6. Extranodal lymphoma

BCL-2 PROTEIN AND mRNA ARE EXPRESSED IN MINOR SALIVARY GLAND (MSG) INFILTRATED BY FOLLICLE CENTER LYMPHOMA OR BY LYMPHOMES OF SJÖGREN SYNDROME (SS) ASSOCIATED WITH NON-HODGKIN'S LYMPHOMA. P. Morel-Vizcaíno, B. K. Ben-Haroush, S. N. Asulin, B. Gosselin, F. Baudouin, A. Janin, CHU de Lille, CH de Lens, and Hôpital Cochin, France.

The expression of the bcl-2 protein in extranodal tissue has been documented in low-grade B-cell lymphoma of mucosa associated lymphoid tissue (MALT) (predominantly small cells), in the "acquired MALT" associated with the Hashimoto's thyroiditis, and in lymphocytes of lip biopsy of 50% of SS patients (pts) with monoclonal gammopathy or lymphoproliferative disorder (Sjögren's syndrome. State of the art, 213-8, M Homma et al eds, Kugler Amsterdam 1994). The high incidence of both monoclonal, and SS-related T-cell infiltrates of MSG in pts with non-Hodgkin's lymphoma (NHL), allowed us to compare the expression of the bcl-2 protein, the bcl-2 transcript, and the p53 protein, by immunohistochemical staining and northern blotting, in MALT of 14 isolated primary SS pts, 6 SS pts who developed NHL (folicular center: 1 pt; small lymphocytic: 1; lymphoplasmaclastic: 2; MALT-type 3;), and 14 NHL pts without SS, displaying the same light chain restriction in MALT and lymphomatous tissue or lymphomatous cells in MSG (folicular center: 8; small lymphocytic: 1; lymphoplasmaclastic: 2; MALT-type 1; diffuse large B-cell: 1; peripheral T-cell: 1). Both bcl-2 protein and aberrant transcripts of bcl-2 were observed concordantly in MSG and lymphomatous tissue in 6 of the 8 pts with folicular center lymphoma, and in the 6 pts with SS and NHL, even in the absence of monoclonal sialadenitis. No expression of bcl-2 was found in lymphocytes of lip biopsy of the 14 isolated primary SS pts. No expression of the p53 protein was observed in each subgroup of pts. However, most NHL pts, with or without SS, had low-grade lymphoma.

Our study suggests that the staining pattern of bcl-2 protein, and the expression of abnormal bcl-2 transcript in lymphocytes of MALT parallel the lymphomatous counterpart in 75% of pts with follicle center lymphoma involving MSG, and in the 6 tested SS pts. The expression of the bcl-2 protein without expression of the p53 protein, previously reported in the "acquired MALT" of thyroiditis and in low-grade lymphoma of MALT-type, can also be observed in the minor salivary glands of SS pts presenting with lymphoma of MALT-type or with nodal lymphomas. These findings may be useful to identify those primary SS pts with an increased risk of NHL.

LOCALISED EXTRA-NODAL AGGRESSIVE NHL. Analysis of 199 patients treated by the two GOELAMS 82 & 83 trials.

DESAIBENS B, FRANCOIS S, COLOMBAT P, BERTHOU Ch., GANJHOUR Ch., TOURANI J-M., LAMY Th., DELWAIL V, GIRARD R, and LE MEVEL A for the GOELAMS Group - CHU AMIENS - 80054 AMIENS - FRANCE.

We report on 189 patients (pts) with an aggressive NHL (from F to I of the WFC, anaplastic and T peripheral types) localised to head & neck areas (except CNS and cutaneous NHL) and treated by the GOELAMS 02 or 03 trials. We separated the 66 pts with a pure nodal NHL (NHL) and the 123 pts with an extra-nodal NHL (ENL) with or without nodal involvement, from which we enrolled 94 En-Nose-Throat, 19 thyroid, 6 parotid, 3 ocular and 1 hypordemic NHL. Comparison shows only 3 differences: more stage II among the ENL group (21.11% vs p < 10^-5); more contiguous involvement (21 vs 3% vs p < 10^-5) and more PS 2 (14 vs 5% vs p < 0.05).

After 3 courses of a CHOP (GOELAMS 03 trial for patients more than 60-65 years) or a double-CHOP regimen (GOELAMS 02 trial) and a localized 40 Gy irradiation, complete remission rates are similar in the two groups: 93% among ENL vs 95%. On December 1993, the median follow-up time was 60 months and crude and actuarial relapse rates are also identical: 15% & 32% among ENL vs 21 & 41% among NHL. Delays and modalities of relapses are identical and the 2 survival curves are identical.

NASCAL LYMPHOMA IS A NEOPLASM OF EPSTEIN-BARR VIRUS INFECTED CYTOTOXIC LYMPHOCYTES

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Expression of cytotoxic granule-associated proteins, T cell intracellular antigen-1 (TIA-1) and perforin, was investigated in 3 cases of nasal lymphomas (NHL) by immunohistochemical (IHC) staining. The results were then correlated with the cell type and the Epstein-Barr virus (EBV) status of each tumor. Phenotypic and genotypic studies showed that 10 cases of natural killer (NK) cell lineage (CD2+CD3+membrane)-CD56+; germinat T-cell receptor (TCR) and immunoglobulin genes and 3 cases of T cell lineage (CD2+CD3+Leu4)-CD56+; rearranged TCR β or γ genes. In situ hybridisation for EBV encoded small RNAs (EBER ISH) and IF for TIA-1 and perforin demonstrated that every case of NL harbored EBV and expressed the cytotoxic proteins. Double labelling of TIA-1 and EBER ISH confirmed that the tumor cells were positive for both signals. These results indicate that NL, of both NK and T cell subtypes, are neoplasms of EBV-infected cytotoxic lymphocytes.
THE CSR PROTOCOL FOR PRIMARY CEREBRAL NON HODGKIN'S CEREBRAL LYMPHOMAS: UPDATED RESULTS


We have recently reported a pilot study of a protocol combining chemotherapy (CT) with drugs that pass the blood brain barrier and radiotherapy (RT) in primary cerebral non Hodgkin's lymphoma of patients with no known cause of immuno-depression (Blood 86:2922, 1995). From 1983 to 1986 and from 1991 to 1994, 25 patients treated for primary cerebral non-Hodgkin's lymphoma and no cause of immuno-depression received a protocol with one course of COP, two courses of COPADEM and two courses of CYM. RT was given 21 to 30 days after the last CYM course at a dose of 20 Gy in whole cranial irradiation plus 30 Gy on the sites of primary tumor. We present here the outcome of this series of patients with a longer follow-up and a comparison with a series of 58 patients with PCL treated in the same institution with different protocols. With a median follow of up of 35 months (minimal follow up of 14 months), the median overall survival (OS) is 106 months and the projected 2, 3, 5 and 8 years OS are 68%, 68%, 59% and 45% respectively. Treatment with high dose methotrexate (HD-MTX) has been previously reported to be an independent prognostic factor for overall survival in PCL (Proc.ASH 1995, abst.1086). We have compared the survival of the CSR series to that of the 58 patients with PCL treated in this institution between 1980-1995 (median follow-up: 40 months). The 23 patients who received HDMTX containing regimens other than the CSR have a median OS of 27 months and a 5 year OS of 23%. The 23 patients treated with CT without HDMTX had a median OS of 7 months and a 5 years OS of 7%, which was not significantly different from that of the 10 patients treated with RT alone (median OS: 5 months, 5 years OS: 11%). Therefore, the CSR protocol yielded significantly improved results in this single institution experience as compared to other regimens containing CT without HDMTX plus RT or RT alone. We are currently comparing the CSR regimen to a less toxic CT regimen in a randomized trial.
TESTICULAR LYMPHOMA: THE SCOTLAND AND NEWCASTLE LYMPHOMA GROUP (SMLG) EXPERIENCE

L. Samuel, J. White and L. Matheson for the SMLG. Dept. of Clinical Oncology, Western General Hospital, Edinburgh EH4 2XU, UK.

Testicular non-Hodgkin’s lymphoma (NHL) is uncommon, but is the most common testicular cancer in men over 60 years. Median survival is usually <1 year. We have reviewed all the cases from the SMLG database of over 6000 patients.

There were 48 cases, median age 67 (range 14 to 85). The majority 27 (56%) were Stage IE and 12 (25%) Stage IV. The other 8 were Stages IIIE and IIIE. Only 5 had 8 symptoms, all stages III/IV. Despite their age 37 (77%) were performance status 1 or 2. 36/41 (88%) were intermediate or high grade (Working Formulation) with diffuse large cell the most common (56%).

There was follow up on 46 (96%) of patients, with a median of 24 months (range 1 to 131). There were 26 deaths, 18 NHL related and 3 treatment related. Using life tables the 5 year survival for the whole group was 41%.

In the Stage IE group the 5 year survival was 49% overall and 68% disease specific. This was despite only 14 (53%) receiving chemotherapy, 5 (18%) received no treatment and 8 (30%) XRT alone. Overall our results are similar to those published from elsewhere, but we need to encourage our group to develop a protocol for these rarely encountered patients.

THYROID LYMPHOMA: CLINICAL AND PATHOLOGICAL FEATURES IN THREE PATIENTS.

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Malignant thyroid lymphoma is a very uncommon form of thyroid cancer, accounting for less than 2% of extranodal lymphomas and only 1%-2% of thyroid malignancies, and most commonly occurs in elderly women. Currently, treatment strategies are based on evidence from a small number of patients.

In this report we describe three cases of NHL of the thyroid gland seen in our center, between 1993 and 1995; diagnosis by fine needle biopsy was successfully confirmed by histology. Three women, age range 70 years, had all a short history of 3-4 months of neck tumor, with rapidly enlarging mass and symptoms of local compression. In a woman the disease was limited to the thyroid gland and cervical lymphnodes (II st EA), in the others the disease was more advanced with substochastic and cutaneous involvement (IV st EA) in one and bone narrow infiltration in the other (IV st BA). Histologic pattern, according to Kiel classification, was different: centroblastic, immunoblastic and histiocytic. All patients had only chemotherapy (CVP, PMU + VP 16, and CHOP, 6 cycles at 21 days intervals). Complete tumor regression was noted in two patients, without evidence of disease for 12 months; one died owing to myocarcid failure. These findings indicate that thyroid lymphoma has a relatively good prognosis. A review of the literature revealed that most thyroid lymphomas are diffusive histiocytic, and treatment and survival rates have been quite variable between institutions.
Posttransplant Lymphoproliferative Disorders in Living Related Liver Transplantation

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Posttransplant lymphoproliferative disorder (PTLD) is a serious complication of cadaveric solid organ transplantation including liver transplantation. We report the incidence, clinicopathologic features and outcome of PTLD in the recipients of living related liver transplantation under FK506 immunosuppression performed at Kyoto University Hospital between June 1990 and July 1995.

Four of 176 recipients (2.3%), one male and three females, were complicated by PTLD between 61 and 174 days (average: 113 days) after transplantation. The age at diagnosis ranged from 11 mos to 4 yrs (average: 26 mos). Of these, three recipients demonstrated repeated episodes of acute cellular rejection earlier in the postoperative course and one had progressed to the acute vanishing bile duct syndrome, which required further immunosuppression including OKT3 administration in two.

PTLD was diagnosed by biopsy in two recipients, who, despite treatment, died of the disease 3 and 16 days after the biopsy, respectively. PTLD was found at autopsy in the two remaining recipients, in one of which a local PTLD was found incidentally.

Histopathologically, PTLD in these cases consisted of a spectrum of monomorphic to polymorphic large B-cell proliferation with or without immunoblastic characteristics showing monodonal to polyclonal intracytoplasmic light chains of immunoglobulin. The latent membrane protein and EBER 1 oligonucleotide of the Epstein-Barr virus were detected in all cases immunohistochemically and by in situ hybridization, respectively.

P53 REARRANGEMENT AND MUTATION IN OCULAR ADNEXAL PSEUDOLYMPHOMA

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Biopsied ocular adnexal pseudolymphoma (OAP) from 20 sequential patients were studied for alterations in antigen gene receptor genes, p53 and oncogenes of bcl-1, bcl-2 and c-myc. Southern blot analysis showed 12 of them had immunoglobulin heavy chain (IGH) gene rearrangements with T cell receptor beta chain (TCRβ) gene rearrangements found meanwhile in two cases. Alterations of p53 gene was analyzed by southern blot and polymerase chain reaction-single stand conformation polymorphism (PCR-SSCP) followed by DNA sequencing to detect the mutation. Gene rearrangements of p53 were found in four cases who had combined with rearranged IGH. Point mutations at codon 193 and codon 222 of exon 6 were detected in two other cases respectively. Both of these two cases had also IGH gene rearrangements. Further studies on configurations of bcl-1, bcl-2 and c-myc oncogenes revealed that for the one case with p53 rearrangement, bcl-2 gene rearrangement happened, for the other case with p53 mutation, rearranged bcl-1, bcl-2 and c-myc genes happened simultaneously. Three genotypic subsets of these OAP can be thus identified by the configurations of IGH, related oncogenes and p53 genes: With germline configurations of IGH genes and related oncogenes (group A); with rearranged IGH but germline configurations of related oncogenes (group B); with rearranged IGH gene and combined altered p53 gene and/or other oncogenes (group C). These results suggest in OAP a spectrum of clonal change evolving from polyclonal to monoclonal population, and further to monoclonal population with abnormalities of p53. None of them developed malignant lymphoma after long-term follow-up, but patients in group C seemed to have tendency of systemic lymphadenopathy or second cancer.

MUSCLE INVOLVEMENT AT PRESENTATION IN NON-HODGKIN'S LYMPHOMA: CLINICAL FEATURES, TREATMENT AND OUTCOME

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Non-Hodgkin's lymphoma (NHL) involving skeletal muscle at presentation is rare, and is thought to be associated with a poor prognosis. We used the SNLG database (over 6000 patients) to review all NHLs involving muscle at presentation (excluding orbital muscle).

There were 13 patients, median age of 69 years (range 2-93) and male: female ratio 6:7. Six patients were stage IE, 5 Stage IV and 1 each in Stages IIE and IIIIE respectively. 9/13 were intermediate or high grade (Working Formulation) and only 3/13 had B symptoms. The most frequent site was lower limb (6/13) and then upper limb (4/13). Only 4/13 had lymph nodes involved, but 5/13 had bone involvement, itself a rare site of NHL.

8/13 received CHOP or similar chemotherapy and only 2/13 radiotherapy alone. 4 patients had combined treatment.

Median follow-up was 2 years (6 months to 5 years) and all deaths were due to NHL. No toxic deaths and 5 year survival (from life tables) was 47%. This was irrespective of grade or stage and much better than expected.

6. Extramedal lymphoma

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Retrospectively, 41 Iranian patients with Mediterranean abdominal lymphoma (MALL) were studied; 21 patients had received anthracycline-based protocols, and 20 patients had been treated with regimens lacking anthracyclines. The study groups were comparable with respect to several factors, including age, performance status, histology of lymphoma, stage of disease, and the average relative dose intensity of their protocols. Our first group had a complete remission (CR) rate of 62%, mean disease-free interval (DFI) of 16.3 months and a 71% overall survival at 30 months. The second group showed a CR rate of 40%, mean DFI of 11.2 months, and a 35% overall survival at 30 months. The differences were significant in survival ($P = 0.012$) and DFI ($P < 0.001$). The incidence of serious toxicities and complications was similar.
6. Extramedullar lymphoma

Is the International Prognostic Index (IPI) for aggressive nodal lymphomas also useful in gastric MALT lymphoma?

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A prognostic model for aggressive nodal non-Hodgkin lymphoma (NHL) was proposed in 1993, based on clinical data from more than 2000 patients. This International Prognostic Index (IPI), based on age, stage, performance status, serum LDH and number of extranodal sites enabled distinction of 4 distinctive risk groups and proved applicable also in follicular and HIV-related NHL.

We studied the value of the IPI in gastric lymphoma and investigated if additional factors as bulky disease (BD), weight loss (WL) and elevated ESR could improve the predictive value excluding the parameter extranodal sites.

We studied 139 consecutive patients with gastric MALT lymphoma during 1976-1992. Staging resulted in stage Ia-II, stage III-IV and stage IV-20 patients. The usefulness of the IPI and additional prognostic factors was tested by selecting the overall survival, and calculated by the log-rank test.

Results: Based on the IPI criteria four groups were formed: low risk (n=12), low intermediate (n=20), high intermediate (n=40) and high risk (n=24). In 31 cases data were incomplete (no LDH determined). These four groups showed significantly different disease free intervals, survival and overall survival rates. The 5 yr survival figures were 91%, 83%, 45% and 23% respectively. After regression analysis the other tested factors (BD, WL, ESR) proved to be of significant additional value (p<0.0001), especially to identify patients with a poor prognosis.

Conclusions:
1. The international prognostic index (IPI) based on simple clinical data only, is useful in gastric lymphoma to determine prognosis.
2. Addition of other simple factors (BD, WL, ESR) clearly improves the prognostic value of the IPI.
3. This new fully clinical index gives a risk estimation independent from the histologic malignancy grading in low grade and high grade MALT lymphomas.

VALUE OF IMMUNOCYTOCHEMISTRY (ICC) AND PCR ANALYSIS IN THE DIAGNOSIS AND THE FOLLOW UP OF CONSERVATIVELY TREATED GASTRIC NHL


The contribution of ICC and PCR analysis to the detection of monoclonality in the diagnosis of gastric NHL was evaluated in endoscopic biopsies of 14 patients (12 low grade MAL T NHL, 2 high grade NHL with residual low grade areas) conservatively treated. Eight of them were analyzed at the onset and the remaining 6 at the onset as well as during antibiotic therapy anti Helicobacter pylori (HP). The expression of B and T cell markers and of bcl 2 protein, as well as the proliferative activity, were analyzed by ICC, while the rearrangement of IgH genes was detected by a seminested PCR using the FR3A and FR2I primers, both on cryopreserved and paraffin-embedded samples. ICC confirmed the B origin and the low proliferative index of the neoplastic cells. Bcl2 expression was observed in only one low grade MALT NHL, which became negative during the course of therapy, and in two high grade NHL. Eight cases showed HP infection. Ercdination of HP by antibiotic therapy was associated with tumour regression in 5/7 positive cases; the remaining case relapsed for HP infection and subsequently showed disease recurrence.

Monoclonal VDJ rearrangement was detected by PCR in 7/13 cases (53%) at the onset and in biopsies during the treatment in 3 of these 7 cases. None of these cases showed any morphological evidence of persistent disease. One of these patients developed tumour progression 4 months later and was subjected to total gastrectomy.

In conclusion, ICC complements the diagnosis of NHL in MALT suspicious endoscopic biopsies, while PCR analysis is a sensitive tool for the detection of residual neoplastic cells in morphologically negative cases.
LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) TYPE WITH PRIMARY EXTRA-GLANDULAR LOCALISATION.


Ospeche Multidisciplinare S. Varese, Italy; Servizio Oncologico Cantoanello, Bellinzona, Switzerland; Istituto Europeo di Oncologia, Milan, Italy.

Twenty-four patients [pts] (18 females and 6 males; median age 55 years, range 24-84 years) with low-grade MALT lymphoma presenting with signs and symptoms due to extra-glandular localisations have been evaluated. The sites of involvement were: small bowel (4 ileum, 3 duodenum, 1 Vater's papilla), large bowel (1 colon, 2 rectum), parotid gland (6), orbit (2), skin (2), thyroid (1), lachrymal gland (1), lung (1), and vagina (1). Stage I disease at presentation was documented in 11 pts (46%). Concomitant involvement of different sites was observed in 7 cases: parotid gland plus spleen (2 pts), lung plus stomach (1 pt), vagina plus rectum (1 pt), rectum plus stomach (1 pt), small bowel plus stomach (1 pt), lachrymal gland plus stomach (1 pt). Bone marrow infiltration was detected in 5 pts. Gastric biopsy showed $H. pylori$ infection in all cases with gastric involvement and in 7 additional pts. Two pts with parotid gland lymphoma and the one with lachrymal gland lymphoma had a previous history of Sjögren's syndrome.

The case of MALT lymphoma in the thyroid was preceded by Hashimoto's thyroiditis. The pts were treated with different modalities: surgery (10 pts), chemotherapy (6 pts), surgery plus chemotherapy and/or radiotherapy (6 pts), chemotherapy plus radiotherapy (1 pt), wait and see (1 pt); antibiotics against $H. pylori$ were given as sole treatment in 1 pt with duodenal MALT lymphoma. 22 pts are evaluable for response, 18 pts had complete remission and 4 stable disease. At a median follow-up of 12 months, 23 pts are alive and 1 pt (a woman, 84 years old, with persistent lymphoma) died for unknown reasons. Autopsy was not done. Primary extra-gastric low-grade MALT lymphoma in our series appears to have an indolent course and a favorable prognosis. Different from other histologic types of extranodal lymphoma, the outcome does not seem to be related with the disease localisation.

HIGH INCIDENCE OF SECONDARY MEYELODYSPLASTIC SYNDROMES FOLLOWING PROMACE-MOPP AND INVOLVED FIELD RADIOTHERAPY FOR LOCALISED GASTRIC NON-HODGKIN'S LYMPHOMAS.

Corti C1, Theodore C2, Baylea C3, Roguer M1, Cozzani M4, Tosset J5, Hayat M6, Ribrag V1.


Between 1985 and 1989, 21 patients with gastric localised non-Hodgkin's lymphomas (stage I to III) were prospectively treated at Institut Gustave-Roussy with PROMACE-MOPP polychemotherapy and involved field radiotherapy. Mean age was 54 years (range 23 to 69 years). PROMACE-MOPP regimen consisted in Doxorubicin 25 mg/m2 day 1, Etoposide 170 mg/m2 day 1, Cyclophosphamide 500 mg/m2 day 1, Prednisolone 60 mg/m2 day 1 to 4, Procarbazine 100 mg/m2 day 1 to 7, Nitrogen mustard 60 mg/m2 day 1 to 4, Procarbazine 100 mg/m2 day 1 to 7, Nitrogen mustard 60 mg/m2 day 8, Methotrexate 500 mg/m2 day 15 every 28 days. 6 to 8 courses of PROMACE-MOPP were given followed by involved field radiotherapy (35 GY to the stomach and regional lymphatic areas) in responsive patients. All these patients had a normal blood count and a normal bone marrow biopsy before therapy. 7 patients died on therapy or relapsed 2 to 20 months after therapy. 14 patients were followed for at least 5 years. Four pts (28%) developed a myelodysplastic syndrome (MDS). Mean age of 4 pts died 22, 24, 65, and 72 months after the end of therapy. 3 of these 4 pts died 22, 22, 18, and 24 months after the diagnosis of MDS. Cytogenetic analysis was performed in 3 cases and showed (13;17)(p10;q20) in one case, -18 in one case, (10;12)(p10;q22), 21q-, 11q+ in the third case. PROMACE-MOPP plus radiotherapy should not be recommended in patients with localised gastric non-Hodgkin's lymphoma with regard to the high probability of secondary myelodysplastic syndromes. In order to evaluate the incident of secondary myelodysplastic syndromes, prolonged follow-up of patients (more than 5 years) treated with recent polychemotherapy regimens used for non-Hodgkin's lymphoma should be reported.
TOTAL ACCURAL OF GASTROINTESTINAL LYMPHOMAS IN SCOTLAND AND
THE NORTHERN REGION OF ENGLAND. FIRST YEAR RESULTS OF A
PROSPECTIVE CLINICO-HISTOPATHOLOGICAL STUDY
A L Lennard,* J Henry, D Levison, N Luicq, J Craig, L Matheson, J White on behalf
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On 01.01.94 the Scotland and Newcastle Lymphoma Group (SNLHG) began a
prospective accumulation of data on all cases of gastrointestinal lymphoma
diagnosed in Scotland and the Northern Region of England. All hospital
histopathology departments have been contacted and all have cooperated in
provision of prospective cases. Histological diagnosis was confirmed by 2
histopathologists with an interest in lymphoma before cases were accepted for the
study. Clinical case records have been reviewed by AL (Northern Region), NL, JC
and LM (Scotland).

Results are now presented for the year 1994. 113 cases (60M: 53 F) per 8 million
people were registered, 49 in the Northern Region (population 3 million) and 64 in
Scotland (population 5 million), giving an annual incidence of 1.4/100,000. Median
age was 66 years (range 21-92). Cases have been further analyzed by site of disease,
SNLHG and International Prognostic Indices, Ann Arbor stage, Manchester
stage, presenting features, histology and presence or absence of Helicobacter (in
stomach lymphomas).

Methods of treatment, types of surgery, chemotherapy regimens, frequency of and
Helicobacter eradication and complications of treatment have also been recorded.

This study provides for the first time a true incidence of GI lymphomas in our area.
It gives important insight into how such patients are investigated and treated in the
wide number of institutions to which they present. The prospective nature of the
study with the large number of patients included will allow detailed analysis of the
natural history of the disease and a comparison of different treatment methods used
on similar patients presenting in different institutions in the same calendar year.

REGRESSION OF GASTRIC LARGE-CELL LYMPHOMA FOLLOWING
ANTI-HELICOBACTER THERAPY.
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Infection with Helicobacter pylori is pathogenetically linked to the development
of low-grade lymphomas of MALT type in the stomach. If localised, eradication
of Helicobacter can induce regression of these low-grade MALT lymphomas.
Many cases of gastric large-cell lymphoma arise through clonal evolution and
histologic transformation of low-grade MALT lymphomas. In such cases, the
ongoing role of Helicobacter in supporting the proliferation of the large-cell
clonal is unclear and the responsiveness to eradication of Helicobacter is
unknown. In this instance, a 73 y.o. woman with stage IVA B-cell diffuse large-
cell lymphoma (DLCI) with dominant gastric involvement refused cytotoxic
treatment, allowing assessment of the efficacy of isolated anti-Helicobacter
therapy. She had a history of histologically proven Helicobacter gastritis of
at least 5 years duration. At presentation she described epigastric pain and
had generalised lymphadenopathy of 3 - 5 cm. Endoscopic biopsy revealed a
bleeding 3 x 2 cm raised malignant ulcer (Biopsies = B-cell DLCI with heavy
Helicobacter infection and gastritis). There was no low-grade MALT component
seen. The patient refused chemotherapy. She received omeprazole, ampicillin
and metronidazole for 14 days and had repeat endoscopy. The lymphomatous
ulcer had healed completely, but ulcerative gastritis was still visible at other
sites. Biopsies from the site of the previous ulcer and throughout the stomach
did not contain any lymphoma, but light colonisation with Helicobacter persisted.
The generalised lymphadenopathy remained unchanged. Although not
suggesting that anti-Helicobacter therapy should substitute for definitive
treatment, this case demonstrates that Helicobacter eradication may contribute
to tumour regression and should be a component of treatment, and further that
in some cases, histologically aggressive gastric lymphomas may remain
dependent, directly or indirectly, upon antigenic stimulation by Helicobacter.

PROSPECTIVELY RANOMIZED TRIAL FOR THE TREATMENT OF LOCALIZED
GASTROINTESTINAL (GI) TRACT LYMPHOMAS (NHL) : PRELIMINARY
REPORT OF A MULTICENTRIC STUDY. D. Brust,* S. Monfardini, C. Secco, H. Klein
reissens, B. Holdini, R. Musella, F. Viseo, E. Vieira, P. Carde, M. Rausi, K.
Ruozenzdai, W. Breed, B. Depauw, A. Elfra, M. Fickers, P. Hupperet, J. Michel, A.

Although more than a thousand of GI-NHL have been reported, the literature does
not indicate a clear therapeutic approach. This is primarily due to heterogeneous
staging procedures and treatment strategies. Therefore, we initiated a prospective
study with European centers using uniformed staging procedures, centralized
pathological review and well defined therapeutic approaches. This prospective
randomized trial is addressed to intermediate and immunoblastic NHL. It compares
radiotherapy (40 Gy) with 3 courses of chemotherapy (a CHOP-like regimen,
CHM:C:A:BV according to the EORTC) in pathological stage IGI-NHL. Patients (pts)
clinical or pathological stage II are treated with 6 courses of the same chemotherapy
(CT) and if complete remission is achieved, they are randomised between,
intercurrent radiotherapy or no further treatment. Between July 88 and March 95, 44 pts
have been registered with a median age of 56 (26-70) years. 63% were males, 82% (32/39)
were localized in the stomach. 76% (32/42) were large cell lymphomas (LFL: C+H). 44%
(16/44) were stage IV and among the 38 stage II pts, 12 (50%) had extended loco-
regional disease. Among 16 pts stage I, all are evaluable for response: 8 were treated
by radiotherapy and 8 received three courses of CT. 14 pts (100%) are in complete response
(CR) and with a median follow-up of 42 (7-43) months. No relapse has been reported in
this group. Among 28 pts with stage II disease, 19 are evaluable for response. 77% are in CR
after CT with 37% of continuous CR. Overall survival is 75% after a median follow-up of
36 (10-73) months. 3 pts were excluded for pathological reasons (W/F: C + melanoma).
4 pts went off study for excessive toxicity. 5 pts died early with progressive disease. No
statistical analysis have been performed because of the low number of pts but these
encouraging results deserve further evaluation.

* Supported by Fondation Lambeau-Marteau

EFFECTIVENESS OF SURGICAL VS MEDICAL TREATMENT OF
INTERMEDIATE/HIGH GRADE RESECTABLE PRIMARY GASTRIC LYMPHOMAS
[HG-PGL]: A DECISION ANALYSIS MODEL.
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F. Boffelli, A. Santoro. Medical and Surgical Oncology, Istituto Nazionale Tumori
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Optimal stage of treatment stage II-II HG-PGL is controversial. Surgery has always been
performed for better diagnosis, staging and prophylaxis of local complications
(hemorrhage and perforation). More recently, conservative approach with C/RT has
been proposed and is currently recommended by many oncologists. The purpose
of the present work is to construct a decision model based on available evidence to evaluate
effectiveness of the two different approaches and to identify key variables that
require further investigation. Assumptions: 1) only pts with monoclonal disease not
infiltrating beyond the submucosa can be treated with surgery alone; 2) local failure is
considered an adverse event as distant relapse; 3) primary surgery (+/- C/RT)
yields optimal local control. Probabilities: perioperative mortality (POM) 0.04
(0.02-0.14); emergency gastrectomy after C/RT 0.05 (0.03-0.15); 2) local failure
after C/RT alone 10 (0.01-0.18); CT mortality 0.05 (0.00-0.15); long term DFS for patients with supradiaphragmatic disease 0.95, for all other stage II-III pts 0.89, long term
survival rate after relapse 0.12; cumulative second cancers after surgery 0.01, after
C/RT 0.04. Results. According to our model, for the average surgical-risk pts
the success rate expected from a primary surgical approach is always superior to primary
C/RT (long term survival rate of 85% vs 75%). Relevant variables are the POM rate
and the rate of local failure after C/RT, while the risk of local complications
and mortality from C/RT do not affect the main outcome significantly. Therefore, for patients
with limited stage I-II non-bulky disease, C/RT offers chances of cure equivalent to
surgery only when POM risk is in excess of 5%, and superior to surgery when the local failure
after C/RT, surgery results a better choice in average to moderate POM risk pts,
while the two options are roughly equivalent when POM risk is in excess of 8%. Conclusions:
for patient with HG-PGL and good-surgical risk, attempt to preserve the
stomach for a better quality of life might increase chances of cure. Therefore, before
we can recommend for these pts primary medical treatment outside a clinical trial, a
better understanding of local failure rate and success rate with salvage gastrectomy
after local relapse are necessary.

6. Extramedial lymphoma

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INTENSIVE ENDOSCOPIC MONITORING OF THE RESPONSE TO ANTIBIOTIC INFUSION (NF) THERAPY IN A PATIENT WITH GASTRIC MALT LYMPHOMA.

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department of oncology, Digestive Endoscopy Unit, Hospital, Milan, Italy.

Objective: To monitor by means of frequent endoscopy the response to anti-HP therapy in a patient with gastric MALT lymphoma.

Methods: A 31-year-old male with no previous significant diseases except for increasing epigastralgia during the last two-three months. The endoscopy revealed a large ulcer in the anterior gastric wall (10 cm diameter). Biopsy diagnosed a low-grade B MALT Lymphoma, HP present; CT detected two pathological lymph nodes near the stomach and pancreatic head. Anti-HP therapy ('three drugs': metronidazole 400 mg, metronidazole 250 mg, clindamycin 1500 mg, daily) was given for six weeks. The following controls and the evolution of the response to treatment are shown in the table below:

<table>
<thead>
<tr>
<th>Date</th>
<th>Endoscopy</th>
<th>Biopsy</th>
<th>HP</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.7.95</td>
<td>Ulcer 10 cm</td>
<td>MALT Lymph.</td>
<td>pos.</td>
<td>2 lymph.</td>
</tr>
<tr>
<td>11.8.95</td>
<td>Ulcer 3 cm</td>
<td>MALT Lymph.</td>
<td>pos.</td>
<td>3 lymph.</td>
</tr>
<tr>
<td>1.9.95</td>
<td>Ulcer 1.5 cm</td>
<td>MALT Lymph.</td>
<td>neg.</td>
<td>3 drugs</td>
</tr>
<tr>
<td>5.10.95</td>
<td>Normal</td>
<td>pos.</td>
<td>neg</td>
<td>neg</td>
</tr>
<tr>
<td>23.11.95</td>
<td>Normal</td>
<td>pos.</td>
<td>neg</td>
<td>Idem</td>
</tr>
</tbody>
</table>

Conclusions: 1) the treatment was well tolerated and eradicated HP; 2) the intensive endoscopic control showed the progressive resolution of the ulcer of the lymphoma; 3) complete response is still present three months after the end of therapy.


INstitute of Clinica Dermatologica and di Anatomia e # Umedicina, Firenze, Italy.

Primary cutaneous lymphoma (CL) is defined as a monoclonal lymphoid proliferation primarily presenting in the skin, with no evidence of extracutaneous disease at presentation and for at least 6 months. Two main groups are recognized on the basis of a clear-cut histology and/or immunophenotypic/genotypic evidence of clonality: cutaneous B-cell lymphomas (CBCL) and cutaneous T-cell lymphoma (CTCL). All newly diagnosed cases of CL in the period 1986-1995 were identified in the files of the Florence University Dermatology Institute and other dermatological departments and clinics in the area. Only cases resident at diagnosis in the province of Florence were selected for the study (101 CL patients: 56 males and 45 females). Seventy-five were CBCL (74.3%), and 26 were CTCL (25.7%). The age range was 25-85 years for CBCL (median 53.0) and 9-81 for CTCL (median 56). According to these preliminary data, the annual crude incidence rates for CBCL and CTCL are respectively 0.64 x 100,000 and 0.22 x 100,000 (0.56 and 0.20 x 100,000 standardized on European population). Cases identification from additional sources outside study area is still ongoing. Information concerning working history and lifestyle habits has been collected through a face-to-face interview, with the aim of identifying possible risk factors for the disease. A large series of population controls, approximately 500, interviewed in a related study, is available.

CHEMOTHERAPY FOR HIGH GRADE GASTRIC LYMPHOMA.

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Surgery has been advocated as the primary therapy for high grade gastric lymphomas. However, in the last 20 years chemotherapy (CT) has been performed on the role of chemotherapy (CT) and surgery. From 1991 to 1995 we observed 12 patients with 7, 3, 6 and 4 patients. Between 1991 and 1993 we observed 12 patients with 7 and 5 patients. From 1994 to 1995 there were 7 patients treated with surgery and 5 patients treated with chemotherapy. In the last 20 years we have observed 12 patients with 7 and 5 patients. All patients who received CT had a complete response after a mean follow-up of 16 months. In the last 20 years we have observed 12 patients with 7 and 5 patients. All patients who received CT had a complete response after a mean follow-up of 16 months. In the last 20 years we have observed 12 patients with 7 and 5 patients. All patients who received CT had a complete response after a mean follow-up of 16 months.
Detection of (t,2)(p23;q35) translocation by reverse transcription polymerase chain reaction and in situ hybridization in CD30-positive primary cutaneous lymphomas and lymphomatoid papulosis.

Mario Beylot-Barry, Laurence Lamant, Béatrice Vergier, Anne DeMuret, Sylvie Fraixig, B. Delord, Pierre Dubois, Loic Vaillant, Guenter Mac Grogan, Claire Beylot, Antoine de Mascarel, Georges Delozel, Jean-Philippe Merlio.

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The (t,2) generates a chimeric NPM-ALK transcript encoded by the nucleophosmin NPM gene fused to the Anaplastic Lymphoma Kinase gene ALK. Using a reverse transcription-esterase polymerase chain reaction assay we have detected NPM-ALK transcripts in 4 out of 9 CD30+ anaplastic primary cutaneous lymphomas and in 1 out of 4 CD30+ pleomorphic primary cutaneous lymphomas. Moreover, the (t,2) was detected in 3 out of 10 lymphomatoid papulosis (LP). All NPM-ALK positive lymphomas and one NPM-ALK positive LP exhibited a clonal rearrangement of the T-cell receptor gamma chain gene. The (t,2) was detected in 2 cases of LP without other evidence for a clonal lymphoid population. In order to identify cells carrying the (t,2) translocation, we used immunohistochemistry to detect the ALK-encoded p80 protein and in situ hybridization for the specific detection of NPM-ALK transcript. Both p80 protein and NPM-ALK transcripts were expressed by anaplastic or large CD30+ lymphoma cells with positive NPM-ALK amplification. The presence of (t,2) in a subset of CD30+ cutaneous lymphoma and LP may indicate a common pathogenesis with a subset of anaplastic nodal lymphoma.

MULTICENTRE RETROSPECTIVE REVIEW OF PRIMARY CUTANEOUS LYMHOPIA EXCLUDING MYCOPIA FUNGODIES.

A Webb1, K McCarthy1, D Cunningham1, J Sloane1, A Lister2, BW Hancock, AG Prentice2, S A N Johnson3, S Milan4. The Royal Marsden Hospital, Sutton, St Bartholomew’s Hospital5, West Park Hospital6, Derriford Hospital7, Taunton and Somerset Hospital8, UK.

Seventy patients from five centres were identified as having primary cutaneous lymphoma (excluding mycosis fungoides and Sézary syndrome). All histology was graded according to the Working Formulation (WF) or updated Kiel classification. Full staging was performed to exclude extracutaneous disease at presentation. The median age was 58 (91-25); male:female ratio 41:29, 46 patients presented with solitary lesions (10 with satellite lesions). In 12 patients the distribution was generalized. There were 12 low grade lymphomas (WF A-C, Pleomorphic small cell) - 9 B-cell, 3 T-cell - and 58 high grade tumours (WF E-H, Pleomorphic large cell, Large cell anaplastic) - 33 B-cell, 10 T-cell, 15 immunohistochemicals were non evaluable. The complete response (CR) rate to any treatment was 84% and the CR rate for solitary lesions was 96%. The lymphoma specific progression free survival was 75% at 1 year, 31% at 5 years with a median of 107 months. Median follow up was 54 months. Cutaneous only relapse occurred in 29% and 11% developed an extracutaneous relapse. The risk factors for relapse were >5 lesions (p=0.01), generalized distribution (p=0.03) and in solitary lesions the presence of satellites (p=0.0004). Overall survival at 5 years was 79% and lymphoma specific survival was 84%. Three patients died of unrelated causes in remission, 4 died with skin lymphoma but no extracutaneous disease, 6 died from disseminated lymphoma. All patients dying from lymphoma had high grade histology. Prognostic factors for poor disease specific survival were age >60 (p=0.007) >5 lesions (p=0.002) and generalised distribution (p=0.01). In conclusion primary cutaneous lymphoma has a high survival rate despite frequent cutaneous relapses.

MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS IN 50 SEVERELY IRRADIATED PATIENTS.

I. Courthaud MC, Cugnolo F, Wellek R, Capello F, Feuillet I, Auphan E. Institut Dermatologique Clinique, and Department of Genetics, Biology and Medical Chemistry, University of Paris, Paris, Italy.

Severe synovitis (SS) is a cutaneous T-cell lymphoma, clinically characterized by a pruritic exfoliative erythroderma, peripheral generalized lymphadenopathy and acral nodular lesions with cerebriform nuclei (Sézary cells, SC) in both peripheral blood and skin. Even if its prognosis is generally poor (lymph survival: 91/2%), clinical and histopathological findings, and more recently, TNF gene rearrangement studies have suggested that SS is a heterogeneous disease and may include forms with a different prognosis. However, according to the Mycosis Fungoides Cooperative Group classification system, all SS patients are generally classified as stage IV, actually, 30 prognostic factors are quite unknown, since it is a rare condition and the reported series are rarely comprised of more than 50 cases.

The aim of our study was to analyze the influence on survival of several clinical, histological and hematolymphologic factors in a series of 50 SS patients diagnosed, treated and followed-up in our unit between June 1973 and March 1994. Biologic criteria were: a) clinical staging of erythroderma and peripheral lymphadenopathies; b) circulating SC greater than or equal to 10% of peripheral blood lymphocytes (100/μl/mm²), detected at light and electron microscopy; c) cutaneous and nodal staging proven involvement. The type of skin lesions at onset of the first cutaneous manifestation and the interval between onset and diagnosis were analyzed. Multivariate analysis of survival was done using a proportional hazard model with regression to define independent prognostic variables.

Median survival time for patients with disease (lymph survival) was 42.5 months. Multivariate analysis indicated that the factors influencing survival as independent variables were the number of circulating SC (p=0.01) and acral LNM levels (p=0.01). A second analysis, performed without these two factors, demonstrated the significance of: CN3/50 ratio (p=0.01), hepatosplenomegaly (p=0.01), achievement of hematolymphologic remission (p=0.01), absolute number of circulating CD2 positive lymphocytes (p=0.01) and CD2 suppression on SC (p=0.01). A third analysis, performed excluding the hematolymphologic remissions (not determinable at diagnosis) and factors emerged from the first one, showed as independent variables: clinical picture at the onset (p=0.01), BSL reactivity (p=0.01) and absolute number of circulating moocyttes (p=0.01). Based on these results, three groups with different prognosis have been formed. Patients in the low-risk group had CN3/50<500, LNM acral levels in normal range, no hepatosplenomegaly, CD2/50 ratio <15 and positive SC (lymph survival: 8/21). Patients in the medium-risk group had CN3/50<5000, LNM acral levels above normal range, hepatosplenomegaly, CD2/50 ratio >15 and negative SC (medium surv: 10/21). No patient was alive 2 years after diagnosis (N=41; 11/31: 0.001). Patients from intermediate-risk group had a median survival of 46.6 months and a lymph survival of 11.6 months. Taken together, our results show that SS may include forms with different clinical prognosis: SS heterogeneity may be probably understood on the basis of a better knowledge of its pathogenetic and physiological mechanism. Multicentric studies are needed in order to assess the relevance this staging has in SS patients' management.

CUTANEOUS ENDOCRINE NEOPLASMS: CLINICOPATHOLOGIC FEATURES OF EXTRACUTANEOUS INVOLVEMENT IN CUTANEOUS NON-HODGKIN LYMPHOMA IN CHILDREN.


Purpose: To determine the frequency of cutaneous involvement among children with non-Hodgkin lymphoma, and to identify the clinicopathologic features and treatment outcome of these patients.

Patients and Results: From 1982 to 1995, 21 of 559 children (3.8%) with newly diagnosed non-Hodgkin lymphoma (large cell, 14; lymphoblastic, 14; small noncleaved cell and B-ALL, 238; other non-Hodgkin lymphomas, 25) had cutaneous involvement. Among these, 14 were large cell, 6, lymphoblastic, 10 were small noncleaved cell, representing 9.5, 4.0, and 6% of their respective histologic subtypes. One child presented with mycosis fungoides. Among the large cell cases, 7 had a T-cell phenotype and 5 were CD30+. Among lymphoblastic cases, 1 had T-cell and 2 had B lineage phenotypes. Four children had disease limited to skin, these included 3 cases of large cell NHL and 1 case of mycosis fungoides. The distribution of clinical stages included: stage I (n=11); stage II (n=2); stage III (n=14); and stage IV (n=4). Although 10 children (48%) have developed recurrent disease despite aggressive treatment in most cases, 18 (86%) are currently surviving free of disease. Two children with disease limited to skin had spontaneous regression of lesions, consistent with lymphomatoid papulosis.

Conclusion: Cutaneous involvement occurs in approximately 3.8% of cases of non-Hodgkin lymphoma in children. The majority of cases are large cell, usually with T-cell CD30 positive phenotype. Those of lymphoblastic subtype frequently have a B-precursor phenotype. Spontaneous remission may occur when disease is limited to skin (lymphomatoid papulosis). However, when other sites are also involved, aggressive multimodality chemotherapy is indicated. Although disease recurrence is fairly common, re-treatment is often successful.
DIFFERENCES IN THE EXPRESSION OF BCL-2 PROTEIN AND ADHESION MOLECULES BETWEEN PROGNOSTICALLY DIFFERENT GROUPS OF PRIMARY CUTANEOUS LARGE B-CELL LYMPHOMAS

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Dept. of Dermatology, Free University Hospital, Amsterdam; Dept. of Pathology, University of Utrecht, The Netherlands.

The large majority of primary cutaneous B-cell lymphomas represent large cell lymphomas with the morphological characteristics of large follicle center cells. Primary cutaneous follicle center cell lymphomas (PCFCC) presenting with tumors or nodules on the head or trunk represent a distinct clinicopathologic entity with an excellent prognosis (5-year-survival >95%). Morphologically similar lymphomas can also present on the lower legs, in particular in elderly females. These patients develop more often recurrent and extracutaneous disease, and their prognosis is less favorable (5-year-survival 45%). The mechanisms underlying this different clinical behaviour in these two groups of PCFCC arising at different sites is as yet unknown.

In this study PCFCC presenting on head and trunk (n = 10) or presenting on the lower legs (n = 10) were investigated for the expression of bcl-2 protein and the expression of a selected panel of adhesion molecules, including CD45RA, CD21, CD54, CD58, and CD44 by routine immunohistochimistry. Bcl-2 protein was detected in 9/10 PCFCC on the lower legs, but not in any of 12 PCFCC on head and trunk. Preliminary studies suggest that bcl-2 expression is not associated with t(14;18) in these cases. With respect to the adhesion molecules, PCFCC on head and trunk expressed ICAM-1 and LFA-1 in 8/10 and 6/10 cases, respectively, and CD44 in 0/10 cases. In contrast, PCFCC on the lower legs did not express ICAM-1 or LFA-1, but stained for VLA-4 in 80% of the cases.

The results of these studies suggest that differences in the expression of bcl-2 protein and adhesion molecules may contribute to the differences in clinical behaviour between these two groups of PCFCC, and also suggest that these groups should be considered separately.

T-CELL POPULATION OF PRIMARY AND SECONDARY CUTANEOUS B-CELL LYMPHOMAS DO NOT EXPRESS THE CUTANEOUS-LYMPHOCYTE-ASSOCIATED ANTIGEN (CLA) *T. Estrach*, **R.M. Hart**, **G. Hausmann**, **M.C. Cid**, **J. Palou**, **J.M. Mascaro**. *Department of Dermatology and **Internal Medicine, Hospital Clinic Barcelona. **Department of Dermatology, University of Lleida

Primary cutaneous B-cell lymphomas (PCBCL) seem to be a group of malignant lymphomas with distinctive clinicopathologic and immunophenotypic features. As in other B-cell lymphomas, benign accompanying population of CBCL includes a variable number of T-lymphocytes whose role is not well known.

In the present study we characterize the immunophenotype of such T-cells in 3 cases of CBCL and compare it with that in 2 cases with specific skin involvement by non-cutaneous B-cell malignancies.

Our results indicate that most T-cells in both primary and secondary B-cell lymphomas are CLA- and CD5- memory/effector helper T-cells which differ from the currently known CLA- and CD5- memory/effector helper T-lymphocytes of the SALT system. However, the endothelial CLA ligand, E-selectin, was expressed on dermal vessels. These data suggest that B-cell environment and/or lack of epidermal involvement promotes the recruitment to the skin of a different, apparently less specific, subset of memory helper T-cells than those seen in T-cell mediated dermatoses.

(Supported by CICYT grants SAF 94-0634-C02-01 and 02)

PRIMARY CUTANEOUS B-CELL LYMPHOMAS

Daniela C. Greiner, MD*, Elisa A. Olsen, MD*, Karen P. Mann, MD*, PhD*; Michael J. Borowitz, MD, PhD*

*Zentrum für Dermatologie, J.W. Goethe Universitat, Frankfurt, FRG - supported by a Fellowship of the Dr. Mishel Schelting Fonds for Krebsforschung ** Division of Dermatology, Department of Medicine, Duke University, USA ** Departments of Pathology, Duke University and Johns Hopkins University, USA

Background: Primary cutaneous B-cell lymphomas (PCBCL) are rare neoplasms that solely involve the skin. Data concerning histologic subtypes, survival and prognosis are sparse.

Object: Evaluation of clinical and histological characteristics of patients with PCBCL.

Methods: Demographic and treatment related data of patients with PCBCL seen in the last 10 years at Duke University Medical Center were reviewed, the histologies reevaluated, including immunophenotyping of frozen tissue and gene rearrangement studies.

Results: Two percent (n=10) of all B-cell Lymphoma patients (n=359) had PCBCL. The mean age at diagnosis was 58.4 years. The main presentation at diagnosis were erythematous violaceous nodules or tumors confined to the trunk or the extremities. Three of ten patients presented with lymphadenopathy. The mean survival was 18.9 months with a mean follow-up time of 18.9 months (3-63 mos). Six of 10 patients are still alive, 4 died (two of metastasis). Eight of 10 cases were classified as diffuse large B-cell lymphoma, the remaining two as an immunocytoema and a marginal cell lymphoma. Three patients achieved a complete remission after the initial treatment and one a partial remission. The mean response duration was 5.5 months.

Discussion: Lymphadenopathy and histologic subtypes had no influence on prognosis. The mean survival was worse than in other mainly European studies. Of interest was the large predominance of diffuse large cell lymphomas (60%). All treatment modalities were ineffective in inducing a prolonged complete remission with radiation therapy demonstrating the best response rates.

Conclusions: PCBCL in the US demonstrates a predominance of diffuse large cell lymphoma with a worse survival prognosis compared to European studies.
INTERFERON INDUCIBLE PROTEIN-10 IS EXPRESSED IN CUTANEOUS T-CELL LYMPHOMA LESIONS ASSOCIATED WITH CYTOKINES TNF-α AND IFN-γ IN THE ABSENCE OF DETECTABLE HTLV-I POL OR TAX PROVIRAL mRNA SEQUENCES.

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Cutaneous T-cell lymphoma (CTCL) is an epidermotropic lymphoma of CD4+ lymphocytes characterized by an indolent clinical course and multiple cutaneous relapses before visceral dissemination. We have previously shown that interferon-inducible Protein-10 (IP-10), a cytokine that is chemotactic for CD4+ lymphocytes both in vitro and in vivo, is upregulated in lesional epidermal keratinocytes in CTCL. IFN-γ and TNF-α are known to individually induce IP-10 and to have synergistic effects when added together. The tax gene of HTLV-I is known to immortalize CD4+ cells, to induce the IFN-γ promoter, and has been detected in a significant, but variable, percentage of HTLV-I seropositive patients with CTCL. We therefore decided to determine the presence of IFN-γ, TNF-α, and HTLV-I tax gene in CTCL lesions in order to determine if these possible inducers of IP-10 might play a role in the pathogenesis of CTCL. We used frozen lesional skin biopsies from 17 HTLV-I seropositive patients with CTCL and RT-PCR with appropriate primers followed by Southern analysis to detect the presence of IFN-γ, TNF-α, and HTLV-I tax or Pol-I sequences. All 17 patients had overexpression of IP-10 determined by immunocytochemistry of CTCL lesions.

The TME status of the patients is as follows:

<table>
<thead>
<tr>
<th>TME status</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/−</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>−/−</td>
<td>1</td>
<td>6</td>
</tr>
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<td>+/−</td>
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<td>12</td>
</tr>
</tbody>
</table>

γ-INF was present in 41%, TNF-α in 36%, and neither TNF-α or IFN-γ in 25% of these 17 patients. HTLV-I tax or Pol-I sequences were not detected by RT-PCR in CTCL lesions in any of the 17 patients. These data suggest that TNF-α and IFN-γ may be involved in the induction of IP-10 and thus contribute to the epidermotropism of CTCL in 71% of our CTCL patients, but other inducers of IP-10, are operative in the remainder 29% of the cases. Candidates are IL-10, IL-18, and IL-6. Additional work is underway to increase the sensitivity of tax gene with PCR, and to detect its presence by serological and immunocytochemical methods.

INTERFERON ALFA-2b (IFN-A) COMBINED WITH PHOTOTHERAPY FOR MYCOSES FUNGOIDES AND SEZARY SYNDROME: A PHASE II STUDY


Mature T cell lymphoproliferative disorders comprises a heterogeneous group of diseases for which there is no standard therapy. Interferon alfa-2b (Intron-A®) has demonstrated significant response rates of 45 to 65% but the responses were often not complete and of short duration.

In order to assess the efficacy of combined phototherapy (PUVA) and systemic IFN-A in patients with mycosis fungoides (MF) and the Sezary syndrome (SS), 24 patients were entered onto a multicentric prospective phase II trial between November 1991 and January 1996 after agreement of institutional human research committees. IFN-A was administered subcutaneously at the dose of 3 million units/m² and increased up to 5 million units/m² in case of poor response. PUVA was adapted to the maximal tolerated dose. The median follow-up is 19 (4-48 months). Patients with all stages of disease were enrolled (stageI, n=2; stage IIa, n=4; stage IIb, n=2; stage IIb, n=4; stage III, n=3; stage IVa, n=3; stage IVa, n=1; SS, n=3). 2 patients are not eligible according to histologic criteria. 9 patients had received previous therapy (PUVA, n=8; chemotherapy, n=4; radiation therapy, n=3) 22 patients are evaluable for response; the overall response is 69% with 46% of CR, 23% of PR, 31% of PD. The median duration of response is 14' (range 4 to 28') months. We did not observe a significant difference in terms of CR rates between untreated or previously treated patients. CR was mostly achieved in early stages of MF. However, 15 patients are alive with a median survival of 28 months. IFN-A combined with phototherapy is effective in cutaneous T-cell lymphomas primarily in patients with less advanced disease.

INTERFERON ALFA-2a AND PHOTOTHERAPY FOR MYCOSES FUNGOIDES (MF) AND SEZARY SYNDROME (SS).

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From 1993 to 1995, 21 patients (pts) with histologically proven MF or SS entered into a prospective non-randomised study. Pts and methods: pts with plaques, papules or eczematous lesions (stage I-II: 14 pts), or nodules (stage IIb: 3 pts), or generalized erythroderma (at III: 4 pts) received a.c. Interferon α-2a (IFN) (escalating the dose until the maximum tolerated dose, three times/week) and PUVA ( méthoxsalen 20-30 mg p.o. followed by ultraviolet A light irradiation), for 1 year. There were 12 males and 9 females; the median age was 62 yrs (range: 27-84). Two pts were pretreated: 1 with retinoids and UVA, 1 with chemotherapy. Pts were staged with chest and abdominal CT scan, bone marrow aspirate and biopsy, peripheral blood smears, lymph-nodal biopsies were performed in selected cases. Results: 10 pts completed the treatment: of these, 9 pts are alive in complete remission (CR); 1 pt obtained a partial remission (PR) and progressed after 3 yrs. Nine pts, with therapy still on-going, obtained a CR. One responding pt refused IFN + PUVA after 3 months and was treated with radiotherapy, another pt refused IFN + PUVA after 1 month and was lost to follow-up. Side effects: The treatment was generally well tolerated. The maximum dose of IFN was 18 MU in 1 pt, 12 MU in 9 pts, 9 MU in 6 pts. Four pts required a dose reduction to 6 MU because of fever and mild thrombocytopenia; a transient dose reduction to 3 MU was necessary in 2 pts because of a thrombocytopenia < 20 000/mm³. One pt stopped IFN after 2 months because of headache with persistent elevation of transaminases level. Conclusions: Interferon α-2a combined with phototherapy seems to be an effective treatment for mycosis fungoides and Sezary syndrome.