EVALUATION OF 479 ADULT PATIENTS WITH NON HODGKIN LYMPHOMAS AT THE NATIONAL CANCER INSTITUTE OF A DEVELOPING COUNTRY.

INTRODUCTION: Aggressive non Hodgkin's lymphomas are one of the most important challenges for the hematologist around the world. Most of the published literature on the subject refers to the experience in developed countries with high technology standards and facilities. The purpose of this study is to analyze the clinical presentation, history, treatment and outcome of these patients.

METHODS: We analyzed the clinical records of the 750 patients with non Hodgkin lymphoma seen at our institution, since January 1999 to September 2001. Patients with the following criteria were included in the present study: recently diagnosed lymphoma, pathology review by panel of hematopathologists from our institution, and no prior therapy. From 750 patients with diagnosis of lymphoma only 479 fulfilled the above criteria and were included in the analysis.

RESULTS: Two hundred sixty five patients (56.1%) had nodal involvement and two hundred seventy (43.9%). Extramedullary presentation, of whom 24.1% were of the GI tract, 20% skin, 11.9%, Waldeyer's ring, 10.5% head and neck 2.4% breast, 1.4% testis, 2.4% soft tissues, 2.4% eye and orbit, 5.8% CNS, 5.8% bone and 13.5%, others. 33% had both nodal and extranodal involvement. Hematopathology subtypes:

- Cline large B cell: 47.2%
- Other aggressive types (follicular large cell, diffuse mixed, immunoblastic large cell): 12.2%
- Indolent (follicular small mixed, and small cell lymphoid): 9%
- Burkitt: 2.6%
- Mantle cell: 2.3%
- MYC gene: 1.8%
- Others: 2.2%
- Others: 23.8%

Clinical stage III and IV 56% stages I and II 44%; B symptoms were present in 33.5% patients, and 30.7% had early disease. 82.3% had chemotherapy as initial treatment, 7.7% Radiotherapy and Watch and Wait policy for 3.1%.

The CR rate was 45.5%, with a median survival of 71 months, and a 5 years DFS and OS of 67% and 48% respectively. 15.5% of patient did not complete their treatment for various reasons.

Of the 2 patients achieved complete remission, 1 patient had aggressive Lymphomas. 53.6% were in stage III and IV.

The median survival of 47 months and median disease free survival was 51 months.

CONCLUSION: The fact that most of the patients presented in advanced stages, and a 16% of them did not complete therapy, our results and experience indicate that CHOP still is a feasible therapy for treating lymphomas in a developing country.

LOW PARTICIPATION RATE TO CLINICAL TRIALS IN FOLLICULAR LYMPHOMAS IN FRANCE.

INTRODUCTION: Follicular lymphoma (FL) is a rare disease but also the most frequent subtype among low grade lymphomas. Although about half of the patients (pts) with localised disease can be cured by radiotherapy, disseminated stages remain incurable. Exciting new drugs become available and need to be thoroughly investigated to evaluate whether they may allow to bring advanced stages into cure.

METHODS: During three years (1995-98), pts with FL have been registered in 145 centres in France (36 haematology, 49 oncology and 60 internal medicine centres). The median number of pts seen in each centre was 4 (range 1 to 58) 21 centres (14.5%) managed 50% of the patients. Data about 1110 pts have been collected which represents about 20% of the expected incident cases during the same time period in France. FL diagnosis has been reviewed. The proportion of registered versus expected pts and the large variety of centres included make this series representative of the current situation in our country.

RESULTS: 24.5% of FL have been included in clinical trials (272/1110). As usual, older patients were rarely included in trials (27.9% if <70 vs 12.8% if >70 - p<0.001) as well as pts with localised stages and low tumour bulk (15.3% low vs 38.1% high tumour bulk - p<0.001). Pts managed in centres recruiting more than 5 pts per year were more frequently included in clinical trials (29/19.9% - p<0.0003).

CONCLUSIONS: Since clinical trial proposal in France was quite high in FL during the same time period, the observed proportion of trial participation should be considered as low. These observations highlight the important efforts which remain to be performed to promote research in this field.
THE DEVELOPMENT OF DIFFERENT HISTOLOGIC TYPES OF LYMPHOMA IN THE SAME PATIENT IS NOT COMMON AND IS ASSOCIATED WITH A MORE SERIOUS PROGNOSIS


Introduction: Distinct types of lymphoma may develop in the same patient (REAL, WHO) and did not include them into the same clinical categories. Therefore, the frequency as well as the clinicopathological and prognostic features of this subgroup of lymphoma are only partially known.

Methods: A retrospective analysis was conducted among 347 consecutive patients diagnosed at our Institution between 1994 and 2000, in order to identify those with at least two different diagnoses of lymphoma, which were defined as "discrepant lymphoma (DL)." Histologic classification was made according to the REAL criteria.

Results: Forty-six cases of DL were identified (13%). As compared to 301 lymphomas with persistent histology, DL presented more often in III-IV stage (83% vs 63%; P < 0.005), the frequency of lymphocytic/lymphoplasmacytic histology was higher (16.6% vs 3%; P < 0.0001) and that of Hodgkin’s lymphoma lower (4% vs 16%; P = 0.04). No differences in age, sex, IPI score and in other histologic types were found. DL was diagnosed at the same time (simultaneous DL) in 14 cases or at different times (sequential DL) in 32 cases. Clinical and demographic features of simultaneous and sequential DL were similar. Lymphadenopathy and bone marrow were most often involved. Seven cases had different immunologic origin. Combination of an indolent and an aggressive histology of the same immunologic lineage occurred in 43% of simultaneous DL and 59% of sequential DL. Four sequential DL presented with an aggressive histology followed by an indolent histology ("downgrading lymphoma"). Four simultaneous DLs and 3 sequential DLs showed combinations of different indolent histologies. DL were treated like persistent lymphoma. The more aggressive histology was selected for treatment in simultaneous DL. Results were: CR + PR 54%, DFS 35% vs 43%.

Histology NE: %:p < 0.05
Persistent 501 95% 85% 54% 67%
Discrepant DL 46 92% 77% 12% 32%

Patients with persistent and sequential DL had similar DFS and overall survival. Conclusion: Lymphomas with discrepant histology represent an underestimated subgroup of lymphoma with frequent relapse and a markedly worse prognosis. They warrant further prospective studies both at the biological and at the clinical level.

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THE INTERNATIONAL PROGNOSTIC INDEX AND THE QUALITY OF LIFE IN PATIENTS WITH AGGRESSIVE NON-HODGKIN’S LYMPHOMA IN TWO DIFFERENT AGE POPULATIONS
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Introduction: Cure is attainable for a considerable proportion of patients with aggressive Non-Hodgkin’s Lymphoma (NHL), including the elderly ones. Even so, patients may experience decreases in quality of life (QOL). It is not yet clear if QOL evaluation with age-specific instrument is needed. The aim of this study was to evaluate the impact of the clinical characteristics on the QOL of patients and to see if it was dependent on their age.

Methods: The QOL has been assessed in a group of 109 patients (median age 59 years, range 18-83) with aggressive NHL, as well as in it’s two subgroups of different age, separately: in 58 patients younger than 60 years and in 51 patients older than 60 years. QOL was measured using the QLD-30 (Aaronson,1995). International prognostic index (IP) and the age-adjusted IPI (aIPI) were used for the assessment of patient’s prognostic characteristics at the presentation.

Results: The majority of the patients (33.0%) and the majority of the elders (33.3%) had high IPI, while the younger ones had the intermediate IPI more frequently (29.3%). In the group analyzed as a whole, patients with high IPI experienced all their functional abilities as significantly lower, in comparison with those of a better prognosis. The exception was their cognitive functioning (CF), that did not depend on the index (p=0,13). The patient’s personal assessment of the most of physical disabilities (fatigue, nausea, pain, dysphonia, appetite loss) also depended on the IPI (p=0,13). In the subgroup of patients younger than 60 years, the only functional abilities independent on the aIPI were the CF (p=0,16) and the social functioning (SF) (p=0,9). Also, 50% of the investigated physical disabilities (fatigue, dysphonia, appetite loss, nausea) were experienced by younger patients as significantly dependent on the aIPI (p<0,01). On the contrary, the SF (p=0,04), the overall assessment of QOL (p=0,008) and the fatigue (p=0,01) were the only QOL components assessed as dependent on the aIPI by the elders.

Conclusions: The changes in the somatic health lead to the person’s experience of lowering own functioning abilities and global QOL. The data suggest that the perception, the experience and the communication of QOL seem to be age-dependent. An age specific instrument for the QOL assessment in the NHL patients is needed.

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QUALITY OF LIFE AND POSTTRAUMATIC STRESS DISORDER AMONG LONG-TERM SURVIVORS OF LYMPHOMA: PRELIMINARY RESULTS
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Introduction: Studies of long-term survivors of cancer patients have shown that psychological distress can be long lasting, including traumatic stress responses. The objective of the present study was to investigate the long-term psychological effects, namely health related quality of life (QoL) and posttraumatic stress disorder (PTSD), in survivors of Hodgkin’s disease (HD) and non-Hodgkin’s lymphoma (NHL) in Israel.

Method: Twenty-four (12 females and 12 males) long-term disease-free survivors of lymphoma (time since end of treatment of 10 years or more) were evaluated in this preliminary study. Age: 30-78 (mean 51 years), NHL:19, HD:5; Stage: I-E, II-1, III-4, IV-3; Treatment: chemotherapy-13, radiation-3, both-8. The patients were administered the SF-36, Personal Symptomatic Scale and the PTSD scale.

Results: Four (16.6%) patients had full PTSD and another five (20.8%) had partial PTSD. This is higher than the general population and similar to previous studies in Israel of long-term breast cancer survivors and of war veterans three years after the Lebanon War. With regard to health related QoL the study group scored significantly lower (p < 0.05) on all eight subscales of the SF-36 (Physical Functioning, Role Functioning-Physical, Social Functioning, Bodily Pain, Mental Health, Vitality, General Health Perceptions) than a comparison group of healthy adults in Israel.

Conclusions: These findings suggest that long-term disease free survivors of lymphoma have an increased incidence of PTSD and lower health related QoL compared to the general population. If more extensive studies confirm this suggestion, then appropriate psychological assessment and intervention should be made available to long term survivors to identify and help deal with PTSD. In the next phase of the study we will try to determine the relative contribution of the disease process and the treatment modality to PTSD and QoL.
DOSIFICATION AND MOLECULAR PROFILING OF MURINE CELL LINES DERIVED FROM CD4+ TRANSCENDENT MICE

MALERBA C, D DIOVOVICH, G. BOWE, A. COLLUTTA, B. ELETTI, L. BASSI and L. GRIBALDI

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Cell lines derived from superficial and deep lymph nodes of transgenic mice, in which CD4+ expression was deregulated, were grown in RPMI 1640 supplemented with FBS 10% and 2-mercaptoethanol 50 μM. Chromosome number has been analysed and both cell line showed a similar triplid karyotype with about twenty structurally abnormal chromosomes with unclear origin. After differentiation, the growth of both cell lines was independent of interleukin-2. The expression of surface and sporadic markers was evaluated by Western Blot. Both IL2+ and IL12+ express CD40, INF-γ, fas, fasl, p55 and p56 but not fas-I and IL-2 Receptor was expressed in both IL2+ and IL12+ cell lines after stimulation with IL-3 or IL-12 100 ng/ml. The IL-12 Receptor was detected at high concentration only in IL12+ whereas only IL12+ express CD40 Ligand. IL12+ cells did not undergo apoptosis and were tumorigenic when inoculated in vivo in nude mice. Whereas IL12 treated cells, were sensitive to apoptosis, induced apoptosis and did not induce tumors in nude mice. The investigation on selenometrics length and seleniums, in order to evaluate the stability of ILA, has been carried out.

Our cell line could provide a useful model to study the perturbation of the homeostasis of the lymphoid subsets of lymph nodes, allowing us, in the meantime, to elucidate the role of cytokines as modulators of differentiation in the lymphoproliferative disorders.

In conclusion, there was a substantial and sustained eradication production with calculated AU values peaking at D3. The actual AU level were constantly normal, as well as creatinine levels, indicating that Rasbuciare prevents the AU accumulation during CT.

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APOTOPSIS RELATED PROTEINS IN VIRUS-ASSOCIATED LYMPHOMAS

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Introduction: Viral proteins may be tumorigenic by interfering to growth and apoptotic pathways of lymphoid tissue. Lymphomas associated with HIV hosts have poor prognosis and the characteristic of Burkitt lymphoma and HTLV-I T cell lymphomas (Hamornosed). Antigaptoptic proteins are involved in chemoresistant neoplastic cells and p53 when it is mutated and overexpressed is tumorigenic and may gain antagonist properties.

Methods: We studied the presence of apoptosis-related proteins: Antigaptoptic bcl-2 and mcl-1 and prosapopptic bax and bak and the protooncogene p53 in: HIV, EBV and HTLV-1-associated lymphomas. The expression of apoptosis-related proteins was determined by immunocytochemistry in paraffin embedded lymphoid tissue from infiltrated lymph nodes or other tissues. Immunopositive specimens were considered the specimens that contain >10% of cells, immunostained by the specific antibody to each of the above referred proteins.

Results: Our results, for each type of lymphomas are summarized in the table:

<table>
<thead>
<tr>
<th></th>
<th>bcl-2</th>
<th>mcl-1</th>
<th>bak</th>
<th>bax</th>
<th>p53</th>
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<tbody>
<tr>
<td>HIV-NHL</td>
<td>4</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>2/J</td>
</tr>
<tr>
<td>Burkitt-L</td>
<td>4</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>1/J</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>4</td>
<td>+</td>
<td>+</td>
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</table>

The therapeutic outcome for HIV-NHL was 2 CR and 2 non-responders. For Burkitt Lymphoma 2 CR and 2 Non-responders and HTLV-1 lymphoma patient died of chemoresistant disease.

Conclusions: Although the number of studied cases is restricted we could point out the absence of bcl-2 expression, except in HTLV-1 NHL and the high expression of p53 protein particularly in Burkitt lymphomas. The effect in the therapeutic outcomes in relation to the presence or absence of these proteins has to be defined.
NEW GRADING SYSTEM FOR EARLY CARDIAC TOXICITY OF ANTITUMOR TREATMENT

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Background: Modern aggressive treatment modalities used in Hodgkin Disease (HD) require comprehensive evaluation of inherent risk profile. Our experience in 378 HD patients followed between 1994 and 1996 showed limited usefulness of current EORTC/ROG and WHO grading system particularly in the setting of combined chemo-radiotherapy.

Patients and methods: To obtain deeper insight into early cardiac toxicity we developed own grading system applied to 110HD patients treated between 1997 and 2001. Electrocardiogram (ECG) and echocardiogram (ECHO) were performed before therapy, during and after drug treatment, during and after irradiation and 1, 3 and 6 months after completion of the therapy.

Results: According to the WHO and EORTC grading system cardiac toxicity was found in 27% of pts and using the presented system in 80%, mainly grades I and II. Conclusions: The suggested grading system allows more objective assessment of morphologic and functional abnormalities of the cardiac muscle, pericardium and valves. It is based on noninvasive examination, user-friendly and unambiguous. The discrepancy in cardiac toxicity rates are due to the progress and widespread use of ECHO and inclusion of a large spectrum of cardiac abnormalities into the suggested grading system.

FLOW CYTOMETRY CHARACTERIZATION OF HAEMOPHIEITIC CELLS FROM UNIRRADIATED BONE MARROW OF HODGKIN’S DISEASE SURVIVORS

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INTRODUCTION: Radical radiotherapy for Hodgkin’s disease (HD) results in permanent aplasia of exposed bone marrow (BM). Unirradiated BM is supposed to be in compensatory activation for the rest of patient life. Earlier we reported the decrease of cellularity and CFU-GM content in aspirations from unirradiated BM of HD patients in 20 years remission which contradicted to apparently normal blood counts. Our further aim was to use flow cytometry method for evaluation of cell populations of unirradiated BM in long-term HD survivors and age-matched controls.

METHODS/RESULTS: Aspirates of bone marrow cells were obtained from iliac crest in 28 HD survivors who received mantle-like RT 20-34 years ago. Age-matched controls were 15 hematologically healthy persons. Median age was 46 and 45 years, respectively. We analysed the total number of CD34+ cells and their proliferative activity, as well as immature subsets of CD34+CD33+, CD19-CD20- cells with no difference found between main and control groups. However, the relative number of the most immature CD34+CD38- cells proved to be significantly lower in HD group. We studied erythroid compartment with monoclonal antibodies to glycoprotein A (GPA), to CD34 and to transferrin receptor (CD71). In HD group the percentage of GPA+ cells was decreased (P<0.000), while for fractions of GPA+CD34+ and GPA+CD71- cells only the trend to decrease was found. Proportion of immature GPA+CD34+ cells of the erythroid compartment did not differ between HD and control group.

CONCLUSION: The study has revealed disturbances involving early stages of haemoepoiesis and its erythroid compartment. Taking into account that unirradiated bone marrow may approach the limits of its functioning capacity further observations with periferal blood control seem to be very important for this cohort of HD patients.

WHO IS PREDISPOSED TO ANTEROYCYCLINES INDUCED CARDIOMYOPATHY FROM THE VIEW OF EOTHEDELIN

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Introduction: The role of endotheII-1 (ET-1) in some special pathological states has not cleared yet. Since it is known that anterocyclines are able to cause cardiomyopathy researchers are investigating the effect of anterocyclines but it is still unknown how to predict whether someone is sensitive or not to the influences of anterocyclines. We have focused on left ventricular systolic and diastolic functions and their association with the level of plasma ET-1 in 31 (18 female and 13 male) patients suffering from Hodgkin’s disease or Non-Hodgkin lymphomas.

Methods: Serum ET-1 level has been measured by ELISA method. Left ventricular function has been described by echocardiography including ejection fraction (EF), tissue velocity integral (VTI), E and A waves, E/A ratio, deceleration time (DT) and we first studied Doppler index in this relation. Statistical analysis was made by the Wilcoxon rank test.

Results: EF and serum ET-1 level have significantly decreased after anterocycline therapy (EF: 56.4 ± 5.6 vs. 48.7 ± 6.5, p < 0.0001; ET-1: 5.63 ± 5.3 vs. 3.1 ± 0.9 pg/ml, p = 0.0006). Deceleration time has also changed significantly (168.1 ± 36.8 ms vs. 206.5 ± 58.8 ms, p = 0.0073). There was no difference in other echocardiographic parameters before and after therapy.

Conclusion: Decrease of serum ET-1 concentration is thought to be a result of direct cytotoxic effect of anterocyclines and the decreased level of ET-1 can play a role in the reduction of EF. Nevertheless, results of further studies on ET-1 are necessary to be able to predict the development of anterocyclines induced cardiomyopathy.
BONE MARROW HARVEST AND TRANSPLANTATION CAN RESULT IN SUCCESSFUL ENGRAFTMENT IN PATIENTS WHO HAVE INADEQUATE PERIPHERAL BLOOD STEM CELL COLLECTION
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High-dose chemotherapy with autologous stem cell transplantation improves survival for patients with Hodgkin's disease (HL) and non-Hodgkin lymphoma (NHL). Previous reports suggest that bone marrow (BMM) harvest in patients who have inadequate peripheral blood stem cell (PBSC) collection is ineffective and results in delayed recovery and a high transplant related mortality (TRM). We have previously examined predictors of poor PBSC mobilization. Herein, we examine the hematologic recovery of patients who underwent BMM harvest and subsequent autologous transplantation after inadequate PBSC collection (defined as ≤ 2×10^6 CD34/kg). Between 10/97 and 6/00, 111 patients underwent PBSC mobilization for HL (21) or NHL (90). Sixteen patients who had inadequate PBSC mobilization underwent BMM harvest and subsequent autologous transplantation with (12) or without (4) the addition of collected PBSC. Median CD34 cell dose for the collected PBSC was 0.93×10^6/kg. Fifteen of 16 (94%) bone marrow transplantation (BMT) patients achieved an absolute neutrophil count of ≥500/μl at a median of 18 days (range 11-40). In comparison, 80 of 95 (85%) who underwent PBSC transplantation reached an ANC of ≥500/μl at a median of 12 days. WBC engraftment ≥1000/μl was met in 13 of 16 (81%) of BMT patients at a median of 15 days, as compared to a median of 12 days in 90 of 95 patients (95%) who underwent PBSC transplantation. 10 of 16 (63%) patients who underwent BMT achieved platelet engraftment above 50,000/μl at less than 100 days (median 41.5 days), compared to a median of 20 days in 82 of 95 (86%) patients, following PBSC transplant. Of the 8 BMT patients who did not have platelet engraftment by day 100, 3 subsequently engrafted (at 105 days, 16 months and 17 months), 2 died of disease progression (at 116 days and 11 months) and 1 is receiving chemotherapy for relapsed disease. There was no TRM. Thus, although hematologic recovery, especially platelets, may be delayed in patients who undergo BM harvest and transplantation after an unsuccessful PBSC collection, a significant proportion achieves satisfactory engraftment and it does not appear to be associated with an increased TRM.

TOTAL-BODY IRRADIATION BEFORE ALLOGENEIC BONE MARROW TRANSPLANTATION: IS MORE DOSE, ALWAYS BETTER?
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Introduction: To retrospectively assess the potential influence of total-body irradiation (TBI) dose in overall survival in patients undergoing allogeneic bone-marrow transplants (BMT) for hematologic malignancies.
Methods: Between 1984 and 1996, 116 patients were conditioned with high dose chemotherapy and total body irradiation (TBI) before allogeneic BMT. The median age was 34 years (range, 3-60 years). The diagnosis was acute myeloid leukemia in 26 patients, acute lymphoblastic leukemia in 33, and myelodysplastic syndrome in 8. Chronic myelocytic leukemia was diagnosed in 30 patients. Eight patients were treated for non-Hodgkin's lymphoma, and 1 patient for multiple myeloma. The TBI dose was delivered in 6 fractions, twice-a-day, over 3 days before BMT. The total dose was 10 Gy in 24 patients, 12 Gy in 66 patients and 13.5 Gy in 26 patients. Results: After adjusting for primary diagnosis, age, sex, presence of GVHD, pre-BMT disease status, and level of T-cell depletion, TBI dose was inversely correlated with overall survival (p = 0.015). Five-year survival was best for patients conditioned with 10 Gy (i.e., 60%), fair for patients conditioned with 12 Gy (i.e., 55%), and worse for patients conditioned with 13.5 Gy (i.e., 46%). Age at BMT was also correlated with overall survival (p<0.03) with the best survival for patients between 17-20 years of age at BMT. Conclusions: A higher TBI dose may not be correlated with a better outcome in patients undergoing allogeneic BMT for hematologic malignancies. This may be especially important in patients younger than 20 or older than 40 years of age with a higher risk of dying after BMT.

ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA: MOLECULAR STUDY OF 21 PATIENTS AT A SINGLE CENTRE
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Introduction: Angioimmunoblastic lymphadenopathy (AILD) is characterised by poor clinical outcomes and complex molecular abnormalities with multiple clones frequently present.
Methods: This study documents the clinical features and treatment outcomes for 21 patients with AILD treated at a single centre, for which phenotypic and genotypic data are available.
Results: Most patients presented with advanced disease (stage III and IV), at a median age of 60 with a high incidence of lymphoproliferative, systemic symptoms and extranodal disease. Electrophoresis revealed paraproteins in 4 patients. A variety of single agent and combination chemotherapy regimens were used with improved prognosis in patients receiving combination chemotherapy. With median follow-up of 16.3 years, the 10 year overall survival is 88%. Patterns of antigen expression for T, B, NK and dendritic cells were similar in most biopsies; CD4 positive T lymphocytes were predominant. There was correlation between activation and proliferation markers. No survival difference was seen according to the immunohistochemical parameters assessed or with EBV infection, found in 15/21 cases. Genotypic analysis revealed clonal heterogeneity; monoclonal T-cell receptor PCR products were detected in 17/21 (81%) of cases while IgH clonal or oligoclonal gene rearrangements were detected in 11/21 (52%) of cases. Patients with IgH gene rearrangements had median survival of 18.3 months (range 3.4-217 months) compared with those without of 5 months (range 0.5-9.8 months).
Conclusion: These data suggest that clonal heterogeneity may be associated with longer survival.

UTILITY OF FREE SERUM EPSTEIN-BARR VIRUS (EBV) DNA IN MONITORING NK-AND T-CELL LYMPHOMAS
RKC Zhang, WJ Liu, JKC Chan, TCC Yip, MMC Cheung, WW Cheng, VC Sin, HMY Yiu, W Cho, HC Cheng, KH Wong and W Foo.
Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong, China.
Introduction: T-cell and NK-cell lymphomas are more prevalent in Chinese, and they are generally more aggressive than B cell lymphomas. Since there is a close association of certain types of T and NK cell lymphomas with EBV, we investigate whether free EBV DNA detectable in the sera of such patients (pts) may serve as a clinically relevant tumor marker in monitoring disease.
Methods: Twenty consecutive Chinese pts with active T or NK-cell lymphomas were recruited from June 2000 to Jan 2002 for serial prospective measurement of EBV DNA in serum samples before, during and after chemotherapy and radiotherapy. They included 15 extranodal NK/T lymphomas of nasal type, 2 peripheral T-cell lymphomas unspecified, 2 angioimmunoblastic T-cell lymphomas and 1 primary cutaneous anaplastic large cell lymphoma. Thirteen pts with NK/T lymphomas presented clinical remission, 5 pts with active B cell lymphomas and 57 thyrotoxic pts without malignancy were recruited as controls. EBV encoded RNA-1 (EBER-1) was measured by q-PCR technique & correlated with the in-situ hybridization for EBER in tumor samples. Results: Serum EBER-1 was detected in the serum of 12 (60%) of the 20 pts (median, 1751 copies/ml; interquartile range 322-4245 copies/ml). Serum EBER-1 was not detected in all the 75 control pts. Among the 15 pts with NK/T lymphomas of nasal type (all EBER positive by in-situ hybridization), serum EBER-1 was detected in 9 (60%). Two of the 9 serum EBER-1+ pts came from the group of 7 pts with localized nasal/nasopharyngeal disease, and 7 from the group of 8 pts with more extensive local disease (stage IE, n=5) or disseminated disease (stage IVA, n=3) (p=0.037, chi-square test), suggesting a possible relationship of serum EBV DNA with tumor burden. The mean EBER-1 level was significantly lower in the former group (55 copies/ml) compared with the latter (818 copies/ml) (p=0.013, Mann-Whitney U test). The majority of the EBER-1+ pts (12 pts (98%) showed concordant clinical and serum profiles. Three pts without detectable serum EBER-1 at diagnosis had at least 1 year follow-up (FU) and all are still alive without relapse (100%). Only 3 of the 12 pts (25%) with detectable serum EBER-1 having adequate FU are alive without disease (p=0.034, chi-square test). Conclusions: Assay of free EBV DNA in serum is helpful for monitoring the response to therapy and the clinical disease in pts with T or NK cell lymphomas. Serum EBER-1 appears to be related to the tumor burden and a poor outcome. Its independent prognostication value in T and NK cell lymphomas should be further explored.
ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA: MOLECULAR STUDY OF 21 PATIENTS AT A SINGLE CENTRE

E Hodges, JL Smith, JC Pellatt, BS Wilkins, JW Sweetenham, PVM Johnson.
Cancer Sciences Research Division, Southampton University Hospitals, Southampton, UK.

Introduction: Angioimmunoblastic lymphadenopathy (AILD) is characterised by poor clinical outcomes and complex molecular abnormalities with multiple clones frequently present. Methods: This study documents the clinical features and treatment outcomes for 21 patients with AILD treated at a single centre, for which phenotypic and genotypic data are available. Results: Most patients presented with advanced disease (stage III and IV), at a median age of 50 with a high incidence of lymphadenopathy, systemic symptoms and extranodal disease. Electrophoresis revealed paraproteins in 4 patients. A variety of single agent and combination chemotherapy regimens were used with improved prognosis in patients receiving combination chemotherapy. With median follow-up of 16.3 years, the 10 year overall survival is 18%. Patterns of antigen expression for T, B, NK and dendritic cells were similar in most biopsies; CD4 positive T lymphocytes were predominant. There was correlation between activation and proliferation markers. No survival difference was seen according to the immunohistochemical parameters assessed or with EBV infection, found in 15/21 cases. Genotypic analysis revealed clonal heterogeneity; monoclonal T-cell receptor PCR products were detected in 17/21 (81%) of cases while IgH clonal or oligoclonal gene rearrangements were detected in 11/21 (52%) of cases. Patients with IgH gene rearrangements had a median survival of 16.3 months (range 3.4-217 months) compared with those without (range 0.5-6.8 months).

Conclusion: These data suggest that clonal heterogeneity may be associated with longer survival.

UTILITY OF FREE SERUM EPSTEIN-BARR VIRUS (EBV) DNA IN MONITORING NK AND T CELL LYMPHOMAS

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Introduction: T-cell and NK-cell lymphomas are more prevalent in Chinese, and they are generally more aggressive than B cell lymphomas. Since there is a close association of certain types of T and NK cell lymphomas with EBV, we investigate whether free EBV DNA detectable in the sera of such patients (pts) may serve as a clinically relevant tumor marker in monitoring the disease. Methods: Twenty consecutive Chinese pts with active T or NK cell lymphoma were recruited from June 2005 to Jan 2006 for a prospective measurement of EBV DNA serum levels. Results: With q-PCR technique & correlated with the in-situ hybridization for EBER in tumor samples. Results: Serum EBER-1 was detected in the serum of 12 (60%) of the 20 pts (median, 173 copies/ml; interquartile range 322-624 copies/ml). Serum EBER-1 was not detected in all the 75 control pts. Among the 15 pts with NK/T lymphoma of nasal type (all EBER positive by in-situ hybridization), serum EBER-1 was detected in 9 (60%). Two of the 9 serum EBER-1+ pts came from the group of 7 pts with localized nasal/nasopharyngeal disease, and 7 from the group of 8 pts with more extensive local disease (stage III, n=5) or disseminated disease (stage IVa, n=2) (p=0.037, chi-square test), suggesting a possible relationship of serum EBV DNA with tumor burden. The mean EBER-1 level was significantly lower in the former group (55 copies/ml) compared with the latter (8418 copies/ml) (p=0.013, Mann-Whitney U test). The majority of the EBER-1+ pts (80%) showed concordant clinical and serum profiles. Three pts without detectable serum EBER-1 at diagnosis had at least lyver follow-up (FU) and all are still alive without relapse (100%). Only 3 of the 12 pts (25%) with detectable serum EBER-1 having adequate FU are alive without disease (p=0.034, chi-square test).

Conclusions: Assay of free EBV DNA in serum is helpful for monitoring the response to therapy and the clinical disease in pts with T or NK cell lymphoma. Serum EBER-1 appears to be related to the tumor burden and a poor outcome. Its independence in predicting survival and NK and NK cell lymphomas should be further explored.