients.

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EXTREME NON-HODGKIN'S LYMPHOMAS OF HEAD AND NECK REGIONAL INDIAN EXPERIENCE

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Lymphomas comprise a diverse group of malignancies and are relatively common in developing countries. The extranodal Non-Hodgkin's Lymphomas commonly involve the head and neck region (approximately 1% to 3%). We present our experience with extra-nodal Head and Neck Non-Hodgkin's Lymphomas. The purpose of this study was to examine the pathological nature and anatomical distribution of extranodal malignant non-Hodgkin's lymphomas of the Head and Neck and to document the treatment and prognosis. The records of fifty two patients treated between 1991 and 2001 at Dr. Bhimrao Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, were analysed. There were 36 males and 16 females, the most common site was Waldeyer’s ring (59%). Approximately 88% of pts were diagnosed at an early stage (I or II), the most frequent histologic type was diffuse large cell lymphoma. Therapeutic approaches included surgery, radiation, chemotherapy or combination. The survival and patterns of recurrences data shall be presented.

LOW RATE OF CNS RECURRENCE IN A COHORT OF 309 PRIMARY EXTRANODAL HEAD AND NECK DIFFUSE LARGE B-CELL LYMPHOMA (HN-DLBC) (IELSG 23)


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Introduction: Head and neck is the second most common site of localized extranodal presentation of non-Hodgkin’s lymphomas and it is at high risk of CNS recurrence.

Aim of the study: To evaluate the clinical outcome, prognostic factors and the rate of CNS recurrence in patients with HN-DLBCL.

Patients and Methods: From December 1982 to June 2004, 309 patients with HN-DLBC (median age 60 yrs, range 19–89) were referred to 9 international centers. The most common sites were Waldeyer’s ring (66%), nose and paranasal sinuses (10%) and thyroid (8%). Adverse prognostic features included: stage II (67%), elevated LDH (16%), bulky disease (11%), No of extranodal sites >10, B symptoms (8%), ECOG-PS >1 and stage-modified IPI (MIP) >1 (50%). Two hundred sixty patients (84%) were given CHOP or CHOP-like regimen a IFRT. Only few patients 25/100(10%) received CNS prophylaxis (Methotrexate 12 mg i.v., median of cycles 3, range 1–6).

Results: Two hundred sixty two patients (85%) achieved a complete remission and 60 (23%) of them eventually relapsed, in the same site (40%), in other sites (53%) and 7% in both. Only 12/34 (0.4%) patients, who did not receive prophylaxis, relapsed in CNS. After a median follow-up of 42 months (range 6–220 months), 5-year estimate of OS, EFS and DFS was 72%, 55% and 73%, respectively. By Cox multivariate analysis, a risk factor >1 according to MIP or predicted a poor EFS.
Conclusions: The present study showed a very low rate of CNS recurrence in high risk patients, who did not receive adequate prophylaxis, suggesting that CNS prophylaxis could not be mandatory in H-N DLBCL patients. This should be confirmed by prospective studies of clinical outcome.

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CLINICOPATHOLOGIC FEATURES OF PRIMARY EXTRANODAL NON-HODGKIN'S LYMPHOMA

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Introduction: The incidence of primary extranodal NHL has increased more rapidly than nodal in last 20 years. The aim of our retrospective study was to evaluate clinicopathologic features of patients with PENHL in Russia.

Patients: 305 cases of PENHL diagnosed in one center between 1990–2000 were analyzed. Median age was 52 (16–87) yrs. Male/female ratio – 1:1.3. 42% of patients were older than 60 yrs. Diffuse large B-cell lymphoma was the most common morphologic type (52% of cases), followed by marginal zone B-cell lymphoma of MALT-type in 31.5%, follicular lymphoma in 6%, peripheral T-cell lymphomas in 5%, Burkitt’s lymphoma in 2.5%, mantle zone lymphoma in 2% and anaplastic large cell CD30+ lymphoma in 1%. 35% of patients had low-grade and 65% – intermediate/high-grade histology. The most frequent site of involvement was stomach (38.7%), followed by bone (14.1%), Waldeyer’s ring (10.2%), testis (6.6%), salivary gland (4.6%), skin (3.9%), paranasal sinuses (3.6%), breast (3.6%), intestine (2.6%), orbit (2.6%), ovary (2.3%), thyr- oid gland (1.3%), uterus (1.3%), lung (1%), soft tissues (1%). More than 1 extranodal organ involvement was seen in 15% of cases. 83% of patients had I-II stage of disease. PS 2 was reported in 20%. B-symptoms presented in 25%, bulky – in 22% and nodal involvement – in 34% of patients. High LDH was observed in 37% of cases, anemia – in 25%, low serum total protein – in 6.9% and low serum albumin – in 7.5%. According to the IPFI 30% of patients were at low risk, 33% – at low/intermediate, 2% – at high/intermediate and 15% – at high risk of treatment failure. All patients received adequate specific therapy, including combined modality in 56% of cases.

Results: 84.6% of patients obtained complete remission, 5.9% – partial remission, 2.6% had stable disease and 6.9% – progressive disease. 32.9% relapsed after initial treatment. Portions of local and disseminated relapses were almost equal – 49.4% and 50.6%. 31.5% of patients died in 74% because of disease progression. After a median follow-up of 44 months (2–240) the 5-year disease-free survival, event-free survival and overall survival rates were respectively 66%, 54% and 69%.

Conclusion: Clinical and histopathologic characteristics of our cases of PENHL were similar to the earlier published data with some differences in the incidence and morphologic types.

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PROGNOSTIC FACTORS IN PRIMARY EXTRANODAL NON-HODGKIN'S LYMPHOMA PATIENTS

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Introduction: Primary extranodal non-Hodgkin’s lymphomas (PENHL) constitute 24–48% of all NHL. The aim of our retrospective study was to identify prognostic factors in patients with PENHL in Russia.

Patients and methods: 305 cases of PENHL diagnosed in one center between 1990–2002 were analyzed with median age of 52 yrs (16–87) and m/f ratio of 1:1.3. 35% of patients had low-grade and 65% – intermediate/high-grade histology. The most frequent site of involvement was stomach (38.7%), followed by bone (14.1%) and Waldeyer’s ring (10.2%). 83% of patients had I-II stage disease. According to the IPFI 50% were at low risk, 33% – at low/intermediate, 2% – at high/intermediate and 15% – at high risk. All patients received adequate specific therapy.

Results: 84.6% obtained complete remission. 32.9% of patients relapsed after initial treatment with local relapse in 49.4% of cases. 31.5% of patients died in 74% because of tumor progression. After a median follow-up of 44 months (2–240) the disease-free survival (DFS), event-free survival (EFS) and overall survival (OS) rates were respectively 66%, 54% and 69%. Statistically significant predictors of a lower DFS, EFS and OS rates among standard prognostic factors (of IPFI) were: stage III and IV disease (5-year OS 22% vs 77%, P=0.0000), high LDH level (5-year OS 40% vs 83%, P=0.0000) and more than 1 extranodal organ involvement (5-year OS 27% vs 74%, P=0.0000). PS 0 vs 2–4 was significant only for DFS and OS (3-year OS 42% vs 73%, P=0.0000). Other factors influencing DFS, EFS and OS were intermediate/high-grade histology (5-year OS 57% vs 87%, P=0.0000), B-symptoms (5-year OS 36% vs 76%, P=0.0000), bulky disease (5-year OS 43% vs 74%, P=0.0000) and anemia (5-year OS 41% vs 75%, P=0.0000). Decreased serum total protein and albumin level had worse impact on DFS and OS (respectively 5-year OS 20% vs 70%, P=0.0000 and 24% vs 71%, P=0.0000). Achievement of CR statistically improved OS (5-year OS 76% vs 16% if CR was not achieved, P=0.0000).

Conclusion: Results of our study showed relatively favorable prognosis in PENHL patients. A number of standard and additional factors found to have statistically significant influence on DFS, EFS and OS rates.

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TRANSCRIPTIONAL SIGNATURES OF GASTROINTESTINAL B-CELL LYMPHOMAS

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INTRODUCTION: The pathogenetic relationship between the different gastrointestinal (GI) B-cell lymphoma entities remains to be elucidated. We performed gene expression studies on GI B-cell lymphomas including 8 extranodal marginal B-cell lymphomas of MALT type (small cell lymphoma, SCL), 14 diffuse large B-cell lymphomas of the GI-tract (large cell lymphoma, LCL) and 10 B-cell lymphomas of the GI-tract with simultaneous small and large B-cell components (mixed, SCL + LCL).

METHODS: Each lymphoma cell compartment was microdissected, amplified and hybridized onto a cDNA array.

RESULTS: Hierarchical cluster analysis separated SCL and LCL well from each other. Unsupervised hierarchical cluster analysis with all micro-dissected samples of SCL, LCL, and SCL+LCL revealed that most samples clustered together in two main ‘small cell’ and ‘large cell’ branches. We found 86 genes differentially expressed between SCL and LCL and 69 genes differentially expressed between the small and large cell components of SCL + LCL; 23 genes were discriminators in both settings.

CONCLUSIONS: The results suggest that SCL and the small cell component of SCL + LCL on the one side and LCL and the large cell component of SCL + LCL on the other have similar transcriptional signatures. The newly identified proteins discriminating between indolent and aggressive lymphoma cells might shed new light on the pathogenesis of progression in GI B-cell lymphomas.

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AGNOR STAINING IN GASTRIC MALT LYMPHOMAS AND H. PYLORI-ASSOCIATED LYMPHOID HYPERPLASIAS

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Introduction: Helicobacter pylori-associated gastritis is a risk factor for gastric mucosa-associated lymphoid tissue (MALT) lymphoma. It may be difficult to distinguish low-grade lymphomas from benign lymphoid infiltrates. Previous results suggested that AgNOR (argyrophilic nucleolar organizer region proteins) technique may be used to differentiate gastric lymphoid hyperplasias and low grade MALT lymphomas.

Methods: We investigated archival paraffin embedded gastric biopsies diagnosed immunohistochemically. 63 cases (17 H. Pylori-associated lymphoid hyperplasias, 15 of low grade MALT lymphomas, 16 moderate grade MALT lymphomas, 15 high grade MALT lymphomas) were stained by AgNOR technique. We analyzed the number of AgNOR-positive cells and AgNOR-dots per cell. The correlation between AgNOR parameters and Ki-67 (MIB-1) expression was determined.

Results: Mean AgNOR number per nucleus in lymphoid hyperplasia was 1.2 +/- 0.03, in low grade MALT lymphoma 1.4 +/- 0.15, in moderate grade MALT lymphoma 2.5 +/- 0.09, and in high grade MALT lymphoma 3.3 +/- 0.6. The comparison of the AgNOR parameters revealed statistically significant differences between the groups of lymphoid hyperplasia and low grade MALT lymphomas (P<0.01), low and moderate
grade MALT lymphoma (P<0.01), moderate and high grade MALT lymphoma (P<0.05). A significant correlation was found between the AgNOR count and MIB-1 index (r=0.776, P<0.01).

**Conclusion:** The morphometric analysis of AgNOR-positive cells and AgNOR-dots per cell may be useful in distinguishing of lymphoid hyperplasias and different grade MALT lymphomas in paraffin sections. AgNOR study can be used as an additional diagnostic method to differentiate gastric lymphoid infiltrations.

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**ANTIGEN RECEPTORS OF MATURE B-CELL NON HODGKIN'S LYMPHOMAS: MALT LYMPHOMAS EXPRESS A DISTINCTIVE ANTIBODY REPERTOIRE WITH FREQUENT AUTOREACTIONIVITY**

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It is assumed that B-NHLs, in spite of their specific genetic alterations, in majority still depend on environmental stimuli for their growth. Specifically, a role for antigen-receptor ligands has been proposed for extranodal marginal zone B-cell lymphomas (or mucosa-associated lymphoid tissue (MALT) lymphomas) and follicular lymphomas (FL). To date however, virtually no studies have indeed assessed the binding capacities of autoantigens expressed by B-NHL and by consequence barely any B-NHL in lymphomas has been defined. We analyzed the structural features of the IgG molecule by a panel of B-NHL entities, first by random comparison, at the amino acid level, of their IgVHCDR3 with IgVH CDRE3 present on germline. This pointed out that FL, diffuse large B-cell lymphomas, Burkitt lymphomas and multiple myelomas expressed a IgVHCDR3 repertoire comparable to that of normal B cells. In accordance with recent reports by others, the CDRE3 of B-CLL displayed frequent CDRE3 homology, in particular with CDRE3 of other B-CLL. A highly distinctive CDRE3 repertoire was found in salivary gland- and in gastric- MALT lymphomas. To assay their specificities, we produced recombinant antibodies of 10 MALT lymphomas (and 4 FLs and 1 B-CLL as controls). By in vitro binding studies, we were able to define the auto-antigenic ligands for 7 of the 10 MALT lymphomas tested. We provide evidence that MALT lymphomas derive from precursor cells strongly selected for this reactivity. Remarkably, MALT lymphomas with the (11;18) lacked the distinctive CDRE3 repertoire. At the meeting, our analyses will be presented in detail.

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**EXTRANODAL MARGINAL ZONE LYMPHOMAS OF MALT TYPE**

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**Introduction:** Marginal zone lymphomas (MZL) have been recently recognized as a distinct entity; they are distinguished in three subgroups: extranodal MZL of MALT type, splenic and nodal. Although the gastric MALT NHL have been studied thoroughly, there are still questions for the biologic behavior and management of the other MALT NHL. We present our experience from the management of patients with non gastric, MALT NHL.

**Patients:** From 580 patients with NHL registered in our unit, 18 (3%) have been classified as non gastric MALT. The median age of the patients [M; 8; R; 10] were 54 years (35–76). The localizations of the disease were: skin (5), lung (5), thymus (1), pleura (2), breast (1), lacrimal gland (2), eyelid (2), conjunctiva (1), thyroid gland (1), parotid (2), salivary gland (1), larynx (1), and Waldeyer’s ring (1). Six patients had systemic disease with involvement of more than one sites. Two patients had intraabdominal lymphadenopathy and two BM infiltration. The stage of the disease was assessed as IV in 9 patients.

**Results:** Five patients, with localized disease, were treated with radiotherapy (RT), 10 (55%) with chemotherapy, two received rituximab + RT and one only rituximab. Twelve patients [67%] achieved complete remission (CR) to the initial treatment and six [33%] partial response. In five cases with relapse a second CR was achieved. Only one patient has died from an irrelevant cause. With a median follow up time of 37 months [12–78], 17 patients are alive and ten of them are in CR (the overall survival is estimated 92%).

**Conclusions:** Extranodal MZL of MALT type usually develop in the gastrointestinal tract. However, MALT lymphomas can involve various non-gastrointestinal sites, most often skin, lung and orbit; they affect older patients without gender preference. They respond to therapy but the remission does not last. They progress slowly and most of the patients survive with the disease.

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**EARLY STAGE GASTRIC MALT LYMPHOMA TREATED WITH ANTIBIOTIC THERAPY: A SINGLE INSTITUTION EXPERIENCE**

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**Introduction:** The aim of this study was to evaluate the effect of eradicating H. pylori infection on the clinical course of early gastric MALT lymphoma.

**Methods:** A total of 51 patients from a single institution with a diagnosis of stage I gastric MALT lymphoma from August 1992 to March 2004 were included in this study. Every gastric biopsy was analyzed for the presence of H. pylori, for histological diagnosis of lymphoma and for immunoglobulin heavy chain (IgH) gene rearrangements.

**Results:** H. pylori infection was documented in all cases studied. PCR analysis for IgH gene rearrangements demonstrated the presence of a monoclonal population in 45 out of 51 cases (88.2%) at diagnosis. All patients were treated with a combination of antibiotics and proton pump inhibitor. The median follow-up of patients was 54 months. Eradication of H. pylori was obtained in 43 out of 51 (84.3%) cases. In this group, the combination of histological and molecular remissions (CR) was obtained in 18 cases (41.8%) at median 21 and 30 months from diagnosis, respectively; in two cases both histology and PCR were consistent with persistence of lymphoma. In all cases with CR no histological relapse of lymphoma was observed and the persistence of molecular remission was documented (median follow-up of 36.4 months). Among the remaining 23 cases, 18 patients showed histological disappearance of lymphoma, with persistence of monoclonal PCR and one case showed persistence of lymphoma with a molecular remission. Histological relapse of disease in spite of persistence of monoclonal PCR was not reported (median follow-up of 44 months). The remaining four cases showed both histological and molecular persistence of lymphoma.

**Conclusions:** These results are consistent with high rate of long lasting complete remission in patients with gastric MALT lymphoma treated with antibiotic therapy. A monoclonal PCR may last for long time, without clinical and laboratory evidence of progression of disease.

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**CLINICAL AND PATHOLOGICAL ASPECTS OF GASTRIC MALT AND NON-MALT LYMPHOMAS**

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**Introduction:** Although the histologic features of gastric low-grade B-cell MALT lymphomas are by now very well described, its relationship with the gastric large B-cell lymphoma has to be determined. We investigated the distinct clinical and pathological aspects in low-grade and high-grade gastric lymphomas, respectively.

**Methods:** We evaluated the clinical and histopathological aspects of 32 cases of gastric lymphomas found in gastroscopy specimens in our hospital, during a 4 years period. There were 14 cases of low-grade MALT
lymphoma (LG), 10 cases of high-grade MALT lymphoma developed in low-grade MALT lymphoma (HG/LG), 4 cases of high-grade MALT lymphoma (HG) and 4 cases of diffuse large cell lymphoma (DLCL).

Results: Mean age was as follows: LG-56.5 years; HG/LG-44.5 years; HG-61.5 years; DLCL-54.3 years. We noticed a male predominance in MALT lymphomas (male to female ratio was 18/10). Macroscopically, the most common pattern of LG MALT lymphomas was the superficial spreading type associated or not with ulceration, whereas HG MALT lymphomas and DLCL exhibited a solitary tumor-forming lesion. B-cell immunophenotype was confirmed in 31 cases, only one case of DLCL was a T-cell lymphoma.

Conclusions: In our study, the prevalence of high grade MALT and non-MALT lymphomas was 56.25%. Our data suggest that some gastric high-grade lymphomas can arise in LG MALT lymphomas through a process of blastic transformation, which seems to take at least ten years.

VALUE OF TRANSLOCATIONS T(11;18) AS A MARKER OF POOR RESPONSE TO CONSERVATIVE TREATMENT OF GASTRIC MALT LYMPHOMA (GML) WITH PEPSI 105 ALKYLATING AGENTS


Introduction: Oral monochemothotherapy with alkylating agents has been proposed in gastric MALT lymphomas (GML) to non-responders to H pylori eradication and to initially H pylori-negative patients. The aim of the present study was to determine the impact of translocation t(11;18) on response to oral alkylating agents.

Methods: 53 patients (median age 54.2 yrs; median follow-up 3.6 yrs) with a GML were studied: 33 stage IE, 8 stage II and 10 IV. H pylori-positive patients (n = 34) received anti-H pylori treatment and H pylori-negative patients (n = 19) or patients who failed to respond to anti-H pylori treatment, received oral alkylating agents: t(11;18) was detected by RT-PCR from frozen gastric biopsies.

Results: t(11;18) was detected in 17/53 (32%). It was more prevalent in H pylori-negative patients than in H pylori-positive patients (12/19 vs 5/34, p = 0.0005). In stage IE, IV, proportion of t(11;18) was 20% in t(11;18), 62% in t(11;18) and 50% respectively. Among 31 H pylori-eradicated patients, t(11;18) was detected in 3 who all failed to respond and it was absent in 28: 21 (75%) were in remission and in 7 (25%) were in failure (p = 0.03). Among 21 patients who received an alkylating agent, t(11;18) was detected in 12: 5 (42%) were in remission and in 7 (35%) were in failure; it was absent in 9: 8 (89%) were in remission and in 1 (11%) was in failure by the end of treatment. 4 patients in remission relapsed during follow-up (median: 7 yrs): they all had t(11;18). Durable remission was histologically confirmed in 8 of the 9 patients (89%) without t(11;18) versus 1 of the 12 patients (8%) with t(11;18) (p = 0.0003).

Conclusions: t(11;18) is predictive of resistance to oral alkylating agents in GML with less than 10% of durable remission in long term follow-up. Presence of t(11;18) might be used to select patients requiring more aggressive treatment.

TREATMENT OF PRIMARY GASTRIC DIFFUSE LARGE-CELL LYMPHOMA WITH RITUXIMAB AND CHOP. PRELIMINARY RESULTS OF A PROSPECTIVE, MULTICENTER PHASE II STUDY

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Introduction: The optimal treatment of primary gastric diffuse large B-cell lymphoma (PG-DLBC) has not yet been defined. In most circumstances, a stomach-conserving approach is favored. Recently, Rituximab along with full-dose CHOP chemotherapy has been shown to improve the outcome in elderly patients with nodal DLBCL. However, no such data are available in patients with PG-DLBC.

Methods: In March 2003, we initiated an ongoing, prospective, multicenter phase II study in patients with PG-DLBC with 6 to 8 cycles of Rituximab (R; 375 mg/m²) plus CHOP-21 in order to evaluate the safety and efficacy of this approach. Per protocol, no surgery or radiotherapy were allowed, while eradication of H pylori was mandatory in cases with documented infection. Reference pathology was performed in all cases.

Results: At this stage, 13 patients with a median age of 77 years (range 38–87) were recruited. 85% of the patients were in stages IE and III according to the modified Ann Arbor classification. Only 1 of the 13 patients received emergency gastrectomy due to severe bleeding prior to initiation of R-CHOP therapy. Full-dose R-CHOP therapy (median of 5 cycles; range 1–6) was generally feasible, although 3 patients required dose reduction or dose delay due to WHO grade III/IV haematological toxicity. Severe non-hematological toxicity was not observed, except for one 76 year old patient who developed transient cardiac failure which required re-hospitalisation. No treatment-related deaths were observed. R-CHOP treatment was highly effective with all patients responding so far; responses occurred within 2–3 cycles of treatment. On histologically and endoscopically confirmed rate of complete remissions (CR) after 3–4 cycles was 57%, while 43% were in partial remission at this stage. With a median follow-up of 11 months (range 1–23) after treatment initiation, all patients are in clinical CR and none of them relapsed. Interestingly, one patient developed a histologically confirmed gastric carcinoid and ultimately died of this disease. Overall, 10 out of 13 patients had isolated lymphoma recurrence.

Conclusions: These preliminary results indicate that R-CHOP therapy is feasible and effective in this elderly population of patients with PG-DLBC. Longer follow-up and recruitment of additional patients is required and will be presented.
Conclusions: Chemotherapy is effective therapeutic approach for the patients with primary gastrointestinal lymphomas. Patients with initially low value of HB.

RITUXIMAB IN MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA: HIGH COMPLETE RESPONSE (CR) RATE WITH NO TOXICITY

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Background and objective: MALT lymphomas have an indolent course, with long survival, although a relatively high risk of relapse. There is not a gold standard treatment. Since they express CD20, rituximab may be an excellent therapy. The aim of this study was to assess activity and tolerability of rituximab as a single agent in patients (pts) with MALT lymphoma.

Patients and methods: 19 pts (7M/12F; median age: 57 years) with biopsy-proven low grade CD20+ MALT lymphoma treated at a single institution. Treatment consisted of rituximab 375 mg/m² i.v. weekly for 4 consecutive weeks. The primary sites of lymphoma were: stomach (5 cases), skin (3), conjunctive (2), lung (2), rectum (1), breast (1), salivary gland (1) and lymph nodes (2). Clinical and biologic features, as well as toxicity and response to rituximab were assessed.

Results: Five pts received rituximab as first line treatment and 14 at relapse. Six of the 19 pts were re-treated with rituximab after relapse. The antitumoral activity of rituximab, inducing apoptosis, was demonstrated in vitro in 5 pts. Toxicity was negligible. Response and outcome are summarized in the table.

<table>
<thead>
<tr>
<th>CR (%)</th>
<th>Relapses N</th>
<th>Time to progression (Median, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>5</td>
<td>3 (0-5)</td>
</tr>
<tr>
<td>Previously treated</td>
<td>14</td>
<td>11 (70)</td>
</tr>
<tr>
<td>Re-treatment</td>
<td>6</td>
<td>4 (66)</td>
</tr>
</tbody>
</table>

Conclusion: In patients with MALT lymphoma, rituximab given as a single agent has high therapeutic activity.

HCV INFECTION AND SOLID NEOPLASMS IN NON-GASTRIC MARGINAL ZONE B-CELL LYMPHOMA OF MALT

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Aim: Aim of the study was to define the HCV infection and the solid neoplasia incidence in non-gastric MALT lymphomas.

Patients: We studied 113 pts with a confirmed histology of marginal zone b-cell lymphoma of MALT according to the WHO classification, who presented with a clinically prevalent non-gastric extranodal site of disease. The primary site of lymphoma was: orbit (22), Wellewer ring (21), skin (20), salivary glands (20), lung (9), breast (4), liver (3), small bowel (3), femoral popliteal tract (1), multiple mucosal sites (10).

Results: Median age was 64 years (23-86) (73 F, 40 M). Most pts (94%) had not B symptoms and a good PS (92%). 45 pts had stage I disease (39%), 11 stage II (10%), 4 stage III (4%) and 53 stage IV (47%). Bone marrow was involved in 42, and peripheral blood in 7.15 pts (12%) had
spleen enlargement and 44 (39%) nodal involvement (23 loco-regional). 14 (12%) had Hb values <11 g/dl, 13 (12%) abnormal LDL levels, 23 (20%) had a little monoclonal component (14 IgM, 7 IgG, 2 IgA). An autoimmune background was present in 10 pts (9%). HCV-serology was positive in 32 of 94 valuable pts (34%). All HCV + pts showed a single extranodal site and had nodal disease. 18 pts (56%) had active chronic hepatitis. Solid neoplasia was present in 20 pts (18%) (14 E, 6 M) previous in 13, concurrent in 3, subsequent in 4 (breast 7, endometrium 3, thyroid 2, lung 2, other sites 6). In 2 pts the site of cancer and lymphoma was the same (breast and lung). First line therapy consisted of chemotherapy in 58%, local RT in 12%, surgical resection in 7% while 23% were followed without therapy. A CR or PR was obtained in 46% and 17% respectively. After a median F-U of 2.3 years, median OS was 10.1 years and median EFS 1 year. In univariate analysis longer OS was significantly associated with a single extranodal site (P=0.001), localized disease (P=0.006), normal LDH (P=0.009), absence of nodal involvement (P=0.001), and HCV-positivity (P=0.049). In multivariate analysis only multiple extranodal sites had a negative influence on OS (P=0.03).

Conclusions: This survey on a multi-centre series of non-gastric MALT lymphomas shows an evident association with HCV infection and solid cancer; the frequent dissemination at presentation with multiple extranodal sites and/or nodal involvement seems to characterize a subset at worse prognosis.

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PRIMARY MEDISTINAL B-CELL LYMPHOMA (PMBCL): TREATMENT OUTCOME OF 34 PATIENTS TREATED AT MARIA SKŁODOWSKA-CURIE CANCER CENTRE IN WARSAW

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Introduction: PMBCl is a subtype of diffuse large B-cell lymphoma recognised as a distinct clinical-pathological entity. We have reviewed the outcomes of pts treated in our centre either with standard chemotherapy (CT) or with CT followed by ASCT.

Methods: 34 pts with PMBCL were treated (18F/16M). The median age was 29 (range 18-67). 11 pts (32%) presented with CS III/IV, 12 pts (35%) had IPI2, 28 pts (82%) had bulky disease, 25 pts (73%) received CHOP as a first-line treatment, whereas 7 pts (20%) were treated with more intense regimens (6-CODOX-M-IVAC, 1-CT according to GMALL 2002 protocol), followed by ASCT in 5 pts.

Results: Among pts who received CHOP, 11/25 (44%) had progressive disease during the first-line treatment and 6/25 (24%) relapsed within 6 months after completing CHOP. All patients who relapsed/failed the initial treatment had aggressive survival CT. 7/17 pts did not achieve durable responses and died of disease progression. 10/17 pts were qualified for ASCT procedure but 5 pts with primary refractory disease relapsed after ASCT and died. All but one patient who relapsed/failed the initial treatment had bulky disease. Among 12 pts who died, 5 had IPI 2-3 and all had elevated LDH level. 7 pts qualified for early intensification treatment that had bulky disease, elevated LDH and 5/7 pts had IPI 2. 2/7 pts achieved CR with an induction therapy. 5/7 pts who obtained PR had ASCT and all but one achieved durable remissions. Probability of survival at 36 months for all analysed pts is 53%, C.I.95% [38%,69%] and 80%, C.I. [20%, 97%] for the intensively treated group.

Conclusions: Salvage therapy for pts with an initial treatment failure/an early relapse did not induce long-lasting remissions in majority of our pts. Clinical and pathological features identifying poor prognosis pts with PMBCL need to be established since they may benefit from an early intensification treatment including ASCT.

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PRIMARY MEDISTINAL LARGE B CELL LYMPHOMA WITH SCLEOSIS: A CLINICAL STUDY OF 92 PATIENTS TREATED AT A SINGLE INSTITUTION WITH MACOP-B AND RADIO-THERAPY

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Introduction: Primary mediastinal large B cell lymphoma (PMBL/C) represents a distinct clinicopathological entity of large B cell lymphoma occurring preferentially in young females with a bulky mediastinal mass.

Methods: Between 1991 and April 2004, 92 consecutive untreated patients (pts) with PMBL/C were diagnosed and treated at our institution. The median age was 33 years (range 15-61), 68/92 (74%) were females, 72 pts had stage I1 and 20 stage IIE. 43/47% presented B symptoms. LDH was increased in 68(74%), 81(88%) had a bulky mass and 47(51%) had a superior vena cava syndrome. According to age-adjusted IPI score 52 pts had an IPI = 0 and 40 pts IPI = 2. 3. All pts were treated with standard MACOP-B chemotherapy (CHT) and 86 pts underwent mediastinal radiotherapy (RT) at dose of 30-36 Gy. Six (7%) pts did not receive RT (refusal = 3, progression = 2, death = 1). The response was evaluated in all pts after CHT and at the end of RT.

Results: After MACOP-B regimen the response rate was: CR/CRu = 72(78%), PR = 18 (20%), NR = 1 (1%). Toxic death = 1 (1%). Six (6%) PR pts underwent to intensification therapy with high dose therapy and ASCT. After RT pts achieved CR/CRu = 78 (91%), PR = 3 (3%), NR = 5 (6%). After CHT 3 Gallium scan was positive in 51/60 (85%) while after RT was positive in 12/53 (23%) P=0.001. After a median follow-up of 58 months (1-165) relapse was observed in 9 pts. Five of the 9 relapsed pts are alive after second line therapy with ASCT. Five not responding pts had progressive disease and died. To date 82 (90%) pts are currently in continuous CR. Projected 5-years OS and PFS are 88% and 54%, respectively. The 5-years OS was better for pts with IPI 0-1 compared to IPI 2-3 (96% vs 76% P = 0.006).

Conclusions: Combined modality treatment using the MACOP-B regimen and mediastinal RT induces high response and survival rates. Radiation therapy plays an important role in the achievement of these results.

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PRIMARY BONE NON-HODGKIN'S LYMPHOMA: A RETROSPECTIVE REVIEW

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Background: The study presents 16 years of experience (1998-04) in eighteen patients with PBL.

Objective: The aim of this study was to retrospectively analyze clinical and radiological aspects and to evaluate treatment, and outcome in pts with PBL.

Methods: 18 patients with histologically proven PBL.

Results: Ten were men and 8 women; median age 56 years. PS was 0 or 1 in 78%. The most frequent clinical signs was weight loss in 50% and 50% of the patients had a pathological fracture. The long bones were generally involved. Twenty-three of 24 patients had widespread disease at diagnosis. The lymph nodes were involved in 13 patients, the liver in 12 patients, and the spleen in 3 patients. Reticulin fibrosis was identified in 13 patients, and bone marrow involvement was identified in 9 patients. Ten patients died of disease with a median survival of 3 months, and 8 patients were alive with a median survival of 9 months. The median survival for the whole group was 4 months. The median survival time for patients with stage I disease was 12 months, and for stage II disease was 8 months. The median survival time for patients with stage III disease was 6 months, and for stage IV disease was 3 months. The median survival time for patients with grade I disease was 12 months, and for grade II disease was 8 months. The median survival time for patients with grade III disease was 6 months, and for grade IV disease was 3 months. The median survival time for patients with grade V disease was 3 months.

Conclusion: This retrospective study with a small patient accrual demonstrates that primary bone lymphoma is a curable disease following aggressive doxorubicin-based chemotherapy. Based on this study, surgery is not indicated except to obtain a biopsy and to treat mechanical complications.

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PRIMARY MEDISTINAL LARGE B-CELL LYMPHOMA WITH SCLEOSIS: A CLINICAL STUDY OF 42 PATIENTS TREATED WITH MACOP-B CHEMOTHERAPY PLUS RADIATION THERAPY

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NON-HODGKIN'S LYMPHOMA OF THE BONE – A REVIEW OF 28 CASES FROM INDIA

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Non Hodgkin's lymphoma (NHL) arising primarily in the bone is rare and comprise 5% of extranodal lymphomas. We share our experience with this disease. Aim: To study the presentation and survival of NHL arising primarily from the bone.

Material and Methods: 28 cases of NHL with the primary site as bone treated at Regional Cancer Centre, Trivandrum, India form the subjects of our study.

Results: Among the 28 cases studied, there were 24 males and 4 females. The median age at presentation was 41 years. The commonest symptom was pain and swelling with the median duration of symptom being 6 months. The common sites were femur, tibia and vertebrae followed by humerus and ilium, one patient each had involvement of the scapula, ribs and ilium. Left side was involved more commonly. The commonest histology was diffuse large cell lymphoma (14), and diffuse mixed (5). Two patients had lymphoblastic lymphoma and 2 had low grade NHL and in 5, the type was unspecified. Twenty two patients received irradiation, the dose ranged from 35 Gy to 55 Gy with a median dose of 40 Gy. Eleven patients had surgical intervention (excision, laminectomy). Twenty two patients received chemotherapy mostly CHOP. The 2 cases of lymphoblastic lymphoma received protocol MFP 842. The median survival of the series was 36 months with 20 patients alive at 24 months.

Conclusion: NHL bone is a disease of the male and requires multimodality management for cure.

NUCLEAR BCL10 EXPRESSION DOES NOT RELATE TO T(11;18)(Q21;Q21) AND T(14;18)(Q32;Q32) IN OCULAR ADNECA B-CELL LYMPHOMAS AND IDENTIFIES A GROUP WITH A WORSE PROGNOSIS

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Introduction: MALT-type lymphomas is the most frequent type of lymphomas in Ocular Adnexa region. In general non gastrointestinal MALT type lymphomas have been well characterized when considered as whole group, independently by its anatomic localization. But some molecular features seem to characterize MALT-type lymphomas of different sites. By the use of Tissue Microarray (TMA), we studied a large number of markers related to lymphocyte differentiation, cell cycle and apoptosis regulation and cytogenetic status related to the most frequent translocations described in MALT-type B cell lymphomas, t(11;18)(q21;q21) and t(14;18)(q32;q21), both involving MLTI gene expression.

Materials and methods: 59 patients were collected in a period of twenty years. Clinical history was documented for at least 6 months from diagnosis. A series of proteins related to B cell differentiation and regulation of cell cycle (main proteins involved in RB pathway with relative inhibitors and p53 pathway) and apoptosis (bcl2 protein family and main proteins involved in of NF-KB survival pathway) were studied by immunohistochemistry on TMA sections, comprising two cylinders from cases and 2 hyperplastic lymphoid tissue. Moreover FISH study relating t(11;18) and t(14;18) was performed.

Results: The series of patients consisted of 18 male and 21 female. Different therapeutic strategies were adopted, mainly radiotherapy based. Immunohistochemical studies revealed mainly an apoptosis deregulation with abolished caspase 3 activity in all cases and an increased expression of phosphorylated IKB, direct expression of NF-KB activity, in 19/39 cases. Increased expression of some proteins related to cell cycle regulation, such as Cycline A, Cycline E, ki67 and Hdm2, was observed in case with an increase large cells (i.e. high grade MALT-type lymphomas). T(11;18) was not found in examined 36 cases, whilst t(14;18) was found in 5/36 cases. In univariate analysis nuclear bcl10 expression is significantly associated to shorter Disease Free Survival.

Conclusions: Deregulation of apoptosis, as in other districts, seems to be the most consistent alteration in MALT-type OAILs. Differently from MALT-type gastric lymphoma model, bcl10 nuclear expression does not seem to be associated to t(11;18) and relates to a worse prognosis, assuming its specific role, independently from MLTI gene deregulation.
MOLECULAR CLONING OF THE (1;14)(q11;q32) INVOLVING THE MLT/MA1 GENE IN A MALT LYMPHOMA OF THE CONJUNCTIVA
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Introduction: The t(11;14)(q21;q21) and the novel t(14;18)(q32;q21) are the main structural abnormalities in extranodal MALT lymphomas and involve the MLT gene. The molecular genetic characterization of the t(14;18) has only been performed in two cases and revealed a fusion of the entire coding region of MLT/MA1 to the IGH joining region gene 5 (IGHJ5).

Methods and results: We herein report the molecular genetic analysis of a MALT lymphoma harboring the t(14;18) using fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH) and long-distance PCR (LD-PCR). The patient, a 71-year-old female, presented with an extranodal MALT lymphoma of the conjunctiva, stage IEA. Radiotherapy resulted in complete remission and the patient is alive without evidence of disease 3 years after primary diagnosis. FISH with PAC clones 117BS and 58977 revealed a translocation involving MLT/MA1. Further FISH assays with probes hybridizing to MLT/MA1 and IGH revealed the t(14;18)(q32;q21). By CGH analysis no chromosomal gains or losses were detected and FISH with specific probes for the P53, P16, and RB1 genes showed no deletions of these oncogenes. Finally, LD-PCR was performed to delineate the breakpoint within MLT/MA1 and IGH. With specific primers for MLT/MA1 and the joining region of 5 IGH, a fragment of 2kb was amplified. Cloning and sequencing of this fragment revealed a fusion of IGHJ4 to the 5' non-coding region of MLT/MA1.

Conclusion: We conclude that similar to other IGH-associated translocations, such as the t(1;14)(q24;32) and the (3;14)(q27;q32), the breakpoint in MLT/MA1 falls in the 5' non-coding region leaving the coding region of MLT/MA1 intact. Therefore, overexpression of MLT/MA1 by juxtaposition to IGH regulatory elements in likely the pathogenetic relevant mechanism in the t(14;18). Supported by grant 106092 (J.D.) from the Deutsche Krebshilfe.

EXPRESSON OF THE CHEMOKINE RECEPTORS CXCR4, CXCR5 AND CCR7 IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA
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Introduction: Primary CNS lymphoma (PCNSL) is an unusual form of B cell lymphoma with a low propensity to manifest itself extracerebrally. Recent findings indicate that chemokine receptor expression plays an important role in determining the metastatic spread of tumor cells.

Methods: This study investigated the expression pattern of CXCR4, CXCR5 and CCR7 in PCNSL using immunohistochemistry, and compared it with that in systemic B cell lymphoma.

Results: CXCR4, CXCR5 and CCR7 expression was observed in the neoplastic cells in all 29 PCNSL. Positivity for CXCR4 and CCR7 were restricted to the cytoplasmic and, in some cases, to the nucleus (CXCR4); no membranous staining was observed. CXCR4 and CCR7 cytoplasmic location was confirmed by immunofluorescence microscopy. In contrast, membranous expression of CXCR4, CXCR5 and/or CCR7 was observed in 11, 11, and 14, respectively, of the 29 peripheral B cell lymphoma specimens. The lymphoma cell lines Raji and YT, demonstrating a CCR7 and CXCR4 expression pattern similar to PCNSL with intracellular staining but absent surface expression, in contrast to cell lines with membranous expression showed no chemotactic response to the specific ligands.

Conclusions: In PCNSL, the absence of membranous CXCR4, CXCR5 and CCR7 may play an important role in their low disseminating potential.

ORBITAL LYMPHOMA
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Introduction: The extranodal lymphomas represent 20 to 45% of the NHL. The location in orbit in slightly frequent: 2 to 5% of the extranodal and 8 to 11% of the tumors in orbit. The intention of this presentation is to evaluate the characteristics and evolution of a series of carrying patients of this pathology.

Methods: We present 35 cases of NHL of orbit, attended in the Haematology Department of the "Hospital de Oncologia Marie Curie", Buenos Aires, Argentina, from 1991 to 2004.

Results: The average age was 61.5 years (range 23 to 93), m/f: 1:3.3. All the patients HIV negative. In left orbit 54.28%, right 37.14% and bilateral 8.5%. The location in conjunctiva 60%, palpebral 31.4% and 8.5% in lacrimal gland. Stage I: 37.14%, II: 42.85%, III: 11.42%. The time from the beginning of the symptoms and the diagnosis was more than 12 months in 64%. The histological subtypes were: low grade 82.86%, high grade 14.28% and 2.85% without subtype. According with IPI 74.3% were low, 14.3% low-intermediate, 8.5% high-intermediate and 2.85% high. According with the Modified International Prognostic Index (MIPI; Miller et al. 1998), 52.8% were 0 and 1, and 45.71% >1. The LDH was carried out in 26, and normal in 27, the beta 2 microglobulin in 25, and normal in 21. The treatment was radiotherapy in 22 cases, in 5 as the only treatment, and in 17 after the CT. The survival was 6 months to 18 years, with an average of 4.93 years. In conjunctive locations they all reached remission (CR), and 10% died. In the palpebral location 18% reached PR, 82% CR. Died 54.5%, 27.3% of them in systemic relapsing.

Conclusions: The MIPI low grade (0-1) was related with the conjunctive location (73.7%), palpebral 21%, relapsing 21%, 0 dead. The MIPI >1 was related with the palpebral location in 42.75%, conjunctive 37.5%, relapsing 42.75% and 0 dead. The long laping time between the beginning of the symptoms and the diagnosis may be due to the low frequency of this type of NHL and the lack of specified initial symptoms. The lack of an early diagnosis does not restrain that a high percentage of patients reach the CR. The MIPI, with the inclusion of the stage II as a prognostic factor allow to identify 2 different groups of evolution and location. The palpebral location is a risk factor. The beta 2 microglobulin and the LDH were non significant factors for this type of NHL.

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Introduction: Malignant lymphoma of the central nervous system(CNS) is considered to be a rare disease, making up 1-2% of primary brain tumors. PCNSL has been roughly estimated to account for at least 1-2% of systemic lymphomas.

Methods: We examined retrospectively the outcome of patients with PCNSL registered at The MSc Memorial Cancer Centre and Institute from 1995 to 2004 in order to evaluate our treatment strategy for the patients. Description of the patients (39 males, 35 females), symptoms at CNS diagnosis, prognostic factors, treatment and survival were registered. Median age of the patients was 54 years (range 16-90).Low grade histologies (L-NHL) were found in 8 patients and high grade histologies (H-NHL) were diagnosed in 66 patients.

Treatment and results: Patients with L-NHL received COP and CQN. Patients with H-NHL received CHOP, MEVA,MEVA-3D,HD-MTX,CO- DON-IVAC +5+MTX intrathecally (11). Most of those patients, who were in remission after induction chemotherapy, were consolidated with radiotherapy (whole-brain radiation). The radiation dose ranged from 30 Gy to 45 Gy. Twenty one patients were treated with systemic chemotherapy alone, 14patients were treated with brain radiation alone. The survival
time of the 42 patients treated with radiochemotherapy (median 35 months) was longer with chemotherapy alone (median 27 months) or radiotherapy alone (median 11 months). Forty-eight patients died in our study.

Conclusion: We suggest, based on our data, that older patients (>60 years) should receive intensive chemotherapy including high-dose methotrexate. Combined chemo-radiotherapy approach in patients younger than 60 years.

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BRIEF HIGH-DOSE METHOTREXATE-BASED CHEMOTHERAPY (HD-MVPM) WITHOUT RADIATION RESULTS IN PROLONGED EVENT-FREE AND OVERALL SURVIVAL IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)
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Background: PCNSL is a rare tumour with a poor prognosis. The addition of high-dose methotrexate (MTX) to cranial radiation has improved the survival of patients with this disease. However, combined therapy is also associated with delayed neurotoxicity, especially in elderly patients. In an effort to limit the neurotoxicity of treatment, we treated newly diagnosed non-immunocompromised patients with systemic and intrathecal chemotherapy alone.

Methods/Results: Patients at our institution are treated with the HD-MVP regimen consisting of high-dose MTX 3.5 g/m² and vincristine 1.4 mg/m² on day 1, procarbazine 100 mg/m² daily days 1–7, leucovorin rescue, and intrathecal MTX 12 mg on days 3, 5, 8, 10, 12. Eighteen patients were treated between June 1997 and December 2004. Fifty-six percent were male and the mean age at diagnosis was 60 years (range 45–75). Cerebrospinal fluid was involved in 5 patients and 3 patients had ocular involvement. Most patients presented with cognitive and personality changes (n = 12). Patients were treated with a median of 2 cycles of HD-MVPM. Overall response was 72.2% (8 CRs and 5 PRs). Radiation therapy (XRT) was used as second-line treatment in 9 patients resulting in 4 CRs and 5 PRs. The median event-free survival was 39.0 months (1.3–87.9) and median overall survival was 79.3 months (0.2–87.9). With a median follow-up of 49.2 months, 4 patients (22.2%) remained in continuous first CR. Six patients have suffered significant neurocognitive decline (4 patients after receiving XRT for relapsed PCNSL).

Conclusions: HD-MVPM therapy, a brief, dose-dense regimen, has a good overall response rate and induces lasting remissions in some patients with PCNSL. Delayed neurotoxicity appears to be less frequent than with XRT or combined modality therapy.

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PRIMARY TEMOZOLOMIDE CHEMOTHERAPY IN ELDERLY PATIENTS WITH PRIMARY CNS LYMPHOMA (PCNSL)
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Introduction: In some PCNSL patients over 60 years, standard high-dose methotrexate (HD-MTX) therapy may not be applicable due to comorbidities such as impaired renal function. This prompts the search for other chemotherapeutic agents that can be applied to these patients instead of HD-MTX.

Methods: Progression-free survival, overall survival and toxicity were retrospectively analyzed in patients with primary CNS lymphoma treated with temozolomide alone as primary therapy.

Results: We report 9 patients who had histologically confirmed PCNSL (n = 7) or a discordant-responsive lesion highly suggestive of PCNSL by neuroradiography (n = 2). The patients (62–90 years old) received 1–8 four-week courses of temozolomide (200 mg/m² for 5 days in 7 patients, reduced dose of 100 or 150 mg/m² in 2 patients). The median number of courses applied was 3. Complete responses were achieved in 6 patients, 1 patient had stable disease after 3 courses and therapy was then switched to WBRT due to myelosuppression. 2 patients had primary progressive disease and did not receive any further therapy. In the patients achieving CR, CR persisted for 4, 5, 5, 18, 21 and 48 + months. The 2 patients with short progression-free survival of 5 months had received a reduced number of only 1 or 4 courses of temozolomide. After a median follow-up of 17 months (range 1–48 months), median survival has not been reached yet. One patient died after 1 month due to tumor progression and 8 patients are alive. Acute toxicity consisted of high-grade thrombocytopenia and leukopenia with subsequent infection in one patient who had received 200 mg/m² temozolomide and high-grade leukopenia without further complications in another patient. One patient developed low-grade skin erythema.

Conclusions: Temozolomide appears to be an effective and tolerable therapy for elderly patients with PCNSL and comorbidity who cannot receive HD-MTX. The application of more than 4 courses is advisable.

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ERYTHROPOIETIN IN ANEMIC PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA
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Introduction: Anemia (hemoglobin (Hb) ≤10.9 g/dL, according to the World Health Organization Classification) is the most frequent adverse effect of high-dose methotrexate (HD-MTX) treatment and occurred at a rate of about 50% in 154 patients with primary central nervous system lymphoma (PCNSL) enrolled in a multicenter prospective trial. As the symptoms of anemia may mimic neurologic symptoms related to PCNSL, anemia may even influence therapeutic intervention and outcome. Erythropoietin is known to increase Hb levels and possibly exerts neuroprotective effects.

Methods: In a single center pilot trial, 12 patients with newly diagnosed primary PCNSL and a Hb level <11 g/dL under HD-MTX treatment (4 g/m² x6 cycles) received epoetin alfa 3x10,000 IE/week s.c. until Hb levels were ≥13 g/dL. Endpoints were rise in Hb level and improvement in quality of life evaluated with the FACT-An quality of life questionnaire with 20 anemia-related items and each item ranging from 0 (absence of symptom) to 4 (severe symptom).

Results: Median baseline Hb level was 10.2 g/dL. Median duration of erythropoietin treatment was 6 weeks. The median rise in Hb level under erythropoietin treatment was 1.7 g/dL. Eight patients reached Hb levels of ≥12 g/dL. FACT-An questionnaires were evaluable in 10/12 patients. The median baseline FACT-An score for the evaluable patients before erythropoietin therapy was 2.5 and improved to 1.5 after termination of treatment.

Conclusions: Erythropoietin is able to effectively increase Hb levels in patients with PCNSL and may improve anemia-related symptoms. Patients with extracerebral NHL PCNSL patients treated with HD-MTX should be carefully watched for signs and symptoms of anemia and, if indicated, be substituted with blood transfusions and/or erythropoietin according to the guidelines of the American Society of Clinical Oncology and the American Society of Hematology. Results, however, should be considered preliminary, and confirmation in the setting of a large prospective trial is desirable.
6. Mantle Cell Lymphomas

OVERALL POOR PROGNOSIS OF LEUKEMIC LYMPHO-PROLIFERATION WITH MANTLE CELL PHENOTYPE

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Background: Although mantle cell lymphoma (MCL) is biologically well-defined form of non-Hodgkin’s lymphoma, it belongs to frequently misdiagnosed lymphoma entities. Bone marrow and peripheral blood are very often involved in MCL patients but overt leukemic involvement has been described less commonly.

Patients and methods: Clinical and laboratory data including cytogenetic and molecular genetic analysis from 62 patients with MCL leukemic lymphoproliferation (more than 4x10⁹/μL CD5+; CD19+ and CD23- peripheral blood lymphocytes) were evaluated.

Results: The patients were predominantly male (69%). Median age was 66 years. The median of absolute lymphocyte count was 127x10⁹/l (range 4,1-453,1). 18 pts. showed blastic, anaplastic or prolymphocytic morphologic of neoplastic cells. t(11;14), bcl-1/PDGH or hyperexpression of cyclin D1 were detected in 27/45 (60%) pts. Complex genetic changes without t(11;14) were present in another 7/45 (16%) pts. 47 pts. were treated with chemotherapy, with response rate 44%. 43 pts. died 2-72 months after the diagnosis (median 16 months). 15 pts. is alive with median follow-up 29 months (range 3-82 months). 4 pts. were lost to follow-up. A poor prognosis and short survival (29/32 death, median OS 16 months) were associated with the presence of t(11;14), bcl-1/PDGH, cyclin D1 or complex genetic changes, a better prognosis appeared to be found in a group of pts. with typical MCL phenotype, but without t(11;14), hyperexpression of cyclin D1 and complex genetic changes (no death, median follow-up 43 months).

Conclusions: Leukemic lymphoproliferation with MCL phenotype and with the presence of t(11;14), bcl-1/PDGH hyperexpression of cyclin D1 or complex genetic changes has poor prognosis and very short overall surviva. Supported by grants IGA NC-4790 and MSM 619 895 920.

CENURAL SERNOUS SYSTEM (CNS) INVOLVEMENT IN MANTLE CELL LYMPHOMA (MCL)

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Objective: To ascertain the incidence and prognostic significance of CNS infiltration in patients with MCL.

Patients and methods: 84 patients (pts) (62M/22F; median age: 61 years) diagnosed with MCL at a single institution over a 14-year period. The histological distribution was: blastoid MCL, 28%; typical MCL, 72%. Most patients presented with advanced stage (92%), bone marrow (BM) infiltration (86%), and intermediate or high-risk IPI (85%). Treatment included regimens with high-dose methotrexate in 28 pts.

Results: Eleven of 84 pts (13%; 0.95 CI: 5-20%) developed CNS involvement. In one asymptomatic pt, cerebrospinal fluid (CSF) infiltration was detected during staging. The remaining 10 patients developed CNS involvement during the course of the disease (median time from diagnose, 25 months; range 5-130), as a part of a resistant disorder or generalized relapse. Pts presented with neurological symptoms (facial palsy, 3 cases; sciatialis, 3; paraparesis, 3; diplopia, 2; confusional syndrome, 1) and displayed atypical lymphocytes in the CSF, consistent with MCL. The risk of CNS involvement at 5 years was 26% (0.95 CI: 10-42%). Pts with CNS infiltration more frequently had blastoid histology, 2 extranodal sites, high serum LDH, and high-intermediate or high-risk IPI. Histological subtype (blastoid vs. nonblastoid, P=0.01; RR: 6) and IPI (LR 1 vs. H, F=0.01; RR: 11) retained prognostic significance in the multivariate analysis. 10 pts were treated with systemic chemotherapy and 9 also received intrathecal chemotherapy, with only minor improvement as a delayed due to progression, with a median survival after CNS infiltration of 3 months (range 0.01-19 months).

Conclusions: CNS involvement might be more frequent than previously recognized in patients with MCL. The role of CNS prophylaxis, as well as the optimal treatment of such a complication, warrant further studies.

WHOLE GENOME PROFILING COMBINED WITH GENE EXPRESSION ANALYSIS TO IDENTIFY NEW GENES IN MANTLE CELL LYMPHOMAS

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Introduction: Mantle cell lymphomas (MCL) prognosis is the worst among all B cell lymphomas. Since there is no standard treatment for MCL, new therapeutic targets based upon the biology are needed. We combined array-CGH and gene expression profiling (GEP) to identify new possible targets.

Methods: MCL cell lines and clinical samples were analysed. GEP and arrayCGH were performed using Affymetrix HU133 set and Affymetrix GeneChip Mapping 10K, respectively. Recurrent genomic amplifications and deletions have been identified using Affymetrix CCNT and in-house algorithms developed on the R statistical package. GEP data were analysed using the Bioconductor package. To validate the arrayCGH technique and analysis, the cell lines were studied with karyotype analysis, with CN10 OoChip microarray and with FISH using 12 Vyasa probes.

Results: Nine MCL patients and 4 cell lines have now been studied. Recurrent losses were in 17p, 6q, 8p, 11p, 11q and 13q. Recurrent gains/amplifications were 3q, 8q and 13q. Already known amplifications of cMYC and BCL2 or losses of TP53 and CDKN2A were clearly identified by the combination of arrayCGH and GEP.

Conclusions: The combination of whole genome profiling combined to gene expression is a promising approach to study MCL pathogenesis. New cancer genes identified affected regions will be presented. Partially supported by the SAKK.
ABCM IN THE TREATMENT OF MANTLE CELL LYMPHOMA: A SCOTLAND AND NEWCASTLE LYMPHOMA GROUP STUDY
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Introduction: Mantle cell lymphoma (MCL) is a rare subtype of Non Hodgkin Lymphoma (NHL) accounting for 5% of cases. It is generally believed to have a median age at presentation of around 60 years and median survival of 5 years. However, analysis of 117 patients with MCL on the SNLG database (median age 69), which is population-based and unselected, had a median survival of 22 months. There is no curative treatment.

Methods: Patients with MCL not considered suitable for intensive therapy were entered into this Scotland and Newcastle Lymphoma Group study of treatment with Doxorubicin (30 mg/m^2 iv day 1), BCNU (30 mg/m^2 iv day 1), Cyclophosphamide (100 mg/m^2 d/ally orally days 22-25) and Melphalan (6 mg/m^2 orally daily days 22-25) (ABCM regimen). A total of 6 cycles were to be given, each cycle repeated every 6 weeks. Study patients were treated between April 2000 and November 2003 with follow up to October 2004.

Results: Of the 17 patients entered, 13 were given the treatment as first line and 4 as second line therapy. Median age at diagnosis of the patients receiving ABCM as initial treatment was 67 years (median age 54). 5 patients had ECOG performance status 2, and stage at presentation was IIa (1), IIIa (1), IVa (3), IVB (8). Two patients received XRT in addition to chemotherapy and 1 patient who had orbital involvement was given intrathecal methotrexate. Three patients achieved CR and 5 PR, with 2 having static disease and 3 disease progression, for an overall response rate of 61%. Median survival post ABCM is 18 months (11-33) and for responders 33 months. There were 2 toxic deaths. Four patients were given ABCM as second line treatment (aged 51, 52, 67, 72); response was CR (1), PR (1) and NR (2). Median survival post ABCM was 16 months and all died of lymphoma.

Conclusion: We conclude that ABCM is well tolerated in this older population and shows some promise in the treatment of this difficult condition. The SNLG data suggests that in an unselected population, patients with MCL are older and have a poorer survival than in the literature.

RITUXUMAB-MAINTENANCE AFTER A COMBINED IMMUNOCHEMOTHERAPY SIGNIFICANTLY IMPROVES RESPONSE DURATION IN PATIENTS WITH RELAPSED FOLLICULAR AND MANTLE CELL LYMPHOMA
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Introduction: Rituximab (R) was shown to prolong the time to treatment failure and response duration (RD) in follicular lymphoma (FL) both, given simultaneously in combination or as maintenance after chemotherapy.

Methods: The current study investigated the impact of R maintenance particularly after a combined immuno-chemotherapy. Patients with advanced stage relapsed or refractory FL and mantle cell lymphoma (MCL) were eligible. The initial study design comprised a first randomization between 4 courses of chemotherapy (FCM: Fludarabine 25 mg/m^2 /days 1-3, Cyclophosphamide 200 mg/m^2 days 1-3 and Mitoxantrone 8 mg/m^2 /day 1) versus FCM plus Rituximab (375 mg/m^2 on day 0). Subsequently, patients with a complete or partial remission underwent a second randomization between observation only vs. R maintenance (4 weekly doses of R 375 mg/m^2 at 3 and 9 months after induction). Randomization was stratified for histology and preceding therapy. After the sequential test demonstrated a significant improvement of initial response, progression-free and event overall survival in the R-FCM arm, all subsequent patients received combined immuno-chemotherapy.

Results: 157 of 184 patients went through the second randomization and are currently evaluable. In October 2004 the one-sided sequential triangular test showed a significant difference in favor of the R-maintenance arm. After R-maintenance the median remission duration was not reached at 3 years whereas it was 19 months in the observation arm (P=0.0171). This beneficial effect was also observed after combined immuno-chemotherapy

(R-FCM) (n=119) with the median RD not being reached in the R-maintenance arm vs. 19 months in the observation group (P=0.0208). These differences were seen both in FL and MCL although differences did not yet reach statistical significance.

Conclusion: This study demonstrates that R maintenance after combined immuno-chemotherapy is highly effective and may improve the outcome of patients with relapsed FL and MCL.

ACTIVITY AND SAFETY OF COMBINED RITUXIMAB WITH CHLORAMBUCIL IN PATIENTS WITH MANTLE CELL LYMPHOMA
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We evaluated the efficacy and toxicity of the combination of anti-CD20 antibody rituximab with standard-dose chlorambucil (CLB) in patients with mantle cell lymphoma (MCL) not eligible for high-dose therapy (HDT). A total of 14 pts (M/F ratio: 9/5) were included (2 newly diagnosed, 2 refractory, 10 relapse). There was the presence of the t(11;14) by FISH or conventional cytogenetics, and/or the presence of bcl-1/2 rearrangement, was shown in all pts. Twelve pts evaluated for over-expression of Cyclin D1 were positive. The median age was 63 y (range 43-74). Pre-treated pts had received a median number of prior lines of 1 (range 1-3), including an alkylating agent in all, HDT/ASCT in 8 and rituximab in 1 pt. Median duration of response after the previous line was 10 m (range 5-51). Six patients presented with nonnodal MCL. Therapy consisted of CLB 6 mg/m^2/4d from d1 through d14, in combination with 375 mg/m^2 rituximab given at d1. Cycles were repeated every 28 d, for 4 cycles. A first response assessment was then made, and in responding patients, consolidation with 4 additional monthly cycles of CLB was given. The planned dose of rituximab was given in 12/14 pts. In pts who have completed therapy, the median number of CLB course was 5 (1-8). Among pts evaluable for response (n=13), 8 (62%) experienced an objective response, with 5 (38%) complete responders. Among the responders, 7 achieved molecular (PCR) remission in the BM. Median overall survival (OS) was not reached. Estimated OS at 3 y was 56%. Event-free survival was 7.8 m (95% CI, 0-19.9). So far, 2 of the responders have relapsed. Median duration of response was 8.2 m (range 1-26). Grade 3-4 haematologic toxicities included: neutropenia in 5 (36%), thrombocytopenia in 2 (14%), and infection in 4 (29%) pts. Late events included: cytologic and cytogenetic changes (20q, -5q) suggestive of myelodysplasia in 2, lung cancer in 1, and hemolytic anaemia in 1 pt. There were no toxic deaths. These results suggest that CLB plus rituximab may have remarkable antitumor activity in pts with MCL, including pts in relapse after ASCT. This warrants further evaluation of this regimen in MCL.

MOLECULAR RELAPSE IN PERIPHERAL BLOOD PREDICTS EARLY CLINICAL EVOLUTION IN PATIENTS WITH MANTLE CELL LYMPHOMA AFTER COMPLETE REMISSION: RESULTS FROM A PROSPECTIVE SINGLE CENTER STUDY
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Introduction: Mantle-cell lymphoma (MCL) is of relatively poor prognosis due to frequent relapse thus exhibits a poor prognosis. It is frequently associated with the t(11;14), resulting in BCL-1/2 rearrangement at diagnosis. Over 90% and 40% of patients are informative for IGH and BCL-1/2 rearrangements, respectively.

Methods: Twenty patients with MCL, who reach complete remission after polychemotherapy and intensification with stem cell transplantation, were enrolled. Initial molecular assessment was performed by qualitative PCR for BCL1/IGH and IGH VD-JD1 clonality from blood or tissue samples. All patients were informative by IGH and 7 (35%) also by BCL1-IGH.
The patients had a regular molecular follow-up by classical PCR on peripheral blood (PB). Nine patients were also followed-up, using quantitative real-time PCR (Q-PCR) amplification of the IgH clonal rearrangement with sensitivity for 10^4–10^5 normal cells.

Results: After a median follow-up of 50 months (20–84), 7 patients were in clinical relapse. In all patients, PB molecular relapses by qualitative PCR for IgH or BCL1JH preceded clinical relapses tested by a median of 8 months (6–24). Q-PCR IgH predicted clinical relapse earlier for all cases tested (n = 6). All patients with persistently negative classical and Q-PCR PB molecular results remain in complete clinical response.

Conclusions: Molecular monitoring of peripheral blood is a useful tool to predict clinical relapse in MCL. It reflects the latency between molecular and clinical relapse being sufficiently long for therapeutic intervention. IgH Q-PCR may be the most appropriate form of molecular monitoring since it is informative in more than 90% of cases and provides optimal sensitivity.

HIGH DOSE THERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION AS FIRST LINE THERAPY IN MANTLE CELL LYMPHOMA: A MONOCONCENTRIC EXPERIENCE WITH EXTENDED FOLLOW-UP

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Introduction: This retrospective study has investigated with an extended follow-up the outcome of newly diagnosed patients with mantle cell lymphoma (MCL) treated with high-dose therapy (HDCT) and autologous stem cell transplantation (ASCT) in first response.

Method: Thirty patients under 65 years of age treated in Nantes between 1990 and 2003 met these criteria.

Results: Their median age was 53 years. The disease was disseminated in all cases. Forty percent had LDH above normal. All but one patients were transplanted in first response (CR = 17%; PR = 80%) after 1 or 2 lines of chemotherapy for respectively 23 and 6 patients. One patient was transplant in response <50% after 3 lines of chemotherapy. With a median follow-up of 55 months, the 5-year overall survival (OS) is 62% (median survival = 72 months) and the 5-year progression-free survival (PFS) is 40% (median PFS = 37 months). Patients with LDH (n = 12) (62% versus 19%; P = 0.04). No ASCT-related death was observed.

Conclusion: This study suggest that ASCT in first response is an effective and safe treatment for patients under 65 years of age with normal LDH at diagnosis.

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RADIOIMMUNOTHERAPY (RIT) OF RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA (MCL)


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Background: Two agents, 90Y-ibritumomab (Zevalin®) and 131I-tositumomab (Bexxar®), have been approved in the USA for treatment of relapsed CD20+ low grade or follicular lymphoma. MCL is generally responsive to initial chemotherapy, but remissions tend to be short and median survial is approximately 4 years. The vast majority of MCL express CD20, suggesting that anti-CD20 RIT might have activity in this disease.

Methods: We retrospectively evaluated RIT in patients with relapsed or refractory MCL treated at our institution. 90Y-ibritumomab was dosed at 0.3 mCi/kg for platelet counts between 100 and 149 x 10^9/L and 0.4 mCi/kg for platelet count >150 x 10^9/L. 131I-tositumomab was dosed at 65 cGy total body dose (TBD) for platelet counts between 100 and 149 x 10^9/L and 75 cGy TBD for platelet count >150 x 10^9/L except for one patient who had received pre-transplant chemotherapy with bone marrow involvement. Patients were evaluated for best response to therapy and time to progression.

Results: 10 patients with relapsed or refractory MCL were identified who underwent RIT. 4 received 90Y-ibritumomab and 6 received 131I-tositumomab. Patients had received a median of 4 prior therapies (range 1–8), including one patient with prior SCT. There were no drug-related serious adverse events. 2 patients achieved a partial response (both received 131I-tositumomab) and 3 patients had stable disease (2 received 90Y-ibritumomab and one 131I-tositumomab). 5 patients had disease progression.

Median time to progression (TTP) for patients with PR or SD was 4.5 months (range 3–15 months).

Conclusion: These results suggest that RIT has limited activity in relapsed or refractory MCL. While other investigators have reported a higher response rate using 90Y-ibritumomab in relapsed MCL, TTP was similar to this study. Alternate strategies, such as front line treatment or in combination with other therapeutic or radiosensitizing agents may improve the activity of RIT in MCL. Such studies are currently underway.

AUTOLOGOUS STEM-CELL TRANSPLANT + RITUXIMAB FOR NEWLY DIAGNOSED MANTLE CELL LYMPHOMA: UP-DATE OF A PHASE II TRIAL


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Background: We previously reported that 20 patients with newly diagnosed stage III/IV mantle cell lymphoma (MCL) treated prospectively with autologous stem-cell transplantation (ASCT) and rituximab achieved superior progression free survival (PFS) compared with 40 matched, historical controls treated with conventional chemotherapy.

Methods: Eligible patients were treated with 4–6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) followed by high dose therapy and ASCT. Rituximab was given once 5 days prior to stem cell collection (as an in vivo purge), and as two, 4-week courses 8 and 24 weeks post ASCT. Historical control patients matched for age, stage and gender were randomly selected from a lymphoma database maintained by the British Columbia Cancer Agency. Two control patients were selected for every trial patient.

Results: Median follow-up is now 4.2 years. Four-year overall survival (OS) and PFS are superior in patients treated with ASCT + rituximab compared to matched, historical control patients treated with conventional chemotherapy (4y OS 79% vs. 48%, P = 0.005; 4y PFS 76% vs. 22%, P = 0.001).

Conclusions: Patients with newly diagnosed MCL treated with ASCT + rituximab have significantly improved OS and PFS compared to matched, historical controls.

HYPERCVAD-MA/R FOLLOWED BY AUTOLOGOUS SCT AS THE FIRST LINE THERAPY FOR MCL (MANTLE CELL LYMPHOMA) PATIENTS - MULTI-CENTER PRLG (POLISH LYMPHOMA RESEARCH GROUP) STUDY

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Introduction: HyperCVAD-MA/R a regimen developed at MD Anderson, is an effective therapy for MCL patients. In the absence of active randomized study, PRLG decided to check this protocol, followed by auto - SCT (autologous stem cell transplant) in high risk MCL patients.

Methods: 18 patients with advanced MCL lymphoma were evaluated. Completion of the whole protocol, response rate and PFS were assessed on intention to treat basis.
Results: All 11 patients in CR after chemoinmunotherapy are disease free 3–42 (average 24) months after the transplant procedure. Two further patients achieved a durable CR (EFS of 12 and 36 months) although they didn’t complete the protocol, due to its toxicity. Prognosis of 5 patients who achieved only a PR after HyperCVAD-MA-R was poor (3 of them died, 16 and 18 months after the end of the first line therapy, 2 are still in PR 12 and 24 months later). None of the 3 patients transplanted in PR ever achieved CR, regardless of the type of the conditioning regimen (BEAM, TBI, CBV).

Conclusions: In our study CR achieved after the first line therapy was the best predictor of outcome. In the whole group 2 year EFS and OS is 66% and 83% subsequently.

Methods: Expression of PPARγ and biologic consequences of PPARγ activation by ciglitazone were investigated in a panel of mantle cell lymphoma cell lines (Jeko-1, NCEB, Granta and REC) using immunoblotting and growth inhibition assays.

Results: Western blot analysis indicated that all MCL cell lines expressed PPARγ. Treatment with ciglitazone induced a dose-dependent inhibition of growth with the Jeko-1 and NCEB being the most sensitive cells. The ability of ciglitazone to modulate important molecular targets in MCL cells, such as cyclin D1 and c-myc, is currently investigated.

Conclusions: Collectively, these data suggest that selective PPARγ agonists, alone or in combination with other anticancer drugs, should be considered for treatment of MCL. The low toxicity of PPARγ agonists makes them promising therapeutic agents in the management of this disease.

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GOOD RESPONSE RATE AND ACCEPTABLE HEMATOPOETIC TOXICITY OF FCM-R FOLLOWED BY ZEVALIN IN MANTLE CELL LYMPHOMA (MCL) PATIENTS – POLISH LYMPHOMA RESEARCH GROUP (PLRG) STUDY

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Introduction: FCM-R (Fludarabine, Cyclophosphamide, Mitoxantrone, Rituximab) is one of the most effective regimens for MCL patients not eligible for transplant procedures. RIT (radio-immuno-therapy), although potentially interesting was not particularly beneficial for MCL patients with large tumor burden.

Methods: In our current PLRG study, RIT was given to MCL patients with good PR achieved after 3–6 FCM-R cycles.

Results: So far 9 patients have completed the protocol (further 6 are expected by June 2005). Haematological toxicity assessed by FBC, trephine biopsies and culture studies of clonogenic capacity was acceptable; not worse if compared to control group (patients with relapsed follicular lymphoma, treated with Zevalin before proceeding by any chemotherapy). Response rates evaluated by clinical examination, imaging studies, trephine biopsies and 3-color flow cytometry are summarized below:

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<th>Patient group</th>
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<td>4 CR</td>
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<td>PR after 1st line</td>
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Conclusions: FCM-R followed by Zevalin is a well tolerated regimen with acceptable hematological toxicity. Response rates are promising, however there are no overall nor event free survival data yet available.

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THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR γ (PPARγ) AGONIST CIGLITAZONE INHIBITS GROWTH OF MANTLE CELL LYMPHOMA CELL LINES

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Introduction: Mantle cell lymphoma is a very aggressive B cell lymphoma with poor prognosis. Defects in apoptosis and cell cycle pathways appear to play important roles in the pathogenesis of this disease. PPARγ is a nuclear receptor and ligand-activated transcription factor. PPARγ agonists, such as the antidiabetic thiazolidinedione drugs, have significant pro-apoptotic and differentiation-inducing properties in several cancer cell types. PPARγ agonists are able to modulate the expression of multiple genes involved in cell proliferation and apoptosis making them good candidates for the treatment of MCL.
ANALYSIS OF VH GENE MUTATION STATUS IN DIFFUSE LARGE B-CELL LYMPHOMA REVEALS PROGNOSTIC CORRELATIONS IN YOUNG AND OLD PATIENTS

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Introduction: VH gene mutation status is an independent prognostic marker in B-CLL. However, previous studies analysing VH gene mutation in aggressive NHL reported inconsistent results. In this study, we investigated the prognostic impact of VH gene mutation in patients with diffuse large B-cell lymphoma (DLCL) enrolled in the prospective, randomized NHL-B trial of the DSHNHl.

Methods: Paraffin-embedded lymph node samples from 86 patients with primary DLCL were analysed. DNA was amplified using a consensus primer set according to the BIOMED-2 protocol. Cut-off levels of 98%, 95% and 90% sequence homology for defining a mutated VH status were applied. Kaplan-Meier analysis was performed to assess the prognostic significance of VH gene mutation.

Results: Considering a 98% homology rate as the cut-off point, somatic hypermutation was observed in 78 cases, only 8 cases were unmutated. In the whole study population, no correlation between mutation status and treatment outcome was observed. However, regarding only patients 560 years, a mutation rate above 10% was associated with a significantly longer TTF compared to a mutation rate less than 10%. In contrast, patients older than 60 years with a mutation rate above 10% had a significantly shorter TTF compared to those with a mutation rate less than 10%.

Conclusions: In this analysis of patient samples from a large prospective trial, prognostic differences based on VH mutation status in aggressive lymphoma were observed. However, why young and old patients with a high VH gene mutation frequency seem to have a different prognosis remains unclear.

INCIDENCE AND RISK FACTORS FOR CENTRAL NERVOUS SYSTEM (CNS) OCCURRENCE IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) HOMOGENOUSLY TREATED WITH PROMACE-CTABOM DERIVED PROTOCOLS: A GIUL RETROSPECTIVE STUDY

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Introduction: CNS recurrence of systemic non-Hodgkin’s lymphoma is a well-recognized and uniformly fatal complication. However, CNS prophylaxis should be considered only for patients recognized at high risk.

Methods: GISL is currently conducting a survey of DLBCL treated with PROMACE-CytabOM derived protocols. No prophylactic intrathecal treatment was administered in any patient. So far, 623 DLBCL cases achieving CR were retrieved. The risk of and survival after CNS recurrence were estimated using Kaplan-Meier analysis. Poisson regression analysis was employed to construct a predictive model of CNS relapse.

Results: After a median follow-up of 51 months, 172/623 cases relapsed (28%); a symptomatic CNS recurrence was demonstrated in 11 of them (1.8% of the entire study population, 6.4% of the relapsed cases). The median time to CNS recurrence was 2 months (range 1-15), while the remaining relapsed cases experienced a median time to relapse of 14 months (range 0-108). Regression analysis on relapsed cases identified the following three independent risk factors for CNS relapse: elevated LDH (RR = 5.49, P = 0.042), more than one extranodal site (RR = 5.86, P = 0.019) and a white blood cell count above 10 x 10^9/L (RR = 1.22, P = 0.001). The median overall survival of CNS relapsed group was 6 months.

Conclusions: Preliminary results of our survey suggest that CNS recurrence is lower than expected. Although CNS relapse confers a poor prognosis and the identification of patients at higher risk is feasible, the establishment of a prophylaxis of CNS relapse should be further investigated.

PROGNOSTIC SIGNIFICANCE OF HEPATOCELLULAR GROWTH FACTOR (HGF) AND MET PROTO-ONCOGENE (MET) EXPRESSIONS IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: HGF is a multifunctional factor of mesenchymal origin and acts as a mitogen, motogen and morphogen, depending on the cell target and cellular context. The receptor for HGF is the product of c-Met that has the characteristics of a tyrosine kinase receptor, and the HGF/c-Met receptor system is important for the multifunctions of HGF. Several studies have shown that c-Met is over-expressed in malignant lymphoma. Furthermore, HGF/c-Met are reported to be associated with tumour invasion. High serum HGF levels are also reported in patients with malignant lymphoma. So we analysed the expression and prognostic significance of hepatocyte growth factor (HGF) and its receptor c-Met in 96 cases with diffuse large B-cell lymphoma (DLBCL).

Method: Tissue sections were immunohistochemically stained for HGF and c-Met.

Result: The prognosis of patients with HGF- and/or c-Met-positive DLBCL was significantly poorer than negative cases (HGF: P = 0.0036, c-Met: P = 0.0003). In addition, in the low-risk of international prognostic index (IPI) group, HGF/c-Met negative cases had a significantly better prognosis than positive cases (HGF: P = 0.0009, c-Met: P < 0.0001). However, HGF and c-Met did not influence survival in patients with high-risk IPI.

Conclusion: Our results suggest that HGF/c-MET is a useful clinical marker of prognosis of patients with DLBCL.

PROGNOSTIC RELEVANCE OF EXTRALYMPHATIC INVOLVEMENT IN AGGRESSIVE LYMPHOMA - RESULTS FROM A LARGE RANDOMIZED MULTICENTER TRIAL OF THE DSHNHl

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More than 50% of patients (pts) with aggressive B-NHL have extralymphatic disease involvement (E-I). Most data presented so far were collected from smaller retrospective analyses. Therefore, definite conclusions about the prognostic and therapeutic relevance cannot be drawn.

Methods: All pts with documented E-I (n = 780/1339; 57.9%) from the NHL B1/B2 trial of the DSHNHl (Pfreundschuh et al., Blood 2004) were analysed for the presence of primary or secondary E-I and prognostic factors.

Results: 798 different E-I were examined. B1-trial (pts 1 E-I), B2-trial (pts >60 yrs): n = 390, of these 172 with >1 E-I, 20/22/6% (B1/B2 trial) were primary E-1, presenting in GI-tract (10/3/1.5%), bone (8.5/11.6%), connective tissue (4.9/6.8%), lung (4.5/5.8%). The presence of E-I was significantly correlated with ECOG-1. E-I were less frequent in DLBCL lymphoma than in other B-NHL. There were 171 different combinations of E-I lesions. In univariate analyses, specific sites of E-I carry significant prognostic impact. However, in a multivariate analysis, IPI factors and no single combination or location of E-lesions are prognostically important.

Conclusions: In a large multicenter prosptive trial, 50% of pts have extralymphatic disease. The presence of E-I is correlated with decreased performance status. In a multivariate analysis adjusted for the IPI, the presence or absence of E-I is not an additional significant factor.

PROGNOSTIC MODEL FOR AGGRESSIVE NON-HODGKIN LYMPHOMA (SINGLE CENTER EXPERIENCE)

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Unlike the indolent lymphoma, aggressive lymphomas are fatal in several weeks or months if untreated. However, the therapy available nowadays makes this group of patients with aggressive Non-Hodgkin’s lymphoma curable. Autologous stem cell transplantation used as first-line therapy can improve overall survival in selected patients with aggressive Non-Hodgkin lymphoma. To make the right and optimal therapeutic approach we need to stratify those patients in order to recognize patients with “high” and “low” risk, which was achieved with this study. This study comprises 211 patients with histopathology diagnosis of aggressive Non-Hodgkin’s lymphoma treated at the Department of Hematology in the period 1989–2002, which gave us the observation period of 6 to 183 months. There were 138 male patients, median age 53 years and 73 female, median age 52 years. The patients were treated with anthracyclin included regiments. After initial chemotherapy complete remission was achieved in 60%, partial response in 4% and there was no response in 32% with early deaths in 4. According to the univariate analysis the following parameters had significantly influence the overall survival in the patients with aggressive Non-Hodgkin’s lymphoma: initial anemia, initial LDH, the stage of the disease, ECOG score, bone marrow infiltration, number of sites of extranodal infiltration, lymphoma subgroup according to various classification systems, morphology of the lymphoma cell, immunophenotype profiles and gene sequence information as well as the new therapeutic approaches would improve therapeutic results and overall survival.

VALUATION OF SELECTED PROTEIN KINASE C ISOPHORMS FOR DIFFUSE LARGE B-CELL LYMPHOMA OUTCOME PREDICTION

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin’s lymphoma, characterized by its clinical heterogeneity. Global gene expression profiling subdivide the DLBCL into two main clinically and biologically distinct subgroups. Gene expression signatures characteristic of particular subgroups include different isoporphs of protein kinase C (PKCs). According microarray analyses, the increased expression of PKC-delta (PKCD) and PKC-gamma (PKCG) is present in DLBCL with favourable prognosis, while PKC beta 1 (PKCBI) and II (PKCBIIB) is present in fatal or refractory DLBCL.

Methods: We used Reverse-Transcription PCR (RT-PCR), Quantitative Real-Time PCR (QRT-PCR) and immunohistochemical (IHC) analyses to validate the expression of selected PKCs isoporphs in formalin fixed and paraffin embed (FFPE) tumor specimens from 52 patients treated for DLBCL between 1996 and 2003.

Results: 1) We developed modified technique for RNA isolation from FFPE tumor specimens producing RNA of sufficient quantity and suitable quality for RT-PCR and QRT-PCR. 2) Using the IHC, RT-PCR, QRT-PCR and DNA sequencing we confirmed that B-lymphocytes do not express PKCG. 3) We found that DLBCL of the patients who achieved complete or partial remission after the first course of chemotherapy, and patients remained alive at 20-month follow-up, express low level of PKCD mRNA ($P=0.0089$ and $P=0.0064$ respectively).

Conclusions: Data from microarray analyses need to be interpreted cautiously. PKCD seems to be potential predictive and prognostic marker in DLBCL.

CLINICAL SIGNIFICANCE OF BCL-2 IN AGGRESSIVE NON-HODGKIN LYMPHOMA

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Overexpression of bcl-2 gene leads to cellular resistance to programmed cell death and it is overexpressed in approximately 50% of high-grade lymphoma.

Aggressive Non-Hodgkin lymphoma (NHL) is heterogeneous group with important clinical, histopathological and evolutive features. The International Prognostic Index (IPI) has provided a widely accepted prognostic set of criteria to design therapy. However, IPI does not determine whether routine phenotypic features, besides IPI, may influence survival. We evaluate the prognostic significance of Bcl-2 protein expression in relation to clinical presentation and outcome.

In the period 1989–2002, two hundred eleven patients with newly diagnosed aggressive NHL were recorded in our Department. In this study we included patients with available biopsy sample. Protein expression was analyzed on paraffin embedded tumor tissue by immunohistochemistry in relation to clinical factor and outcome. The expression of more than 20% of neoplastic cell was considered positive for bcl-2. Comparison was made by x² test. Survival curves were calculated by Kaplan-Meyer method and compared by the long-rank test. Sixty seven patient were recorded and their characteristic were: median age 53 years, stage III and IV, 67%; present B symptoms 44%; bone marrow infiltrating 29%, elevated LDH 58%, performance status more than 1-26%; extranodal sites more than 2 –34%. All 62 patients received anthracyclin based combination chemotherapy, 72% CHOP regimen. Overall survival was 52% with a follow up 6–183 months. Bcl-2 expression was observed in 35,5% (22pts). Overall survival was influenced by bcl-2. Bcl-2 positive cases were significantly associated with lower overall survival (20% vs. 58% (p<0.01). Bcl-2 monoclonal antibody immunostaging appears to be a simple and reproducible method of determining biological potential of tumor cells and provides useful prognostic information in patients with aggressive NHL.