Peripheral blood mononuclear cells of a patient with advanced Hodgkin's lymphoma, give rise to permanently growing Hodgkin-Reed-Sternberg cells

A novel Hodgkin's disease (HD) derived cell line, L1236, was established from the peripheral blood of a patient with advanced Hodgkin's disease. Analysis of immunoglobulin (Ig) gene rearrangements revealed a biallelic Ig heavy chain and a monoallelic Ig kappa light chain gene rearrangement, pointing to a B-lymphoid origin of these cells. No DNA of Epstein-Barr virus was detected in L1236. The cells expressed the HD-associated surface antigens CD30 and CD15 as well as the transferrin receptor (CD71). Cytogenetic analysis of early passages of L1236 cells revealed a grossly unbalanced karyotype including cytogenetic aberrations described previously in other HD-derived cell lines. The Hodgkin/Reed-Sternberg (H-RS) cell origin of L1236 cells has been further confirmed by Kamzil et al., who found identical Ig gene rearrangement sequences in L1236 cells and H-RS cells of the same patient's bone marrow. Thus, for the first time the H-RS cell origin of a HD-derived cell line is proven on the molecular level. L1236 cells expressed antigens necessary for a frequent antigen presentation to T-cells including HLA class I and II, CD71 and B7.2 as well as adhesion molecules ICAM 1 and LFA 3. The cells secreted the interleukins (IL), 6, 8, 10, tumor necrosis factor (TNF) alpha, interferon (IFN) gamma, transforming growth factor (TGF) beta and the granulocyte-macrophage colony stimulating factor (GM-CSF). Subsequent inoculation into SCID mice, a necrotic regression of initially growing tumors at the injection site was followed by disseminated intrathoracic growth. Our findings demonstrate that H-RS cells of B-lymphoid origin may be present in the peripheral blood of patients with advanced Hodgkin's disease of B-cell origin. These cells exert a malignant phenotype with regard to their in vitro and in vivo characteristics.

DO EPSTEIN-BARR VIRUS, Bc1-2 OR p53 HAVE ANY RELEVANCE TO CLINICAL OUTCOME IN PATIENTS WITH HODGKIN'S DISEASE?

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Introduction: past publications have confirmed that Epstein-Barr virus (EBV) genome, the Bc1-2 protein, and p53 are present in Sternberg-Reed cells of a proportion of Hodgkin's disease (HD) cases. A study has been undertaken to examine the clinicopathological relevance of these molecular markers in patients with HD. Methods: all 53 newly diagnosed patients had been treated at St. Bartholomew's Hospital and selected on the basis of availability of suitable material, immunohistochemistry and in situ hybridisation were the methods used, and clinical information extracted and analysed from the data bank. Results: there were no statistically significant correlation between age, gender, histology, stage, treatment & response and any of the factors independent of each other. However, 50% of EBV positive cases (8/16) were in the age group 29-37 years, whilst only 19% of negative cases were found in this age range. In those cases that were Bc1-2 positive, 5/16 (31%) were mixed cellularity sub-type. Only 11% of the Bc1-2 negative cases were of this histology. Of the 53 p53 positive cases, 12 were male (92%), in contrast to 61% of males in the p53 positive group (22/36). Kaplan-Meier plots for the presence or absence of each factor was drawn against freedom from recurrence and overall survival. There was no statistically significant correlation between any of the factors and response rate, freedom from recurrence or survival, with a median follow up of five years. Conclusion: although all three may have an important part in the pathogenesis of Hodgkin's disease, within the context of current therapeutic strategies they do not have clinical relevance.

3. Hodgkin's disease
INDOLENT, RELAPSING PATTERN IN NODULAR LYMPHOCYTE PREDOMINANCE HODGKIN'S DISEASE (NLPHD): THE GELA EXPERIENCE IN A SERIES OF 69 PATIENTS.


Objective: Among Hodgkin's disease, the NLPHD subtype is recognized as a separate entity because its histological picture and its indolent course. To explore the different approaches of therapy in NLPHD, we retrospectively reviewed the outcome in 69 patients (pts) treated between 1/1976 and 12/1994 in 11 centers. Patients: sex ratio M/F: 5.5; median age: 33 years; stage I: 61%, II: 22%, III: 17%. Sites of disease were mainly single cervical, axillary or inguinal lymph nodes, mediastinal involvement was uncommon (7 pts) and no bulky; a total of 45 pts (65%) had disease confined in supradiaphragmatic areas; only 5 pts had B symptoms, and 2 an ESR>50.

Treatment: 13 pts were treated with radiotherapy (RT) alone; involved-field or mantle (IFM) 13 pts, STNI 1 pts; 39 pts with combined modality (CMT): MOPP, ABVD, or MOPP-ABVD (3 cycles) and either IFM (23 pts) or STNI (16 pts); 17 pts remained untreated. Results: all the 32 treated pts achieved complete remission. Among the 69 pts, 17 pts progressed (median 38 months from diagnosis; range 10 to 203), 4 of them with a subsequent large-cell non-Hodgkin's lymphoma (NHLL at 12, 35, 39, and 52 months from diagnosis). Since median follow-up durations were different according to treatment (watch and wait policy: 20 months; RT: 48 months; CMT: 84 months), no conclusion can be yet drawn to predict freedom from relapse. A total of 5 pts died. Causes of death were NHL in 3 pts, NLPHD in 1 pt, lung carcinoma in 1 pt. With a median follow-up of 67 months (range, 6 to 271), the 5-year overall survival rate is 92.7%. Conclusion: the excellent survival rate in spite of a high rate of late relapse in pts with NLPHD raise questions about the type and extent of initial therapy needed in this disease, and led to further investigate a watch and wait conservative approach in the setting of low tumor burden.

IMPACT OF HISTOPATHOLOGY ON SURVIVAL AND RELAPSE OF PATIENTS WITH HODGKIN'S DISEASE. RESULTS FROM THE GERMAN HODGKIN STUDY GROUP.


Universität Köln, Frankfurt, Leipzig and Hannover

More than 2,600 HD patients were recruited and treated according to the protocols HD-1 to HD-6 since 1984. Histological classification of the diagnostic biopsies was performed by 4 experts as reported formerly. 1,349 protocol treated and evaluable patients were classified according to the RYE system into LPHD: 4.1%; NSHLD: 64.6%; NSHLD grade 1: 55%; NSHLD grade 2: 19%; MCHD: 19.1%; LDH: 0.7%; others 11.4%. Results are as follows: (1) NS grade 1 revealed significant better survival and FFTP than grade 2, even in advanced stages. (2) MCHD was significant worse than NSHLD of both grades, these differences, however, were lost in advanced stages. (3) LPHD was mostly detected in clinical stage I (32%), only 8% were in higher stages. Distribution of clinical findings to histopathology will be presented in detail; for instance localization of HD infiltrates correlated with histologic groups. It is concluded, that HD patients enrolled into the 4 main groups by histopathology can be distinguished by their prognosis and relapse rate even under protocol therapy especially when early and intermediate stages are evaluated.

REDUCTION OF RADIOTHERAPY IN EARLY STAGE HODGKIN'S DISEASE: RESULTS OF A RANDOMIZED TRIAL IN PATIENTS PS I/II


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In early stage Hodgkin's Disease (HD) radiotherapy is still considered as standard therapy. Reduction of radiotherapy in dosis and volume seems possible without loss to treatment results. Therefore we initiated a randomized trial to compare 40 Gy extended field (EF/arm A) to 30 Gy EF +10 Gy Involved field (IF/arm B). Between 1988 and 1994 399 patients clinical stage I/II A/B were recruited. All patients underwent staging laparotomy according to the treatment protocol. Histology and quality of radiotherapy were reviewed by an expert panel. 366 patients were evaluable for response. Patients characteristics were equal in both groups for histology, gender, age and pathological stage (PS).

There was no difference in complete remission rate (arm A: 92.6% vs arm B: 97.7%), survival and freedom from treatment failure with a median follow-up of 32 months. Apart from histology, quality of radiotherapy influenced significantly prognosis (p=0.0048).

We conclude that reduction of radiotherapy is possible in HD-patients PS I/II without decline of treatment results. This leads to a considerable advantage for the patient by shortening duration and decreasing intensity of treatment.

3. Hodgkin's disease

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PROGNOSTIC FACTOR BASED MANAGEMENT OF CLINICAL STAGE I AND II HODGKIN'S DISEASE.

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The outcome of 219 patients with clinical stage I-II Hodgkin's disease managed at the Princess Margaret Hospital between 1987 and 1991 was reviewed. Analysis revealed treatment and patterns of failure. The median age was 27 yrs (range 14-82). Male:female ratio was 1.09. There were 77 patients with stage IA disease, 31B, 104-II A and 35-III B. Histologic types were LP in 28 pts, NS-145 pts, MC-36 pts and LD-1 pt. 206 pts (94%) had supradiaphragmatic and 6% (13 pts) infradiaphragmatic presentations. Initial treatment was RT alone in 57% (124 pts), CT+RT in 38% (83 pts) and CT alone in 5% (11 pts). CT+RT treated group included all patients with stage I-IIIB, 17% with IA, 36% with IIB, 69% with ES+R=40%, 97% with large mediastinal mass. Of supradiaphragmatic presentations treated with RT alone 76% received extended field RT. In combined modality patients, 93% received 2-7 courses (median 6) of ABVD or MOPP/ABVD combinations.

With a median follow-up of 5.8 years (range 0.2-8.3 yrs), the 5-year overall actuarial survival was 95%, cause-specific survival - 97% and the failure free rate - 85%. Thirty patients relapsed following initial therapy. Median time to relapse was 1.8 yrs. range 0.5-6.4 yrs. In the favourable cohort of 87 patients defined as clinical stage IA-II A, age < 40 yrs, LP-NS histology, sedimentation rate < 40, and without large mediastinal mass which were treated with RT alone to a median tumour dose of 35 Gy in 20 fractions over 4 weeks, the 5-year actuarial failure free rate was 89%. Overall actuarial survival 100% and cause specific survival 100%. Only 2 local failures were observed in this favourable cohort. The introduction of prognostic factor based management of clinical stage I and II Hodgkin's disease produced excellent results with an actuarial risk of relapse of 15% at 5 years and overall survival of 95% in the entire cohort of patients.

SEQUENTIAL CHEMOTHERAPY (CEMM) AND INVOLVED FIELD RADIOTHERAPY FOR RESCUE TREATMENT OF HODGKIN'S DISEASE WITH INITIAL BULK INVOLVEMENT.


Between March 1987 and September 1994, ten patients (2 females & 8 males, median age = 27y, 10-43 yrs) with Hodgkin's disease were treated after failure of a first line treatment by sequential rescue regimen associating chemotherapy and involved field radiotherapy. They initially presented as stage IA in 2 cases, II B in 8, IIIA in 1 and IV in 1. All had massive involvement of the mediastinum with a Mediastinum/Thoracic > 0.35. Initial chemotherapy consisted of 3 cycles of MOPP in 2 cases, MOPP/ABV in 5 and ABV in 3. Eight patients received the study because of an inefficient response after the first line therapy (Partial Response < 75% or PR > 75% with persistent B- or inflammatory signs : elevated fibrin, accelerated ESR) and two because of relapse occurring after PBST.

None of the patients received irradiation prior inclusion in the trial. Rescue regimen consisted of 3 monthly cycles associating chemotherapy and a 15 Gy mantle-field irradiation (10 x 1.5 Gy in 2 weeks), between Day 15 to Day 28 after initiation of chemotherapy.

CEMM 15 Gy D1→D3 15 Gy D15→D28 D30 15 Gy D15→D28 D30

CEMM Cyclophosphamide 500 mg/m² D1-D3, Etoposide 100 mg/m² D1-D3, Methotrexate 500 mg/m² D1, Methotrexate 30 mg/m² D3.

In the presence of a significant cytopenia (OMS grade ≥ 3), doses of chemotherapy were reduced to 50% but no reduction in doses of irradiation was proposed. Five patients received the complete therapy in 3 months, 4 in 4 months and one in 6 months. A complementary lombo-splenic irradiation was realized in 8 cases (35-40 Gy). Chemotherapy was reduced to a 50% in half of the patients during the 2nd and 3rd cycles. All patients entered a complete remission with the disappearance of B- or inflammatory signs and reduction of masses < 80%. No relapse, no secondary leukaemia and no death were observed at time of analysis with a median follow-up of 54 months (15-78) after the end of treatment. Toxicity was acceptable. The critical point was hematologic toxicity (OMS grade ≥ 3 for leukocytes and granulocytes in 5 cases), we observed no other significant reaction except mild mucositis in 5 cases. This sequence of treatment is the conclusion of the complete chemoradiotherapy in 3-4 months, offers an interesting alternate treatment to the standard approach.

EVA CHEMOTHERAPY (ETOPOSIDE, VINBLASTINE, DOXORUBICIN) PLUS SUBTOTAL NODAL IRRADIATION AS PRIMARY THERAPY FOR UNFAVORABLE LOCALIZED HODGKIN'S DISEASE (CALGB 9013)


The use of combined modality therapy for localized Hodgkin's disease (HD) has increased since the demonstration of the utility of non-alkylating agent containing regimens. Pulmonary toxicity, occasionally severe, complicates bleomycin containing regimens. The EVA regimen (Etoposide 100mg/m²/day 1-3, vinblastine 6mg/m²/day 1, doxorubicin 50mg/m²/day 1, all i.V.) was given every 28 days for 3 cycles followed by subtotal nodal irradiation (3600-3900Gy) for localized low-stage (IA-IIIA) HD with unfavorable prognostic features (bulky mediastinum; PSIII, IIIA1 (<5 nodes); CS/PS-Ilass with any of 2 age >50, 4 sites, ESR > 40; mixed cellularity/lymphocyte depleted; E disease; a node > 5cm). 53 patients were in stages IA 15%, IB 6%, IIA 41%, IIIA 30%—all but 4 were CS; PS IIIA 8%. Mediastinal masses were present in 91% (91% > 5 cm; 38% > 10cm). 85% had nodular sclerosis. After 3 cycles of EVA, 92% responded (15% CR, 77% PR) and following RT (64% CR, 28% PR). In a median follow-up of 3.5 years, 11/49 responders (22%) have progressed (65% CR, 5/15 PRs)—all but 3 within 14 months. 6/11 relapses occurred in extranodal sites (pleura, lung, bone), the remainder in bulky nodal sites. The primary toxicity was myelosuppression (62% grade 3-4 neutropenia; one patient had grade 3 dyspnea). Only 3 deaths have occurred from patients (<2%). Three cycles of EVA/RRT offers an alternative regimen for localized HD with unfavorable prognostic factors and when there is clinical concern for possible bleomycin toxicity. For a fraction of EVA are insufficient but also may not be cross-resistant to alkylating agent regimens and allow for effective salvage therapy.

COMPARISON OF COPP/ABV AND COPP/AVP/MEP IN THE TREATMENT OF HODGKIN'S DISEASE RESULTS OF HD5 AND HD6 STUDIES OF THE GERMAN HODGKIN'S DISEASE TREATMENT STUDY GROUP.


Objectives

Theoretical considerations suggest that a more rapid alternation of drug administration and a higher number of different drugs in a multi-drug chemotherapy should curtail the development of tumor cell resistance. This study aimed to test whether this proposed effect gives increased efficacy to the regimen COPP/AVP/MEP in comparison to the standard COPP/ABV.

Design.

1413 patients were randomized into the trials HD5 (intermediate stage) and HD6 (advanced stage) and randomized into arm A and arm B after balancing HRS stages I and II with risk factors; stage IIIA A1 2A COPP/ABV or B 2A COPP/AVP/MEP,

followed by 30 Gy radiotherapy to the extended field and 40 Gy to sites of initially bulky disease;

HD6 stages II B, IV (A: 4C COPP/ABV or B: 4C COPP/AVP/MEP),

followed by 30 Gy to sites of initially bulky disease and to slow responding areas, and 40 Gy to residual disease.

The two chemotherapies were applied over a complete-cycle duration of 37 days (A) and 43 days (B) respectively.

Results.

87% of patients are evaluable. The median follow-up times are 36 months for HD5 and 45 months for HD6.

No difference in the complete remission (CR) rate, in survival (OS) or in freedom from treatment failure (FFTF) between the two arms could be detected in either trial.

The CR rate was 95% for HD5 and 76% for HD6. 16% of HD6 patients had progressive disease during therapy. Kaplan-Meier estimates of FFTF at 5 years after diagnosis were 87% (HD5) and 79% for HD6.

Significant differences in acute chemotherapy-related toxicity were observed between the two arms. Leucopenia was more frequent with COPP/ABV/MEP (94% of cycles with WHO grade 3 or 4, 4 vs. 33%, p=0.001), but COPP/ABV caused more emesis (22% vs. 8%, p=0.001). Patients older than 60 years experienced more haematological toxicity and infections than younger patients when treated with COPP/AVP/MEP. This age-effect was not observed under COPP/ABV.

Conclusion.

The rapidly alternating chemotherapy COPP/AVP/MEP showed no measurable superiority over COPP/ABV. However, there were considerable differences in acute toxicity between the two regimens.

PRIMARY CHEMOTHERAPY OF ADVANCED AND UNFAVORABLE LOCALIZED HODGKIN’S DISEASE (HD) WITH ETOPOSIDE, VINBLASTINE, DOXORUBICIN (EVA)

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Doxorubicin containing regimens devoid of classic alkylating agents have become more extensively used for systemic therapy of advanced HD. Uncertainty as to the contribution of bleomycin, DTIC and the pulmonary toxicity of the former led to a pilot trial of EVA in patients with advanced and unfavorable localized HD. Etoposide 100mg/m² day 1, vinblastine 6mg/m² day 1, and doxorubicin 50mg/m² day 1, all i.v. every 28 days for 6 cycles. Fifty patients previously untreated with systemic therapy were treated stages: bulky II A/B 26%, PS IIIA 1 12%; CS IIIA 2 B 24%. CS IV A/B 18% radiation relapse 20%. The median age was 31, 70% males, 78% NS. 38% received radiation to sites of bulk disease. 98% responded with complete or good partial responses; median progression-free survival is 35+ months. Seventeen (34%) relapsed with the major recurrence at 14/17 occurring in 0-14 months. Relapse-free survival for stages bulky II-III A 1 84% and IIIA-IVB 52%. Sixteen were treated with alkylating agent regimens (13 Chl/VP, 3 ICE, 1 too early +/- RT) with 3 going on to ABMT. 11/16 are NED following salvage therapy. Only 4/16 proceeded and died following second-line therapy and one died of BMT toxicity (2,6,11,12,16 months). 44/50 (88%) are alive NED with primary or secondary therapy. Toxicity was primarily myelosuppression with no secondary tumors or pulmonary fibrosis. Conclusion: 6 cycles of EVA +/- RT may be equivalent to ABVD but without pulmonary toxicity. Absence of cross-resistance to alkylating agents/RT is suggested by a high salvage rate even in patients who fail early.

FILGRASTIM AS AN ADJUNCT TO COMBINATION CHEMOTHERAPY IN HODGKIN’S DISEASE.


Dose intensity is important in the chemotherapy of Hodgkin’s Disease (HD). In a prospective, open label, multicentre, randomised study the West of Scotland Lymphoma Group tested the hypothesis that administration of Filgrastim (+ measles G-CSF, Amgen) to patients receiving MOPP or MOPP/EVAP chemotherapy for HD could ameliorate the incidence of leukopenia (WBC < 1.0 x10⁹/L) and thus increase dose-intensity of chemotherapy. Patients with haematologically confirmed HD aged 15-75 years were randomised to receive MOPP or hybrid MOPP/EVAP chemotherapy for a maximum of 8 cycles with or without Filgrastim 5µg/kg/day subcutaneously (days 15-27 for MOPP and days 11-27 for MOPP/EVAP). Between 1990 and 1993 53 patients were recruited into the study. 43 patients were included in this analysis. Median age of the patients was 29 (range 19-68), 28/43 (65%) patients were male, 28/43 (65%) patients had B symptoms. Stage at entry to the study included stage IB 6/43 (14%), stage II 13/43 (30%), stage III 14/43 (32%), stage IV 10/43 (23%). Filgrastim was well tolerated with essentially no side-effects being observed in treated patients. Analysis indicates that Filgrastim administration results in a significant difference in the nadir WBC in patients receiving MOPP or MOPP/EVAP chemotherapy compared to control patients receiving either chemotherapy regimen. However the administration of Filgrastim did significantly shorten the duration of leukopenia in patients receiving MOPP chemotherapy (p=0.026) compared to control arm MOPP treated patients. This effect was not observed in patients receiving the MOPP/EVAP hybrid schedule (p=0.159). Filgrastim administration had no statistically significant effect on the dose intensity of chemotherapy in either treatment arm. Nor did filgrastim reduce myelosuppressive morbidity in either treatment group. These results would suggest that routine use of colony stimulating factors to increase dose intensity in conventional chemotherapy for Hodgkin’s Disease is not warranted.

COMPARISON OF A SEVEN DRUG HYBRID REGIME WITH MOPP IN THE TREATMENT OF HODGKIN’S DISEASE.


Between 1986 and 1993, 206 patients with Hodgkin’s Disease requiring first line chemotherapy were entered into this study from 14 hospital groups in the West of Scotland. All patients over 14 were eligible and it is estimated that over 90% of potential patients were entered. 7 patients were excluded on histological review leaving 93 randomised to MOPP and 106 to Hybrid (Maxime 6mg/m² IV, Vincristine 1.4mg/m² maximum 2mg Day 1 (IV), Procarbazine 100mg/m² Day 1-7 (o), Prednisolone 25mg/m² Day 1-4 (o), Vinblastine 6mg/m² IV Day 8, Adria- mycin 25mg/m² (IV) Day 8, Etoposide 70mg/m² (IV) Day 8 and 150mg/m² (o) Day 9 and 10. Four courses initially were given followed by restaging. Complete remitters received a total of six courses with radiotherapy to sites of initial bulk or residual disease. Good partial remitters (0-70% bulk reduction and loss of symptoms) could receive up to eight courses if confirmed response documented. Patients in the MOPP arm, with failure to respond after two courses, good PR after four, or CR after six courses received up to four courses of EVAP (exposide, vinblastine, Adriamycin and prednisolone). The two arms were equivalent for patients with previous radiotherapy, overall (11%), clinical stage I-II (45%), IV (27%), B symptoms (67%), male sex (58%), median age 34, nodular sclerosing histology (48%), mixed cellularity (32%) and lymphocyte depleted (8%).

Compared to MOPP the Hybrid regime: a) showed less haematological toxicity (severity of thrombocytopenia p=0.005, transfusion requirements p=0.034, no difference in neutropenia (p=0.001); b) first four courses completed with >85% dose intensity in more patients (84 v 71%, p=0.05). No significant difference in survival is yet apparent (relative death rate, intention to treat, MOPP: Hybrid (1.32 CI 0.79-2.23, p=0.29). However relapses are less frequent in the Hybrid arm (MOPP: Hybrid 2.24 (CI 1.13 - 4.45, p=0.014).

This study adds to the evidence that multi drug regimes are less toxic and probably more effective than the standard MOPP regime.

PROBABILITY OF RELAPSE AND SURVIVAL OF BNL1 PATIENTS IN SUSTAINED COMPLETE REMISSION.


The long term prognosis of patients who have been treated for Hodgkin’s disease and attained a complete remission is of considerable importance in medical legal cases and for patients who wish to emigrate or adopt children, or to obtain credit for loans, mortgages, life assurance etc. To determine this we have analysed the data on 2005 patients with Hodgkin’s who achieved a complete remission lasting for at least 5 years.

The actuarial risk of relapse during the subsequent 10 years was approximately 12% whilst patients who remained relapse free for 10 years had a risk of relapse during the subsequent 10 years of only 4%, there being no significant difference in these relapse rates between patients with stage I or 2 disease and stage 3 or 4 disease at presentation. Once remission had been maintained for 5 years, the rate of relapse in subsequent years was broadly similar regardless of whether the 5 year remission occurred after 1st, 2nd or 3rd line therapy.

The overall survival of patients who attained sustained complete remission from their initial treatment compared to the survival expected in the general population was related to the age of the patients at the time they were treated. The survival of patients who were under the age of 50 at time of initial treatment was only about 4% less than that expected up to 15 years follow up, rising to approximately 15% at 20 years follow up. The survival of patients who were 50-59 years of age at time of initial treatment was approximately 10%, 18%, 29% and 34% less than that expected in the general population at 3,10,15 and 20 years follow up, respectively. The decrease in survival of patients aged 60-69 at the time of initial treatment compared to that of the general population was almost identical at 5 & 10 years follow up to that of patients aged 50 - 59.

3. Hodgkin’s disease

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DETECTION OF RELAPSE FOLLOWING TREATMENT FOR HODGKIN'S DISEASE (HD): IS THE ROUTINE INVESTIGATION OF ASYMPTOMATIC PATIENTS OF ANY VALUE?

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One of the most important purposes of follow-up after treatment for HD is early detection of relapse. At each follow-up visit, patients (pts) attending this institute are given an opportunity to volunteer symptoms, are examined for evidence of recurrent disease, blood is drawn for a blood count, ear and biochemical profile and, for pts with mediastinal involvement at presentation, an erect posterior-anterior chest radiograph is performed. In this study, the route by which relapse was detected in 135 pts who had achieved first remission was determined by a retrospective review of the hospital notes.

113 (84%) pts. reported symptoms (most commonly, the finding of a lump, pain, sweats or weight loss) and it was the appropriate investigation of these that led to the diagnosis of relapse. For the remainder (622), the presence of symptoms had not been recorded and relapse was suggested either by physical examination (=14) or an abnormal test result (chest radiograph alone, 4; ear alone, 2; ear and biochemical profile, 1; ear and chest radiograph and blood count, 1). Although detection of relapse in an asymptomatic patient might have been expected to confer an advantage (lighter tumour burden), survival from relapse showed no difference between the two groups.

This study suggests first, that the majority of relapses in HD are detected as a result of the appropriate investigation of symptoms, second, that physical examination is the best method of screening asymptomatic pts, and third, that routine investigations appear to be of only limited value in this setting. Follow-up policy and in particular the role of routine investigation should be re-considered in the light of these findings.

ETOPOSIDE, IFOSFAMIDE, AND CISPLATIN (VIP REGIMEN) IN RELAPSE OR REFRACTORY HODGKIN'S DISEASE (HD)

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42 patients (pts) with refractory (15 pts) or relapsed (27 pts) HD were included from 01/89 to 05/95 in this prospective study. Sex ratio (MM): 23/19, median age: 27 (15-57). Histology: nodular sclerosis: 28, mixed cellularity: 10, lymphocyte depleted: 4. Previous therapy: chemotherapy: radiotherapy: 31, chemotherapy alone: 11. 29 pts relapsed or were refractory to MOPP/ABV, 4 pts to MOPP followed by ABVD, 4 pts to ABVD or EBVP and 1 pt to MOPP alone. Among the 27 relapsed pts, 16 pts relapsed less than 12 months after completion of first line therapy. 5 pts had previously obtained a first CR of more than 12 months, the 6 other pts were in second or third relapse. VIP regimen stands as follow: VP16: 75mg/m2/day (6) d1 to d5, Ifosfamide: 1.2 g/m2d1 to d5, Cisplatinum: 20 mg/m2d1 to d5, one course every 4 weeks. If pts obtained an objective response (>50%) to VIP, high dose chemotherapy followed by autologous bone marrow transplantation (ABMT) was planned. No toxic death was observed. 60% of pts had grade IV granulocytopenia which was associated with grade II inflection in 20% of cases. 40/42 pts had measurable disease. After 2 courses of VIP, 26/40 (65%) of pts obtained an objective response (>50%) including 10/26 (38%) CR. Among the refractory pts 9/15 obtained an objective response with 2/9 CR. 24 of these pts went on to ABMT. 14/42 (33%) pts are in CR 44 months (8-70 months) after therapy including 12/24 (50%) transplanted pts. These results showed that VIP regimen is effective in relapsed or refractory HD and allowed high dose therapy with ABMT in responding pts.

PROGNOSTIC FACTORS FOR DISEASE PROGRESSION IN ADVANCED HODGKIN'S DISEASE (HD): AN ANALYSIS IN PATIENTS AGED UNDER 60 YEARS SHOWING NO PROGRESSION IN THE FIRST SIX MONTHS AFTER STARTING PRIMARY CHEMOTHERAPY (CT)

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High dose chemotherapy (HDC) with autologous stem cell rescue is increasingly being used to treat patients with advanced HD who progress during initial therapy, relapse within 1 year of completing therapy or who are in second or subsequent relapse having received 2 or more conventional CT regimes. Overall, 40-50% of such patients achieve prolonged progression-free survival (PFS) using this approach. The role of HDC in the initial treatment of advanced HD is a question of importance but is currently only felt to be appropriate in patients who progress during primary treatment if a high risk group could be identified on features known at presentation, then it may define a population in which the role of HDC could be assessed - e.g. by defining eligibility for a randomised trial.

Between 1975 and 1992, 453 patients aged under 60 years who did not progress in the first six months following the start of CT had their hospital notes reviewed. The outcomes analysed were early disease progression (in the 6-18 month window following the start of chemotherapy) and disease progression in the whole of the follow-up period. Cox regression was used to investigate the combined effects of a number of presenting characteristics on these outcomes. Despite the presence of significant effects on the relative rate of progression, the absolute effects in a group identified as having the poorest prognosis, were not especially poor. The table below shows PFS in different prognostic groups. No group could be defined with a PFS <72% over 6 to 18 months and the two prognostic group which included only 53 patients, had an overall PFS of 57±5% at 5 years.

PERCENT P.F.S.

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<th>Stage</th>
<th>6-18 mos</th>
<th>5 years</th>
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<td>88</td>
</tr>
<tr>
<td>Stage IVa with bulk and/or B symptoms</td>
<td>92</td>
<td>82</td>
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<tr>
<td>Stage IVa with bulk and/or B and (high lymph. count and B symptoms)</td>
<td>87</td>
<td>74</td>
</tr>
<tr>
<td>Stage IVa with bulk and/or B and (low lymph. count and B symptoms)</td>
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Four other prognostic indices (Haasencler et al, unpublished; Proctor et al, 1991, Strauss et al, 1990, Wagstaff et al, 1988) were evaluated using our dataset but none of the indices were more successful in picking out a very high risk group. It is likely that the search for more powerful indicators of prognosis must continue before a place can be found for HDC in the initial treatment of HD.

Treatment results in 67 patients with early-relapsed Hodgkin's disease.


Background: Patients (pts) with Hodgkin's disease who relapse or progress shortly after chemotherapy have a poor outcome with second-line standard chemotherapy and are often given intensive chemotherapy with autologous stem cell support.

Objective: To determine the outcome of patients with Hodgkin's disease in early relapse within 2 years after start of chemotherapy treated with conventional chemotherapy or with high-dose chemotherapy.

Methods: Pts entered in EORTC studies H7 (stages I-II) or EORTC H34 (stages III and IV) and who had relapse/progression within 2 years of start of therapy were identified and type of salvage treatment was analysed. Freedom from second failure was used as major end point. Information was available for 67 pts, H7-study: 52 pts, H34-study: 15 pts. 40 pts received EBVP (etoposibuc, bleomycin, vindesine, prednisone) and 27 received MOPP/ABV as primary treatment.

Results: 38 pts (EBVP: 25; MOPP/ABV: 13) received conventional second line chemotherapy. 29 (EBVP: 15; MOPP/ABV: 14) received high-dose chemotherapy with bone marrow or peripheral stem cell support. Standard-dose chemotherapy and high-dose chemotherapy were not uniform. Of the pts treated with high-dose chemotherapy, 10/29 (34%) were alive in complete remission (MOPP/ABV: 4/14 - 28%; EBVP: 6/15 - 40%). Of the pts treated with standard-dose salvage chemotherapy, 17/38 (44%) were in complete remission (EBVP: 14/25 - 56%; MOPP/ABV: 3/13 - 23%).

Conclusions: Patients with early relapse still have a very unfavorable prognosis, especially after treatment with MOPP/ABV. High dose chemotherapy does not seem to have a major impact on the outcome. New treatment approaches for this group of patients are to be found.
RESPONSES OF REFRACTORY HODGKIN'S DISEASE (HD) TO TREATMENT WITH ANTI-CD30/CD16 BISPECIFIC ANTIBODY (BiMAB): RESULTS OF THE PHASE II STUDY T801 G. Benelli, F. M. Bertoli, M. Cattaneo, W. Jung, C. Deising, M. Juwah and M. Freundschuh. Innere Medizin I, Universitätskliniken des Saarlandes, D-66426 Homburg, Germany.

The anti-CD30/CD16 BiMAB HRS-3A9 with reactivity to the FevR (CD 16 antigen) on natural killer (NK) cells and the Hodgkin's associated CD30 antigen, respectively, has been shown to induce tumor-cell specific lysis of the Hodgkin's derived cell line L540 in vitro and to cure SCID-mice bearing established Hodgkin's tumors using normal human PBL. (Int. J. Cancer 55: 830-832, 1995). In a phase I/II dose-escalation study we treated 15 patients with refractory Hodgkin's disease with increasing doses of the BiMAB HRS-3A9 (four anti-CD30/CD16 BiMAB infusions every 3-4 days at increasing dose levels, starting at 1 mg/m² and doubling the dose at each following level with a minimum of two patients per dose level). Patient characteristics: 11 men, 4 women; average age 40 yrs (25-58), average stage IV with hepatic or pulmonary involvement in 8 pts., average of 3.9 (2-7) previous chemotherapy regimens with ABMT/PBSCT in 7 cases, previous radiation therapy ≥1F in 12 pts. Toxicity: No dose limiting toxicity occurred at doses of up to 6 mg/m² x 4. Observed side effects (WHO grade 1-4) were fewer in 4 pts. (1 with hypotension), pain in involved lymph nodes in 2 pts., and a maculopapular rash after the last infusion in 1 pt. Response: In 15 evaluable patients treated with up to 6 mg/m² for four times 1 CR (at 6 mg/m², for 3+ months) 1 PR (at 4 mg/m², for 3 months), 2 MR (at 1 and 2 mg/m², for 2 SD after previous progress, at 5 mg/m², for 5+ and 6+ months), 1 trend response, and 8 progressive diseases have been observed. Immuno- histology: HAMAs were positive after 4 wks. in 7 out of 9 cases tested so far. All 4 pts. reexposed to the BiMAB showed an allergic reaction, prevention was achieved by pretreatment with prednisolone. Average number of NK-cells and of all lymphocyte subsets were considerably decreased pretreatment without any consistent changes under therapy. Conclusions: CD16/CD30 BiMABs represent an encouraging alternative for the treatment of refractory HD. Further studies are necessary to optimize the substrate of this novel immuno- therapeutic approach in a patient population which often has a pronounced defect in immunological effector cells, e.g. by combined treatment with IL-2 or IL-12.


1. Registre Général des Tumeurs du Calvados, 2. Centre François Baclesse, CHU Hématologie, 14021 Caen, France.

Purpose: To evaluate the influence of medical sequelae on Qol. of long term HDS.

Patients and Methods: In 1993, a population based case-control study was performed including 93 HDS (treated from 1978 to 1996, free of relapse and second malignancy since January 1991) and 186 population controls. The EORTC QLC-C30 core questionnaire evaluating Qol and a second questionnaire exploring factors influencing Qol were completed. Average number of NK-cells and of all lymphocyte subsets were considerably decreased pretreatment without any consistent changes under therapy.

Results: HDS characteristics were: M/F ratio 1.5; mean age 42 years (23-85); localized disease with 67% (64% uni-or-bi-dural). Initial treatment consisted of RT (98%), associated CT in 6% of cases. CT included MOPP (51%), MOPP-like (16%), ABVD (16%), MOPP/ABVD (13%) and EBVP (4%) regimens. 52% (56%) late sequelae were reported in medical records; 38 pts (41%) had two and 16 pts (17%) had three complications. Median time to first complication was 43 mos (8-148). Major complications (22%) occurred heart and vessels (n=5), lung (n=3), sepsisemia (n=2), lympho-nodal disorders (n=1) and nervous breakdown (n=1). Overall, sequelae were not influenced by CT (p=0.94). Most complications (46/52) were observed after MOPP or MOPP-like CT. Sterility (n=7) was associated with ALL and MOPP. All cardiac and lung complications were reported in pts who had irradiated. Pts with pulmonary sequelae more often reported physical dyspnea (p=0.03), role (p=0.01), cognitive (p=0.004) functioning impairments, fatigue and dyspnea (p<0.001). Pts with cardiac sequelae more often reported role impairments (p=0.025) and dyspnea (p=0.05). The six pts with psychiatric disorders more often related physical, role, emotional, social functioning impairments (p=0.01) and fatigue (p=0.01). Medical consumption, however, was not increased in pts with late complications.

Conclusion: This study demonstrates that QoL of French long term HDS highly correlates with late complications which should be detected through careful and regular follow-up examination, even long time after treatment.

Acute and late toxicity of an intensive regimen for advanced Hodgkin's disease (HD): VEBEP plus involved-field radiotherapy (IFRT) J. Bierley, A. Radmell, M. Gospodarowicz, A. Munn, S. Sutcliffe, M. Pinhile and the PMH Lymphoma Group. Department of Radiation Oncology, University of Toronto, Princess Margaret Hospital, Toronto, MSG 2M9, Canada.

A cohort of 611 patients with HD treated at our institution between 1973 and 1984 was reevaluated. 460 were alive and were assessed. A total of 363 (79%) replies were received; 251 had received RT alone, 111 combined modality therapy (CMT), 4 chemotherapy alone. The median time from diagnosis to the survey was 11.4 years (range 7-18 yrs). Of 611 patients, 151 died, 90 of DOD with HD and 21 an interval disease from other sources. Overall survival and cause specific survival were 70% and 82% at 15 years. Twenty patients died of second malignancy, 14 of heart disease, and 9 from respiratory disease. There were 37 cases of second malignancy (11 hematological skin and breast, 1 heart, 1 liver). The overall survival and cause specific survival were 70% and 82% at 15 years. Twenty patients died of second malignancy, 14 of heart disease, and 9 from respiratory disease. There were 37 cases of second malignancy (11 hematological skin and breast, 1 heart, 1 liver). The overall survival and cause specific survival were 70% and 82% at 15 years. Twenty patients died of second malignancy, 14 of heart disease, and 9 from respiratory disease. There were 37 cases of second malignancy (11 hematological skin and breast, 1 heart, 1 liver). The overall survival and cause specific survival were 70% and 82% at 15 years. Twenty patients died of second malignancy, 14 of heart disease, and 9 from respiratory disease. There were 37 cases of second malignancy (11 hematological skin and breast, 1 heart, 1 liver). The overall survival and cause specific survival were 70% and 82% at 15 years. Twenty patients died of second malignancy, 14 of heart disease, and 9 from respiratory disease. There were 37 cases of second malignancy (11 hematological skin and breast, 1 heart, 1 liver).
4. Non-Hodgkin’s lymphoma

MALE REPRODUCTIVE POTENTIAL IN HODGKN’S DISEASE - PRETREATMENT FINDINGS IN 124 PATIENTS

Introduction: Patients receiving chemotherapy for HD are expected to present inadequate semen quality after treatment. In general, these alterations are attributed to toxic effects on the germinal epithelium caused by alkylating agents. We investigated semen quality and hormonal status before chemotherapy or radiation in 124 male patients newly diagnosed HD. The intention was to explore whether gonadal failure was primarily related to toxic regimen or if the disease itself caused testicular inadequacy.

Patients and methods: In a multicentric setting testicular function was assessed in 124 male patients with first diagnosis of Hodgkin’s Disease. 44 subjects were under 50 years of age (median 28, range 18-49). Ann Arbor-classified patients were subdivided in three groups according GHSG treatment protocols HD7-0: 17 patients entered GROUP 1: CS I A/B II A/B without Riskfactors a-e (RF)*. 43 patients were classified GROUP 2: CS I A/B II A/B with RF a-e, CS II B with RF d-e and CS III A without RF. 64 of the subjects showed criteria for GROUP 3: CS II B with RF a-c, CS III A with RF. CS III B and CS IV A/B. Data was correlated to age, stage, A/B-symptoms and histology. Semen analysis was performed according WHO guidelines, after a period of 3-5 days of abstinence.

Results: We found in GROUP 1 (n = 17) 7 patients with normozoospermia and 10 dyspermic patients with single or combined pattern. In GROUP 2 (n = 43) 14 patients showed normozoospermia, 26 patients showed dyspermia - 6 patients with OAT-syndrome. 1 patient was azoospermic. In GROUP 3 (n = 64) we found 14 patients with normozoospermia, 50 patients showed dyspermia - 10 patients with OAT-syndrome and 0 with azoospermia.

Of a total 124 patients dyspermia was found in 89 (71.7 %) of our collective before the onset of treatment.

Conclusion: For patients with Hodgkin’s Disease there is an increased risk for inadequate semen quality even before treatment. Further investigations have to be performed to clarify the mechanisms inducing pretreatment fertility defects in Hodgkin’s Disease patients.

* Riskfactors: a- large mediastinal tumor, b- extranodal involvement, c- massive spleen involvement, d- ESR > 50 mmm (A), > 30 mmm (B) and e- more than three lymph node areas involved.

Department of Internal Medicine I, University Cologne

MALIGNANCIES IN THE FAMILIES OF 60 PATIENTS WITH NON-HODGKN LYMPHOMA (NHL)
W.Weber and A.Zehnder, Clinical Cancer Research Unit, Private Practice for Medical Oncology, Heugberg 16, CH-4051 Basel, Switzerland

Non-Hodgkin lymphoma is the most frequent lympho-hematopoetic malignancy. Its incidence is increasing in industrialised countries. Familial NHL has rarely been reported, and no pattern of inheritance has emerged.

A family history has been elicited with a structured questionnaire in a representative sample of 50 patients with NHL = probands: 29 female and 21 male; median age at diagnosis: 61 years, range 39-86 years; 34 diffuse, 11 nodular and 5 mixed

Analysis of familial clustering is performed by comparing tumor prevalence and spectrum in the families with tumor prevalence and spectrum in the population. The computer program DISEASES contains the data of the population-based Basel Cancer Registry (Head: Prof. P. Gubler). It allows calculations with small numbers by a Markov chain Monte Carlo procedure.

23 (46%) of the probands had one, 13 (26%) had two or more first degree relatives with malignancies. 55 of the 505 first degree relatives were affected (no increase as compared to the general population).

The following malignancies were overrepresented in first degree relatives at p<0.05: gynecologic malignancies in female (n=8), leukemia in female (n=4), esophageal cancer in male (n=4), stomach cancer in female (n=3) and larynx cancer in male (n=3). Lung cancer (n=7) and breast cancer (n=4) prevalence was not increased.

The spectrum of malignancies overrepresented in first degree relatives of NHL patients points to interactions of viral infections with genetic immune dysfunctions.

THE INTERNATIONAL PROGNOSTIC INDEX IN LOW-GRADE NON-HODGKN’S LYMPHOMA: WORKING FORMULATION GROUP A: RETROSPECTIVE ANALYSIS OF 137 CASES FROM THE GILS REGISTRY


*Dipartimento di Emato-Oncologia, Azienda Ospedaliera ‘Bianchi-Melacrino-Morelli’, Reggio Calabria, Italy

In order to investigate the value of the International Prognostic Index (IPI) (Shipp M et al, N Engl J Med 329:987,1993), originally proposed for aggressive non-Hodgkin’s lymphoma (NHL), in low-grade nonfollicular histologies, we retrospectively evaluated the outcome of patients at GILS institutions. From 1988 to 1993, 246 patients with NHL, Group A according to the Working Formulation, were reported to the GILS registry; 137 cases were evaluable with the following distribution in the IPI risk groups: low risk (L): 25 cases (18%), low-intermediate (LI): 64 cases (47%), high-intermediate (HI): 39 cases (29%), high (H): 9 cases (6%). The overall survival was significantly different in the 4 risk categories (p=0.0001) with 73%, 54%, 59% survival at 80 months for the L, LI, HI groups, respectively: II risk patients showed a median survival of 7.5 months. The similar behaviour of intermediate risk patients suggested a simplified stratification in three groups, high, intermediate and low risk, which displayed a significantly different overall survival (p=0.0001). The impact of both original and simplified IPI on low-grade nonfollicular NHL survival was confirmed by multivariate analysis. In conclusion, our experience the IPI stratification is prognostically valid for low-grade nonfollicular lymphoid neoplasms; in addition, a simplified classification in 3 risk groups can be useful in these histologies to choose among different therapeutic options, such as no treatment, conventional or aggressive therapy.

THE INTERNATIONAL PROGNOSTIC INDEX FOR AGGRESSIVE LYMPHOSS IN USEFUL FOR LOW GRADE LYMPHOMA PATIENTS? APPLICABILITY TO STAGES III - IV PATIENTS

C. Foussard, B. Desablain, L. Sensobo, S. Francois, N. Milpied, E. Deconinck, V. Delwail, J. Dupuy, T. Lamy, C. Ghandour, A. Le Mevel, M. Malsonneuve, P. Casassus, P. Colombat for GOELAMS Group (France)

The International Prognostic Index (IPI), based on age, disease stage, serum lactacid dehydrogenase (LDH) level, performance status, and number of extranodal sites of disease, is a widely used predictive model for aggressive Non-Hodgkin’s Lymphomas (NHL). Both prognosis and clinical course of Low Grade NHL are highly variable and currently available prognostic factors are not fully satisfactory. Management of these low grade lymphomas is not clear and clinical prognostic-factor models are required to identify specific risk groups.

The IPI was applied to patients with disseminated stages III and IV) NHL, including mantle cell lymphoma, enrolled in a prospective multicentric trial. According to their tumor burden, patients received, delayed or not, the same polychemotherapy regimen consisting of cyclophosphamide, etoposide, vindesine and prednisone, given monthly for six cycles. Among 220 patients treated from 7/87 to 12/93, 160 had initial data necessary to complete the International Index and were included in the study. Patients were assigned to one of four risk groups on the basis of their number of presenting risk factor: 0 or 1, low risk (1); 2, low-intermediate risk (2); 3, high intermediate risk (3); 4, high risk (4).

Patients age at diagnosis and follow up were respectively 64 years and 54 months (range 24 - 105), 134 patients being > 60 years old. The median overall survival duration was > 70 months. Survival curves (Kaplan-Meier method) demonstrated a high significantly difference for the 4 groups (logrank: p<0.0001). Median survival for the low risk group (1): 78 months has yet to be reached, while that for the three other groups are respectively: 65 months (logrank: 2-44 ps), 34 months (3 group: 4-44 ps), and 12 months (4 group: 14-78 ps). The survival rates are also statistically different for each of the 4 factors of the IPI:

- age: <60 vs >60 (logrank: p<0.002).
- performance status: 0 vs 1 > 1 (logrank: p<0.0001)
- LDH levels: normal vs anormal (logrank: 0.0001).
- extranodal involvement: 0 vs 1 > 1 (logrank: p<0.0001)

In this study the IPI has been found an important prognostic tool in NHL and may be used in the selection of appropriate therapeutic approaches for individual patients.
Kinetics of leukemic dissemination in Non Hodgkin's lymphomas after ablative chemotherapy and peripheral stem cell support. Pachmann K., Roedelken E., Schubel B., Adler A., Straka C., Emmerich B.

In B-cell Non Hodgkin's lymphomas peripheral dissemination obviously is more common than previously assumed. A situation where potentially all lymphoma cells are eliminated from the periphery would allow to study the kinetics of leukemic dissemination. Therefore peripheral blood B-cell counts were monitored prospectively by flow cytometry in patients treated for advanced lymphoma with high dose chemotherapy (busulfan/ cyclophosphamide) and peripheral stem cell support. Patients which relapsed within one year were compared to patients which are still in complete continuous remission (CCR). In four patients remaining in CCR peripheral B-cell counts started from 1-2% and followed the kinetic of an asymptotic curve levelling off at about 10% of lymphocytes with a correlation coefficient of 0.9 indicating an extremely exact maintenance of normal peripheral B-cell proportions. In contrast, in patients which relapsed, the previously normal B-lymphocyte line rose continuously from 1-2% at the time of peripheral stem cell transfusion until relapse with a doubling time of about 90 days indicating that the increase was due to dissemination of the malignant B-cells. This was verified by Southern Blot and PCR analysis. The increase followed a second order exponential kinetic which was very uniform in all patients with a correlation coefficient of 0.85 indicating some sort of synchronization and was confined to patients with relapses.

Patients at risk are now under investigation in order to disclose whether monitoring of peripheral B-cell counts may contribute to clarify a) to what extend leukemic dissemination of lymphoma cells accompanies or precedes relapse, b) whether leukemic dissemination is correlated with the treatment of the lymphoma cells and c) whether such studies can provide insight into the growth kinetics of the malignant B-cell clones.

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WATCH AND WAIT POLICY FOR PATIENTS WITH NON HODGKIN'S LYMPHOMA CLINICAL STAGE I OR IE WITH NO LYMPHOMA LEFT FOLLOWING DIAGNOSTIC SURGERY


A subset of patients with non-Hodgkin's lymphoma with clinical stage I or IE at presentation is left without other obvious lymphoma localizations following surgery performed for diagnostic purposes (histology). It remains controversial whether to treat these patients with either locoregional radiotherapy or chemotherapy or to adopt a watchful waiting policy. Since 1988 we have adopted a watch and wait policy for these patients. From 1988 to 1993 we have observed 50 patients with no remaining signs of lymphoma following diagnostic surgery, 23 males and 27 females, median age 59 years (range 23 - 82). The median observation time is 43.5 months (range 6 - 96). The initial lymphoma localizations were: solitary supraclavicular lymph node (cervical or axillary) in 18 patients, inguinal or scapular lymph node in 8, tonsil in 12 and skinetibuctis in 12 (cutaneous T-cell lymphomas were not included). According to the Working formulation 9 patients had low-grade histology, 26 had intermediate grade, and 15 had high-grade (immunoblastic) histology. Within the observation period lymphoma relapses occurred in 10/50 patients (20%), 8 within the first year of observation and 2 after 26 and 30 months; in relapse the lymphoma clinical stage was I or IE in 4/10 and III in 6/10 patients. Relapses were observed in 1/18 patients with initial supraclavicular nodal in 3/8 with inguinaltibuctis, in 2/12 with cutaneous and in 4/12 with tonsilar localization (no difference with the Fischer exact probability test). According to histology, relapses occurred in 2/9 patients with low grade, 3/25 with intermediate grade and 5/15 with immunoblastic histology (no difference with the Fischer test). According to clinical stage at relapse patients were treated either with locoregional radiotherapy or chemotherapy. Four patients subsequently died of lymphoma. At the moment 46/50 patients (92%) are alive and lymphoma free. Thus it seems that the majority of patients as described in this study has an excellent prognosis and would not benefit from additional therapeutic procedures following diagnosis of non-Hodgkin's lymphoma.

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S-CA125 AND LDH LEVELS AS A NEW PROGNOSTIC INDEX IN PATIENTS WITH NON HODGKIN'S LYMPHOMAS.


CA125 serum level (s-CA125) was measured by radioimmun assay (CIS international) at diagnosis in 137 patients with non Hodgkin's lymphoma (NHL). There were 74 men and 63 women with a mean age of 57 years (range 16 - 80 years); fifty three patients were low grade and 87 high grade NHL. Ann Arbor stage was: IV in 71 patients (51.8%) of which more than one extra nodal site 1. III in 20 cases, 6 in 22 cases, and in 24 cases. B-lymphomas were present at diagnosis in 32 patients and a bulky tumoral mass was found in 34 patients. All patients were homogenously treated according to the GOLMANS protocols. s-CA125 was abnormal (> 30 U/ml) in 87 patients (44.5%). s-CA125 level was closely related to the stage of the disease. In stage I, only 10 patients (7.8%) had high s-CA125 levels whereas 47 patients (36.7%) had an abnormal dosage in stage III-IV patients (p = 1x10^-7). LDH levels were also related to the stage of disease. In stage I, only 8.1% of patients had elevated levels whereas 37.0% had abnormal levels in stage III-IV patients (p = 7x10^-5). B2 microglobulin (B2) levels were also related to the stage of disease. In stage III, none of the patients had elevated level whereas 26.3% had an abnormal dosage in stage III-IV patients (p = 1.6x10^-5). None of patients with stage II had both elevated s-CA125, LDH and B2 levels increase, opposite to 31.3% of patients with stage III-IV disease (p = 2x10^-5). No difference was observed according to histological grade. 125s were evaluated in response to induction therapy (Table 1). Complete remission (CR) rate was found significantly higher in patients with normal s-CA125 or LDH levels than in other patients. When taking both markers together, patients with normal LDH and s-CA125 levels responded better to therapy than patients with normal s-CA125 and elevated LDH levels and much better than patients with both elevated markers. We conclude that the combination of s-CA125 and LDH is a good prognostic index in patients with NHL.

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CR: complete remission; PR: partial remission; N: normal; A: Abnormal.

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SIGNIFICANT PROLONGATION OF DISEASE FREE INTERVAL IN ADVANCED LOW GRADE NON HODGKIN LYMPHOMAS BY INTERPERON Lymphomas MAINTAINANCE AND ITS RELATION TO INITIAL CYTOTOURETIVE TREATMENT


The current multicenter study was initiated to address two major questions in the treatment of advanced stage low grade Non-Hodgkin's lymphomas (NHL): 1. the activity of two different cytotoxic regimens and 2. the impact of interferon alpha (IFNα) maintenance. Patients with advanced stage III and IV B-cell center lymphomas (TCL) = centroblastic centrocytic NHL according to the Kiel classification and mantle cell lymphoma (MCL) = centrocytic NHL were randomized to initial therapy with either prednimustine/interferon (PnM) or cyclophosphamide/vindesine/procarbazine (CVP). Responding cases underwent a second randomization for IFNα or observation only. In contrast to other studies IFNα was given without a fixed time limitation until relapse or toxicology at a dose of 5 x 10^6 Uid 3 x weekly with dose adjustment to side effects. Until January 1995, 419 patients were randomized for initial cytoreductive therapy; 85% of the evaluable patients achieved a complete or partial remission. After induction therapy overall response rates were equal for PnM (85%) and CVP (86%) but significantly more CR were obtained after PnM (73%) vs. 22% (p<0.003). 247 cases were randomly assigned for IFNα vs. observation only. As of June 13 randomization was terminated because the sequential Logrank-Test, used for the monitoring of the study, indicated a significant advantage in favor of IFNα. In the IFNα group median DFS estimated according to the proportional hazard assumption is 37 months as compared to 20 months in the control (Logrank-Test: p<0.003) and the projected DFS at 4 years accounts to 49% versus 27%, respectively. Analysis of IFNα in association with initial cytoreductive treatment shows a tendency to a more beneficial outcome for the patients plus IFNα combination with an estimated median DFS of 45 months as compared to an estimated median DFS of 31 months for COP plus IFNα and median DFS of PnM or COP only of 21 months and 16 months, respectively. These data indicate a significant prolongation of DFS by IFNα maintenance and strongly suggest that this effect is associated with the degree of initial cytoreduction.

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4. Non-Hodgkin's lymphoma
INTERFERON ALPHA2B AFTER POLYCHEMOTHERAPY (mBCGACO) IN THE TREATMENT OF LOW AND INTRACRANIAL GRADE NON HODGKIN Lymphomas (mBCGACO) in patients with histologic nodular pattern and achieving significant partial remission: RESULTS OF A MULTICENTER STUDY.


Interferon alpha and chemotherapy are reported to have effects in patients with non-Hodgkin lymphomas. A double blind study was designed in order to evaluate the possible benefit of administration of recombinant interferon after a polychemotherapy (mBCGACO) in patients with low and intermediate grade into.

MATERIAL AND METHODS

213 (122m/105p) patients with NHL (64 according /504 according to working formulation -WF-) were enrolled. 114 pts (49.6%) with II G NHL (22 pts of WF), 104 pts (44%) with III G NHL, and 13 pts (5.8%) with intermediate unspecified NHL. The mean age was 56.4 years (17.40). 147/151 pts had an advanced disease (III -IV stage -72.8%). All the patients were treated with 4 courses of mBCGACO. If patients achieved CR, they underwent 2 courses of CHOP and then were randomized in two groups: first one (81) underwent maintenance treatment with alpha2b IFN 3x106 UI i v twice a week for 12 months (46 pts); the second one (32) was followed up (42 pts). If patients, after 6 cycles of mBCGACO, achieved significant partial remission (PR; partial remission >70%) were randomized in two groups: the first one (81) was treated with alpha2b IFN (1x106 IU i v 3x a week) for 12 months (28 pts); the other one (32) was treated with alpha2b IFN (same dosage) associated with 2 courses of mBCGACO and then only with alpha2b IFN for 12 months (32 pts). The mean follow up was 22.1 months.

RESULTS

After 4 mBCGACO courses 26 patients got out of the study (3 for death; 8 for no compliance to the therapy and 15 too "early" for evaluation). In the valuable 205 patients we observed 90 CR (43.9%), and 63 PR (30.7%). CR+PR=74.9%. The responses related to histologic pattern were: "nodular" CR=51.9%, PR=39.1% - "diffuse" CR=45.8% and PR=54.5%. 10 relapse have been observed in the 83 CR (12.1%) (Progression Rate (PR) -9.8%, Disease Free Survival (DFS)-24.4%) and 6 in the 82 CR (7.4%, DFS=20.3%). There was no significant difference between the 2 groups 63 and 83 concerning the RR and the DFS. 15 disease progressions have been observed in the 81 group (Progression Rate (PR) -33.5%; freedom from progression - FFP=21.0%) and 12 in the 82 group (PR=37.5%, FFP=25.4%). We did not observe a difference in terms of RR and FFP between the 81 and 82 groups. A significant statistical difference between 81 and 82 has been observed in the pts with nodular-pattern - 9 vs 37{p<0.05} and in pts with less than 2 prognostic factor, according to TSS definition - 16 vs 35 months (p=0.025).

CONCLUSION

Alpha2b IFN shows some effect in pts with NHL in i v infusion, the association (CRT+IFN) gives better progression-free and longer freedom from progression in patients with less than 2 prognostic factors and nodular pattern at diagnosis.

PROLONGED FAILURE-FREE SURVIVAL IN ADVANCED-STAGE INDOLENT LYMPHOMAS TREATED AT DIAGNOSIS WITH AN INTENSIFIED HDS CHEMOTHERAPY PROGRAM.


Combined use of hematopoietic growth factors along with mobilized progenitor cells (PBPC) has widened the applicability of high-dose sequential (HDS) regimen and G-CSF support in patients with indolent lymphomas at diagnosis. So far, 35 pts aged less than 60 years have been enrolled; histology according to WF was: A: 10 pts, B through D (16 pts), discoid nodular/diffuse (9 pts). Patients had stage III-IV disease. 29 had overt marrow involvement; 18 had bulky disease and 18 presented with tumor-related symptoms. The initial 5 pts received the original HDS, while the remaining pts received an intensive dualbing (2 full-dose APO courses ± 2 DHAP courses), and then the modified HDS as follows: VPI (2 g/m²) --> MTX (8 g/m²) --> dexamethasone --> CTX (7 g/m²) followed by PBPC harvest; finally, mitoxantrone (60 mg/m²) + L-PAM (100 mg/m²) PBPC autologous were delivered. Seven pts are currently under treatment, 2 are evaluable. There were 2 treatment-related deaths due to cerebral hemorrhage in a patient on oral anticoagulants for DVT, during APO and in the only patient grafted with BM cells, during recovery after autograft. CR was achieved in 21 pts (75%); highest responses were observed among follicular (82% CR) and discordant (98% CR) histologies. Response was durable and the 5 year projected DFS is 75%, with 11 pts in CRC in 2 and 5 years. Preliminary PCR-based molecular analysis failed to detect minimal residual disease in approximately 50% of the tested patients. Thus, in indolent lymphoma a front-line HDS-based approach: i) does not imply increased risk of tumor progression; ii) may induce long-lasting tumor regression.

DOES COMBINED-MODALITY THERAPY (CMT) OF LYMPHOMAS INCREASE THE ACUTE TOXICITY OF RADIATION THERAPY ? RESULTS OF A 2-YEAR PROSPECTIVE AUDIT.

R. Tsang, M. Gospodarowicz, S. Sculier, W. Wells, A. Berajka, J. Breyer, L. Lenz and the PMH Lymphoma Group, Princess Margaret Hospital, Toronto, Canada.

The standard treatment of many patients with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) consists of chemotherapy (CT) followed by low-dose radiation therapy (RT).

With the combination of chemotherapy and radiation therapy, we performed a prospective study from April 1992 to April 1994. Weekly assessment of acute radiation toxicity was performed using the Radiation Therapy Oncology Group (RTOG) acute toxicity scale, for the organ systems included in the RT fields. There were 134 patients (HD: 51, NHL: 82; total 144 courses of RT) with 101 courses of RT preceded by CT (CHOP: 47, ABVD or MOPP/ABVD: 59, others: 15), while 43 courses were not. The most common RT techniques were: mantle (52%), upper abdomen (18%), neck (29%), inguinal-pelvic (18%), and inverted Y fields (12). The duration from completion of CT to RT was 4-6 weeks. There was no difference in RT dose in patients given CT versus those that were not (range: 20-35 Gy; median: 35 Gy). The mean peak reaction score, proportion 2 grade 1 or 2 toxicity for each organ system were compared between these two groups. In general the toxicity was mild (no grade 4) and only 2 patients required a 1-week interruption of RT due to myelosuppression. The proportion of patients with grades 10/15% toxicity were: Dryness of mouth 54/15%, 5%, pharyngitis-esophagitis 51/10%, skin erythema 38/6%, mucositis 37/5%, anorexia-nausea 23/16%, diarrhea 19/17%, laryngitis 23/5%, cough-dyspnea 13/6%, lassitude 11/13%, and thrombocytopenia 79/84%. There were no significant differences in the mean reaction score between the CT-treated patients and those that received RT alone. This was also the case for the proportion 2 grade 1 or 2 toxicity, except for cough-dyspnea where RT alone gave more frequent 2 grade 1 toxicity (9/15 for RT vs 8/35 for CMT, p=0.02). When the comparison was restricted to the patients treated with the mantle technique, no significant differences were seen between the two groups (CMT, 34 patients; RT, 18 patients). In conclusion, the acute radiation toxicity of patients treated with combined CMT is mild and not different from a comparable group of patients treated with RT alone. A comparison of late radiation effects (e.g. salivary, pulmonary, thyroid and cardiac function) in these two groups will be desirable.
TREATMENT (RX) OF RELAPSED NON-HODGKIN'S LYMPHOMA (NHL) USING THE 90-14TTRIUM- (90-Y) LABELLED ANTI-C2D MONOCLONAL ANTIBODY (MAB) H 4-2B8: A PHASE I CLINICAL TRIAL (P1 CT)


Radio iodine (131-I) labeled antibodies to B cells have proven effective in the RX of relapse low-grade/intermediate-grade (LD/IG) NHL. 90-Y radiations appear to be superior to 131-I higher energy, pure 8 emissions, longer 8 path length (5-10 mm), shorter 8 (64 h) and allows for outpatient RX where 131-I requires inpatient RX with isolation in isolation rooms. Specific characteristics of 90-Y result in deposition of a larger proportion of the radiolabeled (90-Y) doxorubicin (DOX) in tumor tissue compared with 131-I. Anti-C2D MABs produce good imaging, biodistribution, and clinical activity. We have developed a murine anti-C2D MAB (Idec 2B8) to the 2C2D antigen present on most B- and T-HL NHLs (> 93% are 2C2D-). In this P1 CT, "cold" Idec 2B8 was given prior to imaging to block peripheral blood 2C2D sites and improve biodistribution, reduce spleenic uptake, and reduce urinary excretion of the radiolabeled MAB. It was used with indium (111-In) for imaging and dosimetry (Idec-111In-B28) and with 90-Y for therapy (Idec-90Y-B28). Seventeen patients (pts) were registered: 13 males/females, aged 50 yrs, 12 LG and 5 IG, 16 stage IIIIIv in diagnosis, mean of 2.8 previous chemotherapy (CRX). Mean duration of radiation to last CRX was 3.5 months (mos). Extranodal disease was present in 12 pts. Fourteen of the 17 pts were RX with single doses of Idec-90Y-B28: 3 at 20 mCi, 5 at 20 at 30 mCi, 3 at 40 and 4 at 50. A total of 202 adverse events were reported, 179 were hematological and 66 were grade 3 or 4; 44 at the 50 mCi dose, 44 at 40, 80 at 30, and 54 at 20. There is a trend for deeper nodes and longer time to recovery for pts at higher doses on a mCi/kg basis (~ 0.6 mCi/kg). At the 50 mCi dose level (MTO) all 4 pts had grade 4 toxicities (thrombocytopenia, neutropenia) and 2 required PBPC stem cell support (Idec-90-Y). Pts at levels below 30 mCi do not require PBS-S. At the 40 mCi dose, 2 of 5 pts had grade 4 toxicity but did not require PBS-S. The dose for phase 1 (with PBS-S) is ≤ 40 mCi. There were 4 complete (CR) and 3 partial (PR) responses. Five pts had stable disease (SD) > 2 yrs. 2 had 50% tumor shrinkage but progressed within 3.5 mos. Timo to progression for the 9 responders ranges from 5.9 to 14 mos. with a median of 7.4 mos. (1 pt still ongoing). Three pts (2 at SD RX and 1 at 40 mCi) had transient PN. 2 had a PR (7.1, 14.8 mos) and 1 SD (1.6 mos). One of the 2 rec pt re-gained PBS-S. Single doses of Idec-90-Y-B28 show clinical activity comparable to that of intensive salvage CRX and in this study produced radiation dose exceeding those of 93% prior CRX. Single doses of Idec-90-Y-B28 produce predictable and manageable myelosuppression compared to the recurrences experienced with each cycle of CRX. Broader patient experience will further characterize the safety and efficacy of this promising new treatment.

4. Non-Hodgkin's lymphoma

PRIMARY NON-HODGKIN'S LYMPHOMA (NHL) OF THE MEDIASTINUM: REPORT OF 68 CASES

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68 consecutive patients (pts), aged 18-68 years (median 37) with primary mediastinal NHL have been treated from 1978 to 1992 in our institution. Sex ratio (MF) was 1:1. At diagnosis, clinical symptoms were superior venous cava syndrome (31%), mediastinum involvement (25%), B symptoms and weight loss (15% in 23 cases). Bulky mediastinal disease (> 10 cm) was observed in 100% cases or thoracic CT scan. 11% were stage I, 47% were stage II and 42% were stage III(IV) according Ann Arbor classification. LDH level at diagnosis was studied in 49% of pts and were elevated in 80% cases. Historical review could be done in 61 cases. 54/61 had large cells associated with small cells NHLF; G, H according to the working classification). Sclerosis was present in 17 cases. Treatment consisted in radiotherapy alone 1 case, combined chemotherapy always containing an anthracyclines plus radiotherapy (CMT) 59 cases, chemotherapy alone 7 cases, no treatment case 1 (death before therapy). 80% of pts treated with chemotherapy achieved an objective response (>50% reduction of the tumor mass). Among the 7 pts treated with chemotherapy alone none achieved a complete response (CR). 4 were primary refractory and the other 3 pts had a partial response and relapsed. 59 pts were treated with CMT, 4169 achieved a CR. DFS is 78% at 1 year and median DFS is 49 months. 59/61 pts were primary refractory or relapsed (after a mean CR duration of 4 months). At relapse, disease was present in the mediastinum (90%), cervical or supraclavicular lymph nodes (25%), kidneys (13%). None of the pts treated with salvage chemotherapy achieved a durable CR. The majority of NHL represent a distinctive subtype of NHL of favorable prognosis when treated with combination chemotherapy plus radiotherapy. Pts primary refractory or who relapsed after first line chemotherapy have a poor prognosis.
10 YEAR OUTCOME OF 12 WEEK DURATION CHEMOTHERAPY FOR ADVANCED LARGE CELL LYMPHOMA: THE VANCOUVER EXPERIENCE.


471 patients, aged 16-70, with advanced stage diffuse large cell lymphoma (B symptoms, bulky > 10 cm and stage III or IV) were treated with one of three consecutively defined 12 week duration regimens: MACOP-B (n=127, 4/81-5/86); VACOP-B (n=246, 6/86-4/93) or ACOP-12 (n=198, 5/93-12/95). The backbone of the chemotherapy consisted of 1 drug, given every 2 weeks for 6 doses: doxorubicin 50mg/m², cyclophosphamide 350mg/m² and vincristine 1.2mg/m² (no cap) plus continuous prednisone 45mg/m² every other day with supportive citrovorum, keratoplasty and antimetabolites.

The regimen appears equally effective, although follow up differs: median for MACOP-B is 144 mc, VACOP-B is 87 and ACOP-12 is 16 mc. The 3 year overall survival (OS) were 64% (MACOP-B), 70% (VACOP-B) and 72% (ACOP-12) n = NS. The 3 year disease specific survival (DSS) were 60%, 72% and 77%, n = NS. Within the subgroups defined by the International Prognostic Index (IPI) all the survival were similar. Fatal toxicity by regimen was MACOP-B (6%), VACOP-B (2%) and ACOP-12 (0%).

Pooled survival results for the 471 patients are:

<table>
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<tr>
<th>Group</th>
<th>n</th>
<th>5yr</th>
<th>7yr</th>
<th>10yr</th>
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<td>66</td>
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<td></td>
<td>100</td>
<td>33</td>
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</table>
| * (number of adverse factors; DSS; n = no. of patients)

The risk of death from lymphoma diminishes with increasing time from diagnosis but deaths were still occurring up to 12 years. The cumulative rate of lymphoma related death (n=133) was 51% (5yr), 77% (7yr), 84% (10yr), 92% (15yr) and 98% (20yr).

These results demonstrate that there is still much room for improvement in outcome and that late lymphoma related deaths, contrary to common belief, are not uncommon.

LATE RELAPSES AND TOXICITIES IN ADVANCED STAGE DIFFUSE LARGE CELL LYMPHOMA (DLC) TREATED WITH MACOP-B: AN EIGHT YEAR FOLLOW UP ANALYSIS.


Introduction. Between June 1986 and December 1990 the IMMRNLG treated two hundred patients with advanced stage DLC, age < 61 years, with MACOP-B in a consecutive study (ICO 1992; 10:219). In this report we have analyzed late relapses and late toxicities. International Prognostic Index (IPI) was also verified in this series Patients and results: Median follow-up was 81 months. 71% achieved a CR, 12% PR, 12% NR and 5% died of acute toxicity. Among the 48 Pts or NRs only 9 were salvaged and are alive, 39 died (77% of lymphomas). Forty pts relapsed: 11 are alive in further CR and 29 died (34% of DLC). The DFS at 7 years is 69%. The relapse rate was 18% in the 1st year, 6% in the 2nd, 2% in the 3rd and 1% thereafter till the 8th year of follow-up. Only 4 relapses were observed after 3 years, the last one was at 90 months. Overall survival (OS) at 3, 5 and 7 years is 63%, 61% and 59% respectively. A second cancer occurred in 5 patients: 4 solid tumors (Head and neck, Gastric, Breast, Thyroid) and 1 ANHL. Four died of cancer (3) while in CR of the lymphomas. Five pts suffered from late cardiac disorders: 3 cardiomyopathies and 2 arrhythmias (2 were given mediasinal RT after MACOP B). Femoral head osteonecrosis was diagnosed in 7 patients with a median time of MACOP-B of 15 months, probably due to the prolonged steroid therapy used in this regimen. Moreover the age-adjusted IPI has been tested in this series with LSDL, PS and Stage used as prognostic factors as suggested to define the risk groups.

CR 60% DFS 50% OS 60%
SCORE 0 61 72
SCORE 1 71 67 67
SCORE 2 67 62 48
SCORE 3 50 44 28

The IPI proved to be an excellent prognostic scheme for CR or poor outcome is possible subdividing patients in only two prognostic groups. Score 0+1 (low risk) vs Score 2+3 (high risk) CR 79% vs 62%, DFS 73% vs 59%, OS 69% vs 43% (p<0.001).

Conclusions. These data obtained in a large series of pts with a long follow-up show that more than 50% of advanced stage DLC are alive and free of disease after MACOPB with few late relapses and toxicities. New therapeutic approaches need to be compare with these results.

THERAPY OF HIGH-GRADE NON-HODGKIN'S LYMPHOMAS WITH CHOP (CHOP + ETOPOSIDE) IN 14-DAY INTERVALS. A PHASE III MULTICENTER TRIAL OF THE GERMAN NHL-CONSENSUS TRIAL GROUP.

L. Trümper, Ch. Renner, M. Knoke, D. Hasenclever, K. Schubert, A.C. Feller, M. Loefler, M. Pfreundschuh, Dep, Internal Medicine 1, University of Saarland, D-66421 Homburg/Saar and Institute for Medical Informatics, Biostatistics and Epidemiology, University of Leipzig, D-04103 Leipzig, Germany

No major therapeutic advances have been made in the treatment of high grade non-Hodgkin's lymphomas (NHL) since the introduction of doxorubicin with the CHOP regimen (cyclophosphamide, vincristine, doxorubicin, prednisone) more than 20 years ago. Despite significant increases in dose intensity, third generation regimens have not lead to an improvement in therapeutic outcome in a large multicenter trial (Fisher et al., 1993). Therefore, the CHOP regimen is the current standard regimen for high-grade NHL. Since the treatment responses esp. for patients (pts) with high-intermediate and high risk prognosis are not satisfactory and novel drugs for this disease are lacking, improvement of current treatment protocols is warranted. Dose intensification by interval shortening (14-day instead of 21-day intervals) and addition of etoposide (100 mg/m², d 1-3, CHOP-regimen; Köppler et al, 1989) was shown to be effective and feasible in a phase II trial study (Trümper et al, 1994). The current phase III multicenter trial compares a biphasal statistical design to independently examine the effect of interval shortening and addition of etoposide on the failure-free survival of pts with low-intermediate risk high-grade NHL (<60 yrs of age) and all risk categories (>60 yrs). 550 pts have been randomized as of Jan. 31, 1996. 296 pts are evaluable for risk factor description, and 177 pts are evaluable for the toxicity of 6 cycles of chemotherapy (between 36 and 49 pts / treatment arm. 56% of pts were male, and 49% of pts were younger than 60 yrs. Risk factor description for 298 pts shows that 60.4% of pts > 60 yrs have 3 or more risk factors according to the International Index (Shipp et al., 1993). Analysis of treatment duration confirms that in pts treated with the CHOP-14-regimen followed by application of GC-CSR (d 4-13) recycling on day 15 is possible; therefore, the planned dose-intensity can be given even in elderly patients without undue toxicity.
PERIPHERAL T-CELL LYMPHOMAS RESIST WELL TO VINCristine, ADRIamycin, CYCLOphosphamide, PREDNISolone and EToposide (VACPE) and HAVE a SIMILAR OUTCOME AS HIGH GRADE B-CELL NON-HODGKIN’S LYMPHOMA

L Bergmann, T Karakas, H J Slurte, A Knuth, P S Mitrou and D Hoolter
Medical Clinic III, Hematology/Oncology, University of Frankfurt, FRG

Peripheral T-cell lymphomas (PTCL) represent a very heterogeneous group of T-cell malignancies. Previous treatment studies have yielded conflicting results about the outcome of T-cell lymphomas when compared to their direct B-cell counterparts. In a pilot phase II trial we tested the feasibility and response rate of an intensified chemotherapy on patients with T-cell lymphomas. Twenty-seven patients (age 18-77, median 53 years) with intermediate and high-grade T-cell Non-Hodgkin’s lymphomas (NHL) and 55 patients with high-grade B-cell NHL (age 16-69, median 53 years) have been included to the study. The histological subtypes of the PTCL were pleomorphic (14/27), large cell anaplastic Ki-1+ (6/27), angioimmunoblastic (2/27) and 3 other PTCL. They were treated with vincristin 2 mg i.v. d1, adramycin 25 mg/m2 i.v. d1-3, cyclophosphamide 800 mg/m2 i.v. d1, prednisone 60 mg/m2 p.o. d1-7 and etoposide 120 mg/m2 i.v. d1-3 (VACPE). This cycle was repeated every 3 weeks up to 5 cycles in stages I-Ill and 6 cycles in stage IV. The toxicity was moderate, only one early death due to lethal septicemia occurred. Twenty-six patients are evaluable for response, one patient is still under therapy. In 77% patients (pts) with PTCL and 84% of pts with B-NHL a CR was achieved. 75% of complete responders with PTCL and 70% with B-NHL are in still ongoing CR. The 1-, 3- and 5-year overall and disease-free survival for the T-cell group were 76%, 64%, 48% and 76%, 62%, 62%. Although PTCL presented with advanced stage of disease in a higher percentage (71% vs. 57%) and more risk factors according to the International index (2 3 risk factors, 63% vs. 53%), there was no significant difference regarding the remission rate, the overall-, event-free and disease-free survival compared to high-grade B-cell lymphomas. In conclusion, the VACPE regimen is an effective, feasible regimen in the management of PTCL and B-NHL achieving complete remissions in a high percentage of the patients.

THE NHL-15 PROTOCOL FOR DIFFUSE AGGRESSIVE LYMPHOMAS: 3.5 YEAR MEDIAN FOLLOW-UP ON THE FIRST 100 PATIENTS. J.P.O'Brien, P.O.Knorr, A Alvarez, N Roistacher, D Filippa, R Castellino, D Straus, J Yehabom, A D Zelomet, J B Bertino, C Portlock. Memorial Sloan Kettering Cancer Center, N.Y., N.Y. 10021

The NHL-15 protocol was designed to increase the dose intensity (DI) of doxorubicin (D), vincristine (V) and cyclophosphamide (C) by sequential administration of D 60 mg/m2 weeks 1, 3,5,6, 2.1 4.5 mg/m2 weeks 2,3 & 5 followed by C 2.5 mg/m2 weeks 3,4,5,6 & 7 with G-CSF 5 mg/kg days 3-8 after each cycle. Actual dose intensities achieved were D: 26 mg/m2 wk V: 8.53 mg/m2 wk and C: 1.46 gm/m2 wk representing 91%, 96%, and 97% of projected total doses of these drugs. An increase in dose intensity of 1.57, 1.38 and 1.82 fold for D, V and C, respectively, was achieved compared to standard CHOP. The first 100 patients (med. age: 45, range:17-71) are evaluable for complete remission rate (CR), remission duration (RD), freedom from progression (FFP) and overall survival (OS), with a median follow-up of 4 months (range: 32-58) from protocol entry. Ann Arbor Stage: I-1, II-34, III-15, IV-50. Histologic type: DCLL(including immunoblastic)-40, DML-10, FLC-6, DLSL-4. The 90 patients with DCLL or DML are grouped below by the International Prognostic Index (IPI) Groups (NEJM 329(14):987 1993) and predicted response rates [1] are presented for comparison. FFP for the IPI historical control groups, indicated by [ ], are estimates derived from the published CR and RD rates since actual FFP values were not published.

A PHASE I-II STUDY OF DOSE-escalating CHOP with CR WITHOUT G-CSF FOR AGGRESSIVE NON-HODGKIN’S LYMHPHOMA. T. Okawa, H. Wakita, T. Igashiki, K. Issho, H. Fujii and Y. Sasaki. Division of Oncology and Hematology, Department of Medicine, National Cancer Center Hospital East, 6-5-1 Kashiwa, Chiba 277, Japan

In 12/93 a phase I-II study of a dose-escalating CHOP was initiated to determine the maximum tolerated dose (MTD) of CHOP at 3 week intervals for 6-10 cycles with or without prophylactic G-CSF (Gag/150 or 500ug/150 cc). Cyclophosphamide (CPA) and doxorubicin (DOX) were escalated from 750 mg/m2 and 50 mg/m2 respectively, in cohorts of at least 3 patients up to MTD with the standard dose of vincristine and prednisolone. At first, MTD was determined without prophylactic G-CSF, next with prophylactic G-CSF (day 8). So far, goal of 29 patients was entered in the study. The major toxicities of the all cycles (cycle) were as follows:

<table>
<thead>
<tr>
<th>DOX CPA No.</th>
<th>WBC</th>
<th>Neut</th>
<th>Fever</th>
<th>PLT</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level (mg/m2)</td>
<td>cycle prevalence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>G4</td>
<td>G3-4</td>
<td>G4-2</td>
<td>G4</td>
<td>G4 Reduction</td>
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<tr>
<td>1</td>
<td>50</td>
<td>750 22 (3)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>1000 22 (3)</td>
<td>12</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>1000 24 (3)</td>
<td>12</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>1200 18 (3)</td>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>1200 26 (4)*</td>
<td>7</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>5G*</td>
<td>70</td>
<td>1250 18 (3)</td>
<td>1</td>
<td>2</td>
<td>1</td>
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<tr>
<td>6G*</td>
<td>70</td>
<td>1500 18 (3)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7G*</td>
<td>70</td>
<td>1750 18 (3)</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>8G*</td>
<td>90</td>
<td>2000 18 (3)</td>
<td>7</td>
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<td>5</td>
</tr>
<tr>
<td>9G*</td>
<td>90</td>
<td>2250 5 (1)</td>
<td>1</td>
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*: with prophylactic G-CSF; §, including 15 cycles of G-CSF prophylaxis

The MTD of CHOP at the 1st cycle was level 5 with dose limiting toxicities of persistent leucopenia and neutropenia without prophylactic G-CSF. With prophylactic G-CSF, DOX dose-escalating CHOP up to DOX 70 mg/m2 and CPA 2000 mg/m2 at 3 week intervals is feasible and further dose-escalation is on going. Although cumulative toxicities except cardinotoxicities were observed, six courses were irrelavable.

PROGNOSTIC FACTORS IN ELDERLY PATIENTS WITH NHL

G Hopfinger, N Worel, H Tuchler, R Waldner, E Pittermann, R Heinz, Med. Dept. and LBI for Leukemia Research and Hematology Hanusch Hospital, Austria

The International Index was described as a useful tool to predict risk with respect to survival. However, with the exception of age > 60 years and performance status, only lymphoma-related factors such as LDH, stage and number of extranodal sites were considered. To identify prognostic factors in elderly patients, we retrospectively analyzed clinical data of 813 patients suffering from NHL (excluding chronic lymphatic leukaemia). Overall 341 patients (44%) were under 60 years and 472 patients (56%) were > 60 years of age. The two groups showed no difference with regard to stage, elevated LDH, histology or number of extranodal sites. Elderly patients had a poorer performance status (p<0.05) and response rate was inferior (p<0.05). Overall survival was better in the younger population (p<0.05) with a median of 77 months compared to only 34 months. We evaluated multiformity as a summation of different factors such as renal and hepatic dysfunction, cardiac failure, coronary heart disease, vasculopathy and diabetes mellitus. A summation of these factors was significantly correlated to poorer OS but only slightly to DFS. In elderly patients multiformity has to be taken into account to assess individual risk for dose adjustment, response rate and survival. Influence as an independent risk factor should be considered and will be discussed.
From 1992, following our phase II study on Mitoxantrone and as a part of LEAP-C's trials, 139 untreated pts. with diffuse, large cell NHL (Groups F, G, H, I, K, E) in the over '50s, received CEP regimen. This new trial consisted of 6 cycles every 4 weeks. 111 pts. were in stage III or IV, and stage II was 11. The treatment was repeated every 3 weeks, for 6 courses. The median age was 71 years. 24 achieved PR (19.1%), 35 were NR, or underwent early progression or death (27.7%). Twenty-six patients (26.6%) received additional chemotherapy early in the same year. The major toxic effect was myelosuppression.

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COMPARATIVE EVALUATION OF MANTLE CELL LYMPHOMAS AND FOLLICULAR CENTER LYMPHOMAS AS DERIVED FROM A CLINICAL TRIAL OF THE LOW GRADE LYMOPHMA STUDY GROUP

The improved characterization of lymphoma cells by immunophenotyping and molecular analysis complement the morphologic discrimination of biologic subgroups and provided the basis for the Revised European American Lymphoma (R.E.A.L.) classification that was recently proposed. The current study aims at evaluating the clinical relevance of the new classification for the two subgroups of follicle center (FC) and mantle cell lymphomas (MCL). This analysis is based on a multicenter study of the German Low Grade Lymphoma Study Group comparing Prednimustine, Mitoxantrone (PmV) versus Cyclophosphamide, Vincristine, Prednisone (COP) for induction therapy followed by a second randomization in responding patients for interferon alpha maintenance versus observation in patients with advanced stages III and IV. From the 427 cases that entered the study between 6/88 and 5/94 histology was centrally reviewed in 234 patients;165 of the reviewed patients had FC and 43 MCL. While in MCL both sexes were almost equally affected (47.5% males, 52.5% females); the proportion of males was found in 78% males, 22% females). In addition, median age was significantly lower in FC than MCL (53 versus 64 years, p<0.0001). FC patients had a higher response to chemotherapy with 88% complete (CR) and partial (PR) remissions as compared to 69% CR + PR in MCL (p<0.05). Responding FC patients also experienced a significantly longer event-free interval with a median of 25 months as compared to 8 months only in patients with MCL (p<0.0001). Overall survival for all treated patients was also significantly different with the median not being reached in FC after a median observation time of 4.5 years and 1.7 years for conventional chemotherapy, the initial rituximab agents, systemic retinoids, relapses & death in relapsed patients. The (1;14)(q11;q32) (2) was found in 75% of MCL & 15% of FC.

Patients: 30 pts from 3 institutions (Grenoble, Montpellier and Nice) have been diagnosed as MCL according to the REAL classification and ELT recommendations. Tumor assessment is a prerequisite. MCL are a disease with a lot of immunophenotype. They usually express CD10 and CD23. Characteristic immunophenotype (CD5+, CD10+, 23+) seen in 90/95, 7/95 of the CD+ positive B-cells, the initial rituximab agents, systemic retinoids, relapses & death in relapsed patients. The (1;14)(q11;q32) (2) was found in 75% of MCL & 15% of FC.

Treatment: Rituximab, VAD (12) chemotherapy on days 9-12 and 17-20 and Etonogestrel, VAD-C or VAD-L (18 pts) VAD every 4 weeks with 12 mg chemotherapy on days 20 to 21. 5 pts have received HDT with Mitophan 140 mg/m² (4 pts) or Cyclophosphamide 120 mg/kg (1 pt) + TBI 80 Gy (5pts) and PBCST. The majority (21) were in relapse (R) or refractory (R1), 9 pts; R2; m, n, R3; 21 had received one or more prior chemotherapy, 16 with anthracyclines.

Results: The Follow-Up from Diagnosis (FLD) and first VAD course (FLU) to 0/1/92 are respectively 30.6 and 10.5 months. 22 pts (73%) have a response (10/18, 89% with VAD-C ± 6/12, 50% with VAD). 13 pts are in CR (1/18, 61% with VAD-C ± 212, 17% with VAD, 9 in VAD-C ± 212). Among the 13 CR pts (with FLU + 20, FUV + 20, M, A 17, 17) 6 are alive 17 years after first VAD (3-29), 6 pts are still in CR (14 m, 8 pts) 4 pts have relapsed before death; 4 received HDT with PBCST and are in CR 12.5 m after first VAD (29). Among the 9 PR pts, 3 are in CR (11, 3 after HDT), 6 are death 10 are alive 17 m after HDT but relapse with a leukemic form during TBI. Among the 8 pts without responses, 5 are 4 death 1 (17). The other have no response with other regimens. Conclusion: VAD seems to be an effective regimen to treat MCL lymphomas perhaps better with chlorambucil in association. HDT followed by PBCST appear a real promising perspective for complete responsive young pts.

MANTLE CELL (CENTROCYTIC) LYMPHOMA: LONG-TERM SURVIVAL WITH ADVANCED DISEASE IS POSSIBLE


Coordination center: Div. of Hematology, University of Essen

Within a multicenter prospective therapeutic study for mantle cell lymphoma (centrocytic) lymphoma from 1982 to 1085 65 patients eligible to be randomly allocated to receive chemotherapy according the COP (n = 35 pts) or the CHOP (n = 20 pts) protocol. As published in detail (Hematol Oncol. 7:365, 1989) between the COP- and CHOP-treated patients no significant differences could be demonstrated with respect to initial parameters, ratio of complete response (43% vs 60%), median relapse-free survival (10 months vs 7 months) or overall survival probability (31 months vs 30 months), rates of relapse (all patients within 40 months) and death rate (88% vs 90%), with 4 (11%) patients lost to follow-up in the COP group.

Eight years after onset of the trial the last patient of the COP group had died whereas in the CHOP group 2 patients are still alive 10 years after diagnosis as evidenced in April 1994. These patients with initial stage IV disease do not show any differences from the rest of the population with regard to their baseline characteristics. Tissue material of their lymphomas was examined with molecular genetic methods confirming the original diagnosis.


In patients with HIV-NHL several prognostic factors have already been identified to correlate with survival: low CD4 count, prior history of AIDS and poor performance status (PS). The role of other prognostic factors, such as LDH stage and multiple extranodal sites, has not been clearly defined in intermediate/high grade NHL of the general population is presently unclear in HIV setting. We have investigated HIV-related and standard prognostic factors in 96 pts with HIV-NHL diagnosis and treated with combination chemotherapy (CT) as our Institute between September 1987 and December 1993. Clinical findings and laboratory data were evaluated by univariate and multivariate analyses to investigate prognostic factors potentially influencing survival. Eighty-three patients were males, 13 females, median age was 32 years (range 23-79), mean CD4 count was 48 (50%), in accordance to the overall epidemiology in Italy. Prior AIDS was diagnosed in 21% of pts, median CD4 count was 116/mm³ (range 1-249) at the diagnosis of HIV-NHL. All pts had intermediate or high grade NHL according to the WHO, 73% of pts had stages III-IV, multiple extranodal sites were detected in 59% pts, PS 2 in 4% pts and increased LDH values in 54% pts. Eighty-seven percent of pts were included in prognostic studies with combination CT: CR occurred in 48% pts, while overall median survival was 7 months. The table reports the data on HIV-related and standard prognostic factors determined by univariate and multivariate analyses.

Prognostic factors for survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40 yrs</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>CD4 &lt; 100/mm³</td>
<td>0.005</td>
<td>0.03</td>
</tr>
<tr>
<td>LDH value increased</td>
<td>0.007</td>
<td>0.03</td>
</tr>
<tr>
<td>PS 2</td>
<td>0.004</td>
<td>N.S.</td>
</tr>
<tr>
<td>Prior AIDS</td>
<td>0.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Stage</td>
<td>0.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Multiple extranodal sites</td>
<td>0.3</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

The Cox regression model is:

Y = log (Hazard Ratio) The Cox proportional hazard model.

In conclusion this study shows that in addition to HIV-related prognostic factor, i.e. CD4 count < 100/mm³, also standard prognostic factors, such as age and LDH, are independent and should be included in the design of future clinical trials of HIV-NHL. Study supported by AIRC and ISIS grants.
Hodgkin’s Disease (HD) in HIV-infected and in immunocompetent patients: Pathological, immunological and molecular features.

C. Bellas, A. Santon, A. Manzanal, C. Martin, E. Campo, C. Montalban and the Spanish Hodgkin’s Disease Collaborative Group, Departments of Pathology and Internal Medicine (H. Ramon y Cajal), and Pathology (H. Clinico), Madrid, and H. Clinic, Barcelona, Spain.

The pathological and immunological characteristics, the presence of rearrangements of the IgH gene, expression of Latent membrane protein (LMP-1) and of deletions in the intracytoplasmic domain of the LMP-1 gene were studied in 24 patients with HD infected with HIV. The results were compared with those of a parallel series of 56 patients with ordinary HD. LMP-1 rearrangements were studied with amplification of IgH gene by PCR with F2 and F3 V-region primers with nested primers directed to the J-region; LMP-1 expression was evaluated using a monoclonal antibody (CS 1-4); LMP-1 gene deletions were studied by PCR amplification using primers pairs specific for the N terminal, transmembrane and C terminal domains.

In HIV+ patients HD had a predominance of unfavorable subtypes, being mixed cellularity more frequent than in ordinary HD (p=0.040). Neoplastic cell-rich cases were significantly more frequent (p=0.04) in the group of HIV+ patients (58%) than in ordinary HD (34%). In 25% of HIV+ patients and in 14% of ordinary HD, the neoplastic cell were CD20+(p=0.049). Cytolysis IgH rearrangements were detected in 33% of the HIV-infected patients and in 23% of patients with ordinary HD (p=0.062). LMP-1 was expressed in 100% of HIV+ patients and in 57% or ordinary HD patients (p=0.004). LMP-1 gene deletions were found in 65% of the 16 cases of HIV+ patients and in 32% of the 25 patients with ordinary HD studied (p=0.008).

Conclusions: The presence of deletions near the 5’ extremity of the LMP-1 gene in the majority of HD associated with HIV may be related with the increased aggressiveness of HD in these patients.

BURKHOLDERIA LYMPHOMA (BL) IN 75 PATIENTS (PTS), 46 WITH AND 29 WITHOUT HIV INFECTION: A MONOINSTITUTIONAL STUDY.


Overview: Among the 75 BL patients, in 46 pts with HIV infection, 29 without HIV infection.

Characteristics

<table>
<thead>
<tr>
<th>HIV+</th>
<th>HIV-</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>45/5</td>
<td>14/15</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>34.8 ± 8.1</td>
<td>31.5 ± 21</td>
</tr>
<tr>
<td>Stage (III + IV)</td>
<td>57%</td>
<td>44%</td>
</tr>
<tr>
<td>B symptoms</td>
<td>45%</td>
<td>39%</td>
</tr>
<tr>
<td>CD4 cell count/mm³ (mean ± SD)</td>
<td>189 ± 111</td>
<td>263 ± 150.6</td>
</tr>
<tr>
<td>ESR (mean ± SD)</td>
<td>42 ± 59.0</td>
<td>23 ± 57.6</td>
</tr>
<tr>
<td>LDIH (mean ± SD)</td>
<td>2151 ± 2076.4</td>
<td>2362 ± 2663.3</td>
</tr>
<tr>
<td>Whole blood cells/mm³ (mean ± SD)</td>
<td>3705 ± 2027.2</td>
<td>4217 ± 2753.3</td>
</tr>
<tr>
<td>Platelet/mm³ (mean ± SD)</td>
<td>286.9 ± 150.6</td>
<td>296.3 ± 150.6</td>
</tr>
<tr>
<td>Albinism (pct)</td>
<td>21 (64%)</td>
<td>21 (75%)</td>
</tr>
<tr>
<td>Completer remission (CR)</td>
<td>21 (64%)</td>
<td>21 (75%)</td>
</tr>
<tr>
<td>Intensive CT</td>
<td>11 (52%)</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>CR in pts treated with intensive CT</td>
<td>7</td>
<td><em>Not reached</em></td>
</tr>
<tr>
<td>Overall survival (CNS)</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Survival of CNS pts treated with DFCI in 4 years</td>
<td>75%</td>
<td>75%</td>
</tr>
</tbody>
</table>

*Out of 45 evaluable pts. Medium follow up 60 months (10-183). p values: 1) CR rate was lower in pts with HIV infection. 2) Patients in CR with or without HIV infection were significantly different comparing the subgroups of pts with and without pts with HIV infection. 3) All pts with or without HIV infection were significantly different comparing the subgroups of pts with or without pts with HIV infection. 

PRIMARY CNS LYMPHOMAS IN NON-HIV PATIENTS. Five-year results on 97 cases treated by the POF LCP 88 trial.


Six ratio of our 97 patients (pts) is 0.94 and median age 60 years. Histology done by stereotaxy in 2/3 of pts shows a predominance of the G type: 69%. CSF is involved in 22% of cases and proteinorachia is x 0.60 g in 58% of cases. Occasional involvement in at least 2 pts is 2 and solitary HN is in 4% respectively. An lower steroids is in 70% of pts.

POF LCP 88 trial combines 3 courses of MVBP (MTX 3g/m² D1 & D15, Teniposide 100 mg D2 & D3, BCNU 100 mg D4 et Methotrexate 60 mg D1 to D5), 6 LP and a 40 g IV. For the 231 cases of CNS, the major toxicities is infections in total cerebral 60% for the 1st cycle, 25% and 51% for the 2 and 3 cycles respectively. An apparent CR is in 22% of pts after the 1st MVBP, in 44% after the 3 courses and in 65% i.e., 63 patients after radiotherapy.

On November 1995, the median follow-up time is 41 months and we observe:

- 11 relapses occurring after 7 to 40 months: 6 in situ, 1 meningital, 2 oculaire, 1 disseminated and 1 hepatic relapse followed by a cerebral relapse one year later.
- 47 deaths: 6 septic shocks, 1 angor, 26 failures, 9 relapses, 1 AML and 1 hironephropathies from 6 to 48 months after diagnosis.
- 5 non-related deaths: 2 infections in CR, 2 age-related deaths and 1 aortic haemorrhage.

The 3 and 5-year survival rates after exclusion of the non-related deaths are respectively 52 and 54% for all the 97 pts and 60 and 52% for the 63 pts in CR after treatment.

POF (p<0.02) and seric LDH (p<1.23 N) can determine 3 prognostic groups: the 5-year survival rate is only 11% when these two factors are present and in opposite, the 5-year survival rates are 30% for one predictive factor and 51% in lack of any factor (p = 10-4).


Berzak A, Gospodarovitch M, Pistlise M, Brierley J, Tsang R, Wells W and the PMH Lymphoma Group, Princess Margaret Hospital, University of Toronto, Toronto, Ontario, Canada.

Between 1978 and 1991, 166 patients (pts) with stage I and II extranodal NHL of the Waldeyer’s ring, salivary gland and paranasal sinuses were treated at our Institution. We limited our analysis to 115 pts with involvement of Waldeyer’s ring (nasal fossa, maxillary, ethmoid and sphenoid), most of the 60 pts with T1N and T2N stage 5, intermediate grade in 83, and high grade (or unclassified) in 8 pts. 41 pts had stage IA disease, 67 stage IIIA and 7 stage IIB. Median age was 60 years (range 17-87). 50 pts were treated with radiation alone (RT), 54 with RT+chemotherapy (RT+CT), 10 with CT alone, and 1 had only surgery. In 41 pts treated with RT alone, had less bulky tumors (mean 20 cm) as compared to pts with CT+RT (4.4 cm) and CT alone (4.7cm). Adriamycin-containing CT was given to 4664 pts (375/CT+RT pts, and 910 CT alone pts). The median number of courses was 3 (range 1-12). The median radiation dose was 35 Gy in 20 fractions (range 8-47 Gy). The complete response rate was seen in 106/115 pts. The overall 5yr survival complete response rate was seen in 106/115 pts. The overall 5yr survival complete response rate was seen in 106/115 pts. The overall 5yr survival complete response rate was seen in 106/115 pts. The overall 5yr survival complete response rate was seen in 106/115 pts.
Primary pulmonary lymphoproliferative disorder.


Introduction Primary pulmonary lymphoproliferative disorder (PLPD) includes the neoplastic and reactive conditions, and the distinction between both conditions is often difficult. The aim of this study is to evaluate the methods for making the accurate diagnosis and clarify the nature of this disorder.

Materials & Methods We reviewed 15 cases (age: 27-81 yr., median 65 yr.; M/F: 8/7 cases), which had been diagnosed in our Department of Pathology. The samples of 10 cases were obtained at surgery and 5 cases at biopsy. The mononcytolal of lymphoid cells was studied by an immunohistochecmical examination using various antibodies on paraffin and/or frozen sections, in situ hybridization (ISH) for immunoglobulin (Ig) light chains on paraffin sections, and polymerase chain reaction (PCR) for Ig H. Results We classified 15 cases with PLPD into four groups; 4 cases of malignant lymphoma (ML), high grade (diffuse large or medium cell type) (group 1), 5 cases of ML, low grade, so-called mucosa associated lymphoid tissue (MALT) (group 2), 4 cases of follicular bronchitis/bronchiolitis (group 3), 2 cases of lymphoid interstitial pneumonia (group 4). These tumor forming lesions were cited at the peripheral pulmonary region except for one case of ML. In group 1, 3 cases were of B- and one was of T cell lineage. In group 2, the immunohistochecmical examination revealed the clonal proliferation in 3 of 5 cases. In groups 3 and 4, there were no cases exhibiting the clonal proliferation.

Conclusion PLPD is an entity including heterogenous conditions, and the methods of ISH for light chains and PCR for Ig H are useful to differentiate between neoplastic and reactive conditions.

ENTERPATPHY ASSOCIATED T-CELL LYMPHOMAS: NEOPLASTIC COUNTERPARTS OF ACTIVATED CYTOTOXIC T-LYMPHOCYTES

PC de Bruin, JJ Oudejans, CE Connolly* and CJLM Meijer Dept. of Pathology, Free University Hospital Amsterdam, The Netherlands *University dept. of Pathology, Clinical Science Institute Galway, Ireland.

Background: T-cell non-Hodgkin's lymphomas can be considered as neoplastic equivalents of recirculating functional subsets of tissue restricted T-lymphocytes after antigenic stimulation. Some small intestinal malignant T-cell lymphomas arise as a complication of celiac disease. These are called enteropathy-associated T-cell lymphomas (EATLs). In the present study we investigated whether EATLs could be the neoplastic counterparts of activated cytotoxic T-lymphocytes (CTLs). Neoplastic cells in EATLs of 6 patients, with clinical and histological evidence of celiac disease, were investigated for the expression of granzyme B (GzB), a major constituent of the cytotoxic granules of activated cytotoxic T-lymphocytes CTLs and natural killer (NK) cells.

Results: In 5 of 6 EATL cases strong granzyme B expression was detected in the majority of neoplastic cells. The remaining case was granzyme B negative. 2/3 grB-positive cases were 144B/CD8 (courtesy of dr. DY Mason, Oxford) positive, 2/5 gr-B positive cases were OPD4/CD4 positive and the remaining grB-positive case was CD8/OPD4 positive. Only the OPD4 positive cases were CD30 positive. The grB-negative case was CD8/OPD4 positive. All cases were EBV-negative as investigated by EBER-RISH.

Both in the epithelium of the small-intestine of control patients with celiac disease as in the nonlymphoma-involved, adjacent mucosa in the EATL cases, increased numbers of grB-positive intra-epithelial lymphocytes were observed as compared to the mucosa of normal small-intestine.

Conclusions: A high percentage of EATLs can be considered neoplastic counterparts of activated CTLs which are increased in the mucosa of patients with celiac disease.

PRIMARY LYMPHOMA OF THE INTESTINUM: 3-YEARS-RESULTS OF A PROSPECTIVE MULTICENTER STUDY


In October 1992 we initiated a prospective multicenter study on primary gastrointestinal (GI) lymphoma. Though the chief aim was to evaluate histological features, sites of involvement and therapeutic outcome after a standardized treatment in gastric lymphoma, NHL originating from other parts of the GI-tract were also included. With an incidence of about 0.4-1(100 000)year for intestinal lymphoma in the western countries, prospective studies are missing and information on epidemiology and treatment strategies are contradicting.

In this ongoing study 312 patients have been accrued, 250 being evaluable for clinical features until 15th January 1996. With 73.2% of all GI-NHL originating from the stomach, distribution in the remaining 67 patients is as follows: Small bowel including duodenum 37%, ileocelecal region 24% and colon including rectum 9%. Multicentric GI-involvement occurs in 27%, which in 6/18 patients is restricted to the intestine.

In most cases histopathological diagnosis followed primary surgery for obstruction, tumour of unknown origin or bleeding. With 4.3 months history is short compared to gastric NHL (7.8 mo.) abdominal pain being the most frequent symptom (76%). Enteropathy was rare. Mean age of all patients is 54.9 years, but 47.6 years in ileocecal NHL compared to 60.2 years in NHL of small bowel.

In intestinal lymphoma the distribution of histology is as follows: High grade B-NHL 15.8%, Burkitt's/lymphohistiocytic NHL 10.5% (only in the ileocolic region), T-NHL 13.2% (only in small bowel). In ileocolic lymphoma 81% are in stage I, II and 11% of NHL while the small bowel is localised only in 59% often being multicentric. Estimated freedom from treatment failure at 3 years is 71% for patients with ileocecal lymphoma, 56% for those with NHL of small bowel. There is no statistical significance due to small numbers.

Because of differences in histology, clinical features and probably therapeutically outcome in intestinal lymphomas those of ileocecal region and small bowel should be investigated separately.

PRIMARY LYMPHOMAS OF THE STOMACH: A COMPARISON BETWEEN MALT AND NON-MALT HISTOLOGY

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The best therapeutic approach for patients (pts) with primary lymphoma of the stomach is far from being clearly established, mainly because of the heterogeneity of the reported series, which may mimic complicate other diseases. Some of the issues concern the differences in clinical behaviour and prognostic features between MALT and non-MALT lymphomas and the clinical usefulness of distinguishing low grade from high grade histology in the context of MALT lymphomas.

From January 1985 to December 1993 99 pts with primary gastric lymphomas were referred to our institutions. Pathologic material has been reviewed and diagnoses have been rendered using the REAL classification. 54 pts had MALT lymphoma (34 low grade, 20 with coexistence of follicle high grade lymphomas), 45 had non-MALT lymphoma (32 diffuse large B-cell lymphoma, 11 follicle center lymphomas, 2 other histologies). All the pts have been homogeneously treated with surgical resection, eventually followed by radio- and/or chemotherapy (CVP or CHOP, 8 courses) according to the presence of one or more poor prognostic factors (positive surgical margins, involvement of regional lymph nodes, disease extended beyond the serosa). We did not observe any difference between MALT and non-MALT lymphomas with regard to sex, age, stage (I, II, III, IV), symptoms, LDH, involvement of regional lymph nodes, positivity of surgical margins. The only factor which resulted statistically significant was serosa involvement, which was higher in non-MALT lymphomas (p=0.005). Median follow-up of the whole population is 69 months (25-130). Among MALT lymphomas, 1 pt (2%) relapsed vs 8 pts (18%) in non-MALT group (p=0.03). 5-yr actuarial overall survival curve is projected to 98% for MALT lymphomas vs 83% for non-MALT lymphomas (p=0.05). 10-yr actuarial relapse-free survival curve is projected to 88% and 81%, respectively (p=0.05).

These data suggest that MALT lymphomas possess particular biological and clinical characteristics, which probably request a specific therapeutic approach compared to non-MALT lymphomas, such as anti-Helicobacter Pylori treatment. Among MALT lymphomas, the prognostic role of distinguishing low grade from high grade histology is not yet clearly outlined and requires further investigations.

4. Non-Hodgkin's lymphoma

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GASTRIC B-CELL MALT LYMPHOMA: A CLINICOPATHOLOGICAL STUDY OF 63 PATIENTS.

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Reactive specimens from 63 patients with primary gastric B-cell MALT lymphomas at stage IE (n=40) and at stage IIE (n=23) were examined. Histologically, low grade malignant MALT lymphomas (n=29) have been distinguished from high grade MALT lymphomas (n=11) and without (n=23) evidence of a low grade component.

All gastric MALT lymphomas expressed the B cell associated antigen CD20. The BCL-2 protein was expressed in all low grade lymphomas, but only in 48% high grade lymphomas. On the contrary, overexpression of p53 was detected in 66% (mean percentage of positive cells=66) low grade lymphomas and in 100% (mean percentage of positive cells=69) high grade lymphomas. The mean Ki-67 index was 6.1% (range 1-210) for low grade and 68.7% (range 20-87) for high grade MALT lymphomas.

Tumors most frequently involved the gastric antrum (52.3%), followed by corpus (12.6%), fundus (11%), and antrum and corpus (9.5%). The entire stomach (7.9%) and corpus and fundus (6.3%). The mean tumor size was 3.9 cm (range 1-9) for low grade MALT lymphomas and 6.8 cm (range 3-17) for high grade lymphomas. Seventy-nine per cent of low grade tumors were confined to the submucosa, while 82.4% of high grade tumors involved the muscularis propria or all layers of the gastric wall.

Of a total of 63 patients aged 31-83 yrs (mean age 61.5 yrs), 35 were males and 28 females. Patients with low grade lymphomas were younger (mean age 57.6 yrs.) than those with high grade lymphomas (mean age 64.8 yrs.).

All patients with low grade MALT lymphomas followed after surgery for a mean of 75.7 months (range 14-112) months were alive, while in 62/72 (22%) patients (2 at stage IE and 4 at stage IIE) with high grade MALT lymphomas (mean follow-up 42.6 months) died of their tumor, with a mean survival of 23.2 months (range 5-69) months after the operation.

We conclude that the classification and grading of gastric lymphomas according to the histopathological concept of MALT-derived lymphomas into low grade and high grade lymphomas is an important prognostic factor. The immunohistochemical evaluation of proliferative activity (Ki-67 index), p53 and BCL-2 expression is useful so better characterize low grade and high grade gastric MALT lymphomas.

MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) GASTRO-INTESTINAL AND NON-GASTROINTESTINAL LYMPHOMA PATIENTS HAVE AN IDENTICAL OUTCOME.


82 patients (pts) with MALT lymphoma were analyzed to compare clinical presentation and outcome according to the initial lymphoma location: gastrointestinal tcd (GIT) or outside GIT (non-GIT). 48 pts had GIT initial location, 41 gastric and 5 intestinal. 36 pts had non-GIT initial location: 9 lung, 8 orbit, 8 parotid, 4 skin, 3 thyroid, 2 breast, and 1 pancreas. 72% had stage IE or IIE, 24% stage IV, 15% bone marrow involvement. 51 pts received surgery or radiotherapy with 13 of them adjuvant chemotherapy; 29 pts chemotherapy only; and 2 pts were not treated. 73% of the pts responded to treatment with 68% CR. Response rate was identical in the two subgroups. With a median follow-up of 4 y, 20 pts (33%) progressed after response, 65% in the same organ and 35% in other organs. 2 pts had histologic transformation. Median progression-free survival (PFS) was 6.7 y, 8.9 y for GIT and 4.9 y for non-GIT (p<0.5). 5- and 10-y survival was 88% and 73% respectively for GIT pts and 91% and 78% respectively for non-GIT pts (not different). Shortened PFS and survival was associated with impaired performance status, spleen involvement, anemia, and low serum albumin level. Our results confirm the long survival associated with MALT lymphomas but they showed that this lymphoma may progress and disseminate into the body at least on third of the pts. They did not show any significant difference between GIT and non-GIT MALT lymphoma pts.

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Helicobacter pylori in primary gastric non-Hodgkin's lymphoma.

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Primary gastric lymphomas develop possibly in response to local infection by Helicobacter pylori (Hp). We investigated the presence of Hp and non-Hp intragastric bacterial flora in 47 patients with primary gastric lymphoma, classified as low (14 cases) and high (33 cases) grade histology. Clinical data were evaluated to establish that most of the tumour load was in the stomach and no former nodal localisation was present. Serial sections were stained with haematoxylin-eosin, modified Giemsa (MG), and in addition immunohistochemically (IIM) with a specific polyclonal antibody directed against Hp.

Twenty-six patients (55.3%) showed presence of Hp (IMM+) in the mucosa surrounding the tumour. In the tumour no presence of Hp was found. Remarkable was the localization of Hp in 3 cases, in which no presence of Hp was seen in the superficial epithelial layers, but Hp was found deep in the epithelium.

Using MG staining we saw non-Hp flora in 21 patients (65.9%), non-Hp flora without the presence of Hp flora (MG positive for other bacteria/MM negative) were seen in 15 patients (31.5%). Six cases showed neither Hp nor non-Hp flora. In the low grade tumours we observed Hp in 54.3%, non-Hp flora in 50.0%, non-Hp flora only in 21.4% and no bacteria in 14.3%. In the high grade cases we detected Hp in 51.5%, non-Hp flora in 72.7%, non-Hp flora only in 36.4% and no bacteria in 12.1%. Using the χ2-test, we noticed no significant difference in the distribution of Hp among high and low grade lymphomas, in contrast to the significant difference (p<0.001) in the distribution of non-Hp flora.

Conclusions: 1. Using a specific staining technique for Hp, only about half of the cases of primary gastric lymphomas are positive for Hp, which is also the prevalence of Hp in the normal population, as estimated by serological studies.

2. Hp is found in a similar frequency in low and high primary gastric lymphomas. 3. Our results suggest that non-Hp bacterial flora may play a role in the development of primary gastric lymphomas.
Helicobacter Pylori eradication for the treatment of low grade gastric MALT lymphoma. Follow up together with sequential molecular studies.

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Helicobacter pylori infection is associated with low grade gastric MALT lymphoma, and available data support that the eradication of H. pylori can cause lymphoma regression. In this study, 8 untreated patients with low grade gastric MALT lymphomas treated with amoxicillin, metronidazole and omeprazole for 14 days. In order to assess the response to H. pylori eradication and the evolution of the histological and molecular responses, patients were followed up with sequential endoscopy, mapping gastric biopsies and molecular studies with amplification of the IgH gene by PCR with Fr1 and Fr3 V-region primers with nested primers directed to the 1-region. H. pylori was eradicated in all patients and reinfections were not demonstrated. In 7 of the 8 patients the lymphoma regressed both endoscopically and histologically. In 3 of the 7 histologically cured patients no clonal band was detected by PCR; in the remaining 4 patients, PCR demonstrated a clonal band, that disappeared in all patients after a mean of 9.7 ± 2 months. All 7 patients have a persistent clinical and histological remission after a median follow up of 10 ± 6 months.

Conclusions: 1. H. pylori eradication can produce histological regression of low grade gastric MALT lymphoma. 2. H. pylori should be the initial therapy for stage I low grade gastric MALT lymphoma. 3. Despite histological regression of the lymphoma, a clonal population may persist in some cases. 4. The disappearance of this clonal population may be delayed for months. 5. Patients with histological regression of the lymphoma but with a persistent clonal population should not be treated unless a relapse can be histologically demonstrated. These observations suggest that gastric lymphoma can be effectively cured; still, long-term follow up studies are necessary to assess the ultimate outcome of these patients.

Endoscopic Ultrasound (EUS) in the Evaluation of Gastrointestinal Lymphoproliferative Diseases (MALT).

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Interest in small lymphocytic MALT lymphomas of the stomach has increased since its associate with Helicobacter pylori (H. pylori) infection was reported in 1991. We retrospectively reviewed twenty patients (1992-1994) with gastric MALT lymphomas diagnosed elsewhere by endoscopy (EGD), who then underwent EUS and biopsy at our center. EUS visualizes the five gastric wall layers permitting assessment of tumor size, depth of infiltration and possible lymph node involvement. 16/20 pts had MALT lymphoma confirmed. 11/16 had H. pylori documented by initial EGD biopsy. All 11 pts were treated with antibiotics before EUS documented persistent lymphoma. An obvious infiltrating mass was visualized in 8 and the remaining 8 had a thickening of the gastric wall with or without submucosal infiltration. Lymph nodes were noted to be suspicious in 7/16. These pts were then treated with either surgery (4/16), chemotherapy (8/16) or radiation therapy (4/16). Post-treatment follow-up EUS performed in 13/16 revealed normal gastric walls in 9 pts (biopsy negative) and residual wall thickening in 4 (one biopsy negative, two lymphomas and one gastric adenocarcinoma). These pts received care elsewhere and did not return for post-treatment EUS. Four pts diagnosed elsewhere with MALT lymphomas were found, instead, to have reactive lymphoid aggregates associated with gastric changes of the mucosa. EUS revealed friable, prominent mucosa, but no submucosal infiltration, masses or lymph nodes. All four biopsies were H. pylori positive. None of these pts received prior antibiotic therapy. CONCLUSION: EUS provides an objective measure of MALT tumor size and depth of gastric infiltration; EUS may assist in distinguishing gastric MALT lymphomas from reactive lymphoid aggregates associated with H. pylori gastritis. Serial EUS appears useful in assessing objective responses to lymphoma therapy (i.e. antibiotics, radiation, surgery and/or chemotherapy).
RELATIONSHIP BETWEEN IL-8 AND TNFα EXPRESSION AND SPONTANEOUS REMISSION IN PRIMARY CUTANEOUS CD30-POSITIVE LYMPHOPROLIFERATIVE DISORDERS

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Primary cutaneous CD30+ T-large cell lymphomas (LCL) and lymphomatoid papulosis (LyP) are closely related conditions with a favorable prognosis. Spontaneous remission, which is the hallmark of LyP, but can also be observed in ca. 25% of the cutaneous CD30+ LCL, is considered as the most important criterion indicative of a favorable prognosis. The mechanisms responsible for spontaneous remission are unknown, but a relationship with the number and nature of admixed inflammatory cells has been suggested. Since cytokines may play a crucial role in the recruitment of inflammatory cells, immunohistochemical studies using antibodies against IL-8 and TNFα were performed on skin biopsies of primary cutaneous CD30+ lymphoproliferations showing spontaneous remission, including 3 LyP and 2 CD30+ LCL. 4 primary cutaneous CD30+ LCL without signs of spontaneous remission, and 6 cases of mycosis fungoides (MF) and 5 cutaneous B-cell lymphomas (CBCL).

In 4 of 5 CD30+ lymphoproliferations showing spontaneous remission many dendritic cells/macrophages as well as occasional tumor cells expressed both IL-8 and TNFα. In contrast, in the 4 CD30+ LCL without spontaneous remission, and in all cases with MF or CBCL IL-8 and TNFα were expressed by only few scattered dendritic cells/macrophages. The results of these preliminary studies suggest that IL-8 and TNFα may contribute to the spontaneous remission characteristic of this group of lymphomas.

A NOVEL DIPHTHERIA TOXIN FUSION PROTEIN, DAB44BIL-2, DEMONSTRATES ANTI-TUMOR ACTIVITY IN CUTANEOUS T-CELL LYMPHOMA

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DAB44BIL-2 is a recombinant fusion protein in which the enzymatic and translocation portions of diphtheria toxin have been fused to the sequences for human IL-2 which targets and inactivates cells expressing the high affinity receptor for IL-2. A cohort dose escalation study was performed to establish maximum tolerated dose of DAB44BIL-2 when administered daily times 5 every 21 days. Of 78 patients with biopsy proven cutaneous T-cell lymphoma (CTCL) screened by immunohistochemical analysis for IL-2R expression, 47 (60%) were positive and 35 were enrolled. The median age was 61 (range 40-81). All patients were refractory to prior therapy with a mean of 4 prior regimens, and 17 had advanced disease (Stage III,IV). Five CR and 8 PR were noted for an overall response rate of 37%. Eleven of 13 responses occurred in patients with Stage I-II disease, and there was no association between response and dose level. Responses were seen in patients with cutaneous plaques, tumors, and erythroderma. Median response duration was 8 months (range 2.5-22+ mo.). Toxicities included constitutional symptoms, elevated hepatic transaminases, hypoalbuminemia, hypotension, rash, and sterile pyuria. No myelosuppression or alteration of T-cell subsets was observed. Based on these encouraging results, a Phase III program in CTCL has been initiated.

EORTC CLASSIFICATION FOR PRIMARY CUTANEOUS LYMPHOMAS

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Primary cutaneous lymphomas represent a heterogeneous group of T- and B-cell lymphomas, that show considerable variation in histology, phenotype and prognosis. Recently, the EORTC Cutaneous Lymphoma Project group has reached consensus on a new classification for this group of diseases. In contrast to other classification schemes for non-Hodgkin lymphomas, the EORTC Classification for Cutaneous Lymphomas is not only based on histological and immunophenotypical, but also on clinical criteria. Therefore, it includes a list of disease entities, that have a well-defined clinical presentation and clinical behavior. For that reason, secondary cutaneous lymphomas as well as cutaneous lymphomas arising in immunosuppressed patients are excluded from this classification. In addition, this new classification contains a number of provisional entities, which may display characteristic histologic features, but are clinically not yet well-defined. These provisional entities account for less than 5% of all primary cutaneous lymphomas.

The basic principles of this new classification, the characteristic clinical and histological features as well as the survival data of the different disease entities, will be presented.

Open controlled clinical trial on the use of interferon plus aclacinomycin over interferon plus PUVA in patients with cutaneous T-cell lymphoma (CTCL)

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Recent therapeutic concepts used interferons as immunomodulating substances alone or in combination with PUVA or retinoids for systemic therapy of cutaneous T-cell lymphomas. The reported overall response rate varied between 5% for interferon (IFN) monotherapy to 90% for comparative data on interferon combination therapies available. Therefore an open randomized multicenter phase II clinical study was initiated to compare the efficacy and tolerability of interferon alpha-2a and PUVA in patients with CTCL stage I and II. Patients with histologically confirmed CTCL stage I and II were randomized to be treated either with interferon, starting 3-6-9 Mio IE week 1 to 3-9 Mio IE per week for 1 to 5 months, or PUVA starting with 0.25 J/cm² until the minimal erythema dose was reached (weeks 1-6: 2 weekly, weeks 7-24: 3 weekly). The study period was closed after 48 weeks treatment.

92 patients (68 male and 24 female) were randomized. 47 to the interferon plus PUVA (group 1) and 45 to interferon alone (group 1). All patients received the same dose and duration of PUVA treatment. The patients were subsequently treated as in group 1. The median observation time was 230 days. The overall response rate was 15% in group 1. The mean time to response was 97 days. The median survival time was 250 days. There were no significant differences between the two groups.

In conclusion, the results of this study show that interferon alpha-2a plus PUVA is superior to interferon alpha-2a alone in the treatment of CTCL.

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