HODGKIN’S DISEASE AND HIV INFECTION (HD-HIV) IN PRE AND POST HAART ERA: PERSONAL EXPERIENCE IN 137 PATIENTS

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Hodgkin’s disease (HD) is the most common non-AIDS defining tumour diagnosed in HIV infected patients. Its unusual aggressive tumour behaviour includes a high frequency of unfavourable histologic subtypes, advanced stage and extranodal involvement and a poor outcome. However, the introduction of highly active antiretroviral therapy (HAART) has opened a new prospective in the treatment of patients with HD-HIV. In fact the better control of the underlying HIV infection allows the use of more aggressive chemotherapy regimens, including high dose chemotherapies. This table summarizes the results of the prospective studies performed at our Institution in this setting so far.

<table>
<thead>
<tr>
<th>Regimen</th>
<th># of pts</th>
<th>HAART + CT</th>
<th>Stage III-IV</th>
<th>CR rate</th>
<th>OS</th>
<th>DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>17</td>
<td>No</td>
<td>53%</td>
<td>11 mos</td>
<td></td>
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<tr>
<td>EBVP</td>
<td>35</td>
<td>No</td>
<td>83%</td>
<td>74%</td>
<td>16</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>at 3 mos</td>
<td></td>
<td></td>
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<tr>
<td>Stanford V</td>
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<td>Yes</td>
<td>71%</td>
<td>81%</td>
<td>68% at 2 yrs</td>
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<td></td>
<td></td>
<td>at 2 yrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEDEP</td>
<td>26</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

Since the widespread use of HAART, CR rate is improving and OS and DFS as well. The concomitant use of HAART and chemotherapy is feasible and advisable in our experience. At the present time 26 patients have been enrolled in the third generation regimen VEDEP (vincristine, epirubicin, bleomycin, cyclophosphamide and prednisone) and the preliminary results will be presented at the meeting.

In conclusion, in the HAART era HD seems to be a more successfully treatable malignancy, although at higher incidence and probably with the same aggressive behaviour at the presentation as in the pre-HAART era. Supported by ISS and AIRC grants.

AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) AS SALVAGE REGIMEN IN PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) HIV ASSOCIATED LYMPHOMA (HIV-LY) IN THE HAART ERA: A SINGLE CENTRE EXPERIENCE

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Introduction: The treatment of HIV Associated Lymphoma (HIV-Ly) has changed since the introduction of HAART. However, for pts with R/R disease, second line chemotherapy still offer little chance of survival. A previous report of some of us (J Clin Oncol 21; 4423, 2003) demonstrated that High Dose Chemotherapy is feasible in selected cases, although HIV pts with R/R Ly, often showed comorbidities representing exclusion criteria for ASCT.

Methods: From November 2001 until January 2005, 32 pts affected by R/R HIV-Ly (7 HD and 25 NHL) were enrolled in this study. The GICAT (Italian Cohoperative Group AIDS and Tumors) criteria for inclusion in the ASCT protocol were as follows: PS<3 WHO; Ventricular Ejection Fraction>50%; Creatinine<2mg/dL, Bilirubin<3mg/dL; absence of opportunistic infections (OIs) severe or active, not CNS lymphoma, ongoing HAART and CD4>100 µL.

Results: 28 (62%) pts were male and 4 (38%) were female, M/F ratio of 7:1. Median age was 40 (26-66), 25 (78%) pts were non Hodgkin Lymphoma (NHL) and 7 (22%) Hodgkin’s disease (HD). 3 pts (9%) had HBV chronic hepatitis and 13 (40%) HCV chronic infection. CD4+ median count was 140 mL (4-460), HIV viral load was<50 cpm/L for 12 pts (43%).

Conclusions: The number of pts having at least one major exclusion criterion for ASCT was 14 (44%). Despite the presence of at least one major exclusion criteria, we treated all population with a second line chemotherapy and 13 (41%) had at least a partial response. On the basis of the chemosensitivity, 13/52 received the ASCT, while, by strictly following the GICAT criteria, only 8 pts should have received the same treatment. The additional 5 pts treated with ASCT had an OIs (3 pts), hepatic failure (1 pt), renal failure (1 pt). No pt died by ASCT. The 3yrs projected overall survival were 82% and 15% for cases undergoing or not ASCT, respectively. The 3yrs-projected OS of the entire population was 44%.

ANALYSIS OF IGV GENES IN AIDS-RELATED NON HODGKIN LYMPHOMA: IMPLICATIONS FOR DISEASE PATHOGENESIS AND IMMUNOSUPPRESSION

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Introduction: NHL is a frequent complication of HIV infection and a major source of morbidity and mortality among patients affected by AIDS. AIDS-NHL are a suitable model to study lymphomagenesis in a context of disrupted immunosurveillance and the analysis of IGV genes can provide insights into the pathogenesis of the disease.

Methods: We investigated 67 AIDS-NHL for IGV gene rearrangements. Results where compared to a database of 200 IGV rearrangements from NHL of immunocompetent hosts (IC-NHL) as well as to the normal B-cell repertoire.

Results: A functional IGHV rearrangement was found in 60/67 (90%) cases, a functional IGVK chain rearrangement in 17/38 (45%) cases and a functional IGLV rearrangement in 21/38 cases (55%). 53/60 AIDS-NHL (88%) showed somatic hypermutation in IGV genes. IGV germline rearrangements selectively associated with AIDS-PBL (P<0.001). AIDS-NHL showed a significant overrepresentation of the IGHV4 family (28/60; 47%) and a significant underrepresentation of IGHV3 family (18/60, 30%) compared to aggressive IC-NHL (P<0.001) and to normal B-cells (P<0.002). IGHV4-3 was the IGHV gene most frequently rearranged (17/60; 28%) and was overrepresented in AIDS-NHL versus aggressive lymphoma of immunocompetent hosts (17%; P<0.03) and normal B-cells (4%; P<0.001). The IGVK4-1 gene was the IGVK segment most frequently rearranged (6/17; 35.3%) and its usage was biased in AIDS-NHL compared to normal B-cells (5.3%; P<0.001). A tendency to conserve FR sequences and maintain antigen binding was observed in 24/65 (37%) cases. Selection for high affinity antigen binding was observed in 17/52 (33%) cases. Analysis of intraclonal heterogeneity showed the presence of ongoing mutations in only 3/15 AIDS-NHL.

Conclusions: Most AIDS-NHL derive from B-cells persistently subjected to GC reaction, suggesting a potential role for antigen stimulation in the pathogenesis of the disease. Moreover, the preferential usage of IGHV4-3 and IGVK4-1 genes may suggest a role for a superantigen stimulation of pre-germline B-cells with polyreactive and/or autoreactive activity.

HIGH INCIDENCE OF KAPOSI SARCOMA-ASSOCIATED HERPES VIRUS INFECTION IN HIV-RELATED SOLID IMMUNOBLASTIC/PLASMABLASTIC DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Kaposi sarcoma-associated herpes virus (KSHV) is known to be associated with two distinct lymphoproliferative disorders: primary effusion lymphoma (PEL) and multicentric Castleman disease (MCD)/MCD-associated plasmablastic lymphoma. A small number of KSHV-positive lymphomas without effusions have been described in the literature, usually as anecdotal case reports. These tumors, which usually arise in the context of HIV-infection, have been proposed to represent "extra-cavitary PELs" and are believed to be decidedly rare. However, systematic studies exploring the incidence of KSHV infection in solid HIV-related lymphomas are lacking. We therefore studied the incidence of KSHV infection in a cohort of patients with HIV-related NHLs.

Methods and results: Within a cohort of 99 HIV-related NHLs 10 cases were found to be KSHV positive on the basis of immunostaining for KSHV LNA1-1 as well as KSHV-specific PCR. All but one of the tumors co-expressed Epstein–Barr virus (EBV). Interestingly, all KSHV-positive cases belonged to a distinctive subgroup of 26 diffuse large B-cell lymphomas (DLBCL) characterized by expression of CD138 (syndecan-1) and plasmablastic/immunoblastic morphology. These KSHV-positive lymphomas were preceded by Kaposi sarcoma in 60% and involved the gastrointestinal tract in 80% of the patients. Our results indicate that KSHV infection is not restricted to PEL and MCD, but is also common (38%) in HIV-related solid immunoblastic/plasmablastic lymphomas (SPLs).

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EPSTEIN–BARR VIRUS GENOMIC AMOUNTS AND T-CELL CLONALITY ARE NOT ASSOCIATED WITH PROGNOSIS OF ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA

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Introduction: Angioimmunoblastic T-cell lymphoma (AITL) is peripheral T-cell tumor of unknown etiology and variable biological and clinical presentation. Previous clonality studies have shown a heterogeneous composition of this tumor, with varying clonal restrictions of B- and T-cell populations. A characteristic feature of AITL is the presence of increased numbers of EBV (Epstein–Barr virus) infected cells.

Method and result: We have analyzed 50 AITL cases and found clonal T-cells in 15/50 and clonal B cells in 25/50 tumors. And monoclonal bands of EBV-W in 10/50 tumors. However, there was no relationships between clinical survival rate and T-cell clonality (P = 0.8338). And the clonality of the EBV infected cells was not associated with survival rate, also (P = 0.8336). In addition, we used a real-time PCR assay to quantify the amount of EBV DNA in the tissue. The copy number of EBV DNA in the tissue from EBV infections was not correlated with disease progression (P = 0.3505).

Conclusion: T-cell clonality status and EBV infection had no influence on survival in AITL patients. AITL remains a progression disease with clinical behavior that varies irrespective of these genomic parameters.

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EBV ASSOCIATION WITH PERIPHERAL T-CELL LYMPHOMA

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Introduction: Epstein–Barr virus (EBV) has been associated with various T-cell lymphomas. In this study, we tried to determine the incidence and prognostic significance of EBV association with peripheral T-cell lymphomas.

Methods: The association of EBV with human immunodeficiency virus (HIV)-positive peripheral T-cell lymphoma was examined in 68 Japanese patients, using EBER in situ hybridization, polymerase chain reaction with primers to Bam HI W and immunohistochemistry with monoclonal antibodies to LMP-1.

Results: EBER was detected in 63% of all the peripheral T-cell lymphoma: in 100% of NK/T cell lymphoma, 70% in AILT, and 49% of other types of peripheral T-cell lymphoma. The five-year survival rate was 28% in the whole peripheral T-cell lymphoma, 0% in NK/T cell, 38% in AILT, and 28% in other types of peripheral T-cell lymphoma. The difference in overall survival rate between NK/T cell lymphoma and non-NK/T cell lymphoma was significant (P = 0.0498). Among peripheral T-cell lymphoma patients overall, the group severely infected with EBV had lower 5-year survival rate (8%) than the group that was slightly or not infected group (38%) (P = 0.0013).

Conclusion: Severe EBV infection in NK/T lymphoma predicts a poor prognosis.

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EPSTEIN–BARR VIRUS INFECTION AND RISK OF LYMPHOMA: IMMUNOBLOT ANALYSIS OF EBV-RELATED PROTEINS IN A LARGE SERIES OF LYMPHOMA SUBJECTS AND COMPARABLE CONTROLS IN SPAIN

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Epstein–Barr virus (EBV) has been consistently associated to several lymphoproliferative malignancies. We evaluate the detection of an abnormal serological reactive pattern to EBV infection and the risk of lymphoma in a multicentric case-control study.

Methods: The study included 512 lymphomas and 588 controls. EBV serostatus was evaluated through ELISA for EBNA1(BKRF1) and VCA-p18 (BFRF3). Immunoblot analysis evaluate antibody diversity patterns to EBNA1, VCA18, VCA-p40 (B2RF1) and Zebra (B2LF1). Patients with chronic active EBV infection and aberrant EBV activity were characterized as having a EBV reactive pattern.

Results: Abnormal response to EBV was statistically associated to the risk of all lymphomas (OR = 1.53, 95% CI = 1.13–2.07), to all B-cell lymphomas (OR = 1.49, 95% CI = 1.09–2.07), to chronic lymphocytic leukemia (OR = 3.08, 95% CI = 1.94–4.91) and to T-cell lymphomas (OR = 2.22, 95% CI = 1.03–4.78).

Conclusions: EBV may be involved in a larger subset of lymphomas than previously reported due to a probable underlying lost of immune control of EBV latent infection.

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IDENTIFICATION OF PLASMA MEMBRANE PROTEINS OF CUTANEOUS T-CELL LYMPHOMA

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Introduction: Antibody-based therapy is a promising strategy to treat tumors, especially in cases of lymphomas. 7 FDA approved monoclonal antibodies for cancer therapy are targeted for lymphoma treatment. A prerequisite for this approach are plasma membrane proteins which are specifically expressed on tumor cells. The aim of this study is to find such proteins of Sézary syndrome and Mycosis fungoides, which belong to the group of cutaneous T-cell lymphoma.

Methods: Two rabbit antisera were raised against a plasma membrane enriched fraction of a Sézary syndrome cell line, SeAx. They were used for screening a cDNA-phyte library of the same cell line by SEREX. Interesting candidates of all identified clones were analyzed for overexpression in CTCL patient samples by quantitative real-time PCR analysis. Results: We could detect 4 known plasma membrane proteins: Integrin alpha 4, Ligatin, HLA-A and MT5-MMP. A quantitative real-time PCR showed an interesting expression profile for MT5-MMP. Ku86, a nuclear protein, has been found frequently. We looked for ectopic expression in lipid rafts and could detect a small amount in SeAx cells by western blot.

Conclusions: Rabbit antiserum against plasma membrane fractions of a tumor can be used in SEREX to search for candidates for antibody-based therapies. MT5-MMP was identified and showed increased expression in some CTCL tumor probes. The ectopic expression of Ku86 in lipid rafts opens a possible usage as a target for therapeutic antibodies. These two proteins will be further investigated.
ROLE OF SOLUBLE CD30 ON DEVELOPMENT OF ADULT T CELL LEUKEMIA/LYMPHOMA
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Introduction: Adult T cell leukemia/lymphoma (ATLL) is one of the most aggressive malignant lymphomas, leading to incurable disease. The poor prognosis of this disease is due to not only the high drug resistance of ATLL cells, but also the secondary immune deficiency causing patients to suffer from a variety of opportunistic infections and allowing tumor cells to expand.
Methods: Since recent reports showed that CD30 is involved in the inhibition of T cell immune response, we investigated CD30 expression in PBMCs of acute type and LN cells of lymphoma-type ATLL. We next addressed soluble CD30 (sCD30) expression status in each clinical stage of ATLL. In three cases with acute type, the levels of sCD30, sIL-2R and LDH were analyzed longitudinally.
Results: CD30 was expressed on various numbers of ATLL cells as well as cell lines including MT-2, L540 and Karpas 299. The level of sCD30 increased in ATLL patients with acute type rather than lymphoma-type and decreased following the response to chemotherapy. Refractory cases kept high level of sCD30 during their clinical course and the change of sCD30 was independent on the other serum proteins including sIL-2R and LDH.
Conclusions: We found a part of ATLL cells expressed membrane and soluble form of CD30 and the level of sCD30 affected chemotherapy resistance. Our findings suggest that CD30 expressing ATLL cells play an important role for the development and the aggressiveness of this disease.

FAS GENE MUTATIONS IN MYCOSES FUNGOIDES: ANALYSIS OF LASER CAPTURE-MICRODISSECTED SPECIMENS FROM CUTANEOUS LESIONS
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Introduction: Fas (APO-1/CD95) is a transmembrane protein which mediates programmed cell death (apoptosis). Cells with a mutated Fas gene are resistant to apoptosis and thus accumulate in lesional tissues. This might provide a basis for the development of neoplasias.
Methods: Genomic DNA selectively obtained from Pautrier’s microabscesses in 16 cases of mycosis fungoides (MF) using a laser capture microdissection method was analyzed.
Results: Fas gene mutations were detected in 3 of 16 cases of MF (18.8%); 1 was silent and 2 were missense mutations located in exon 9. One of the 2 missense mutations involved the death domain of the Fas gene, which is essential for apoptotic signal transduction. The missense mutations resulted in the substitution of Ala with Thr at codon 220 and Ile with Thr at codon 314. Mouse T cell lymphoma cells transfected with mutant genes were resistant to apoptosis induced by the anti-Fas antibody, indicating that the missense mutations found in MF were loss-of-function mutations, thus causing the accumulation of cells in the cutaneous lesions.
Conclusions: These findings suggest that the accumulation of lymphoid cells with Fas mutations provides, in part, a basis for the development or maintenance of MF.

INVOLVEMENT OF YY1 AND MICROSATELLITE REPRESSOR SEQUENCES IN THE TRANSCRIPTIONAL CONTROL OF THE CD30 GENE IN ANAPLASTIC LARGE CELL LYMPHOMA
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Introduction: CD30 is a member of the TNF receptor family whose overexpression is a diagnostic marker for Anaplastic Large Cell Lymphoma (ALCL). Our specific interest lies in understanding the molecular events that lead to the very high CD30 expression levels. As our hypothesis is that the level of expression of CD30 determines the nature of the response of the neoplastic cells to cytotoxic signals, interfering with the CD30 control mechanisms may have therapeutic potential.
Methods and Results: The discovery of a polymorphic, tetranculeotide repeat (or microsatellite) which acts to repress transcriptional activity of the CD30 promoter, suggests that this region is involved in dysregulation of CD30 expression in neoplastic cells. Using a 2D proteomics approach we have identified the major microsatellite binding activity as the transcriptional repressor YY1 by peptide mass fingerprinting. Interaction of YY1 with the microsatellite in vivo has been confirmed using chromatin immunoprecipitation (ChiP) analysis. Due to the strong repressive effect of the microsatellite we have also investigated, in single ALCL cells captured by laser microdissection, whether microsatellite instability in the repressor may induce changes in CD30 expression.
Conclusions: Transcription factor YY1 has a major influence in the expression of the CD30 gene and acts through the polymorphic microsatellite located upstream of the CD30 gene.

EXTRANODAL NK/T LYMPHOMA OF NASAL TYPE: THE TORONTO EXPERIENCE
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Purpose: Extranodal NK/T lymphoma of nasopharyngeal type characterized by CD56+ and EBV+ has been reported from Asia but is a rare disease in Western countries. We report the treatment outcome and the pattern of failure in this disease in Toronto.
Methods: 21 patients (pts) with stages I (16), II (1) and IV (4) disease were referred 1994–04. The median age was 52 yrs (range 23–89 yrs), M:F ratio 2:1. Ten pts were of Asian origin, 10 were Caucasians, and 1 additional origin. The treatment plan was combined modality (CHOP to CR, then local radiation) in 19 pts and radiotherapy (RT) in 2 pts. Since 2000, those who responded to CHOP were offered ASCT followed by RT (2 pts), or upon relapse if the disease was chemotherapy (CT) sensitive (1 pt). Median RT dose prescribed was 40 Gy (range 35–50 Gy).
Results: A response to initial CT was achieved in 7/19 pts (CR 5, PR 2, ORR 37%), while 12 pts had no response/progressed (63%). For responding pts (n=7), 5 are alive with no evidence of disease (NED)–including the 2 treated with ASCT (at 0.7, 2.3, 4.3, 8.7 and 9.4 yrs). Non-responding pts (which included the 4 stage IV pts) progressed locally and required urgent RT (11 out of 12 pts), with CR in 4 (36%), PR in 2 (18%), and NR in 5 (45%), and only 1 is still alive with NED (follow up 7.5 yrs). The median survival time of the 12 pts was 4.5 months. The dominant failure sites in the 12 pts included local in 8 (67%), cervical node in 2 (17%), systemic sites in 7 (58%), and CNS in 3 (25%). Two pts were treated initially with RT alone, both died at 0.3 yr and 1.8 yrs due to progressive disease. Overall, 6 pts are alive with NED, and 15 pts died (14 due to lymphoma). The 2-yr disease-free survival was 38% (Asian pts: 30%, Caucasians: 48%, P = 0.35), and overall survival 36% (Asian pts: 30%, Caucasians: 47%, P = 0.37).
Conclusions: Conventional sequential CMT appears inadequate therapy for nasopharyngeal NK/T lymphoma. Salvage RT had limited success. More intensive treatment approaches should be investigated. There were no significant differences in clinical presentation and treatment outcome between Asian and Caucasian patients, although this should be interpreted with caution due to small sample size.

NATURAL KILLER (NK)-CELL NEOPLASMS: AGGRESSIVE NK-CELL LEUKEMIA AND EXTRANODAL NK-CELL LYMPHOMA, NASAL TYPE
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PROGNOSTIC FACTORS IN PRIMARY CUTANEOUS B-CELL LYMPHOMA: A 542 PATIENTS SERIES, THE ITALIAN STUDY GROUP FOR CUTANEOUS LYMPHOMAS (GILC)

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Introduction: Primary cutaneous B-cell lymphomas (PCBCL) are a distinct group of diseases in the general scenario of the extranodal non-Hodgkin’s lymphoma and, particularly, in the cutaneous lymphoma subset. In the literature, conflicting data exist regarding the prognostic factors and these data were evaluated on little numbers of patients. In the present retrospective study, the prognostic factors and follow-up data of a large group of PCBCL patients are reported.

Methods: The study group included 542 patients with PCBCL referred, treated and followed in 11 Italian centers (the Italian Study Group for Cutaneous Lymphomas, GILC) during a period of 24 years (1990–2003). There were four different histologic subtypes: marginal zone lymphoma (MZL), large B-cell lymphoma (LBCL), large B-cell lymphoma of the leg (leg-type LBCL), and follicular center lymphoma (FCL).

Results: The univariate analysis for overall survival (OS) identified age older than 55 years (P=0.001), presence of regional or disseminated cutaneous lesions (P=0.0009), a lower limb localisation (P=0.0001), a histologic diagnosis of LBCL, and a first-line chemotherapy treatment. The univariate analysis for disease-free survival (DFS) showed only the single lesion as statistically significant factor (P=0.001). Multivariate analysis identified all LBCL, others, leg-type LBCL (P=0.039 and P<0.001, respectively) for OS and the single cutaneous lesion (P=0.003) for DFS. The 10-year DFS for patients with leg-type LBCL was 21.5%, compared to 44% for the remaining cases. The global 10-year OS rate of all 542 study patients was 83% and the global 10-year DFS of all 483 cases was 49%.

Conclusions: The results of this large retrospective PCBCL study suggest that patients with LBCL histology (particularly, the leg-type one) and/or the presence of a disseminated disease have a more unfavorable prognosis. In terms of outcome, about 50% of the PCBCL patients are cured.

CLINICAL SIGNIFICANCE OF HEMATOLOGICAL ABNORMALITIES IN ADULT T-CELL LEUKEMIA-LYMPHOMA (ATLL)

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Background: ATLL, i.e. a mature T-cell malignancy associated with human T-lymphotropic virus type-1, has been reported to have some hematological abnormalities at diagnosis. We comprehensively investigated how the hematological abnormalities affect prognosis and other clinical characteristics in ATLL.

Methods: 168 ATLL patients (136 with aggressive type and 32 with indolent type) were evaluated for hematological abnormalities (anemia, thrombocytopenia, neutropenia, neutrophilia, monocytes, eosinophilia, and basophilia), organ involvements (bone marrow, skin, liver, spleen), “B” symptoms, and overall survival. In selected patients, we analyzed plasma concentrations of several cytokines by ELISA.

Results: In all cases, thrombocytopenia was associated with bone marrow infiltration (OR 6.1), hepatic involvement (OR 4.8), and splenic involvement (OR 3.5). Neutropenia and eosinophilia were associated with skin lesion (OR 5.5 and 3.6 respectively) and basophilia were associated with “B” symptoms (OR 2.4 and 3.5 respectively). Unfavorable prognostic factors were the presence of neutrophilia, monocytosis and...
THE VIP-ABVD REGIMEN IS NOT SUPERIOR TO THE CHOP 21 FOR THE TREATMENT OF NON-ENTEROTROPIC PERIPHERAL T CELL PROSPective "LTPC" GOELAM PROTOCOL

Introduction:
There is no consensus today for the treatment of PTCL. The five-year OS with the CHOP regimen is estimated to be 40% and 63% with the VIP/ABVD regimen (see abstract laguno 2005).

Aim of the study and methods:
To confirm the superiority of the VIP/ABVD in first line pts with PTCL. We have compared the 2 years EFS of pts receiving 8 × CHOP21 or 6 alternating VIP/ABVD in a random manner.

Results:
88 pts were included: 45, CHOP and 43 VIP/ABVD. 53/88 pts (60%) achieved a CR (34) or PR-75% (19). With a median follow-up of 26.5 months EFS and OS are respectively: 40% at 2 years and 40% at 4 y. There is no difference between the two groups. Two factors: age and stage of the IPI score significantly influenced the survivals: histologic types and AA stage.

Conclusion:
The VIP/ABVD is not superior to the CHOP regimen for the treatment of PTCL. The combination Amr Arbor stage and the histologic pattern is the best predictive factor of the survivals. New innovative approach are mandatory to improve the prognostic of PTCL.

CHOP CHEMOTHERAPY PLUS CAMPATH-1H (CHOP-C) AS FIRST LINE TREATMENT IN PATIENTS WITH PERIPHERAL T-CELL LYMPHOMA (PTCL)

Introduction:
The prognosis of PTCL is very poor, with a 5-year overall survival ranging between 25% and 40%. High-dose chemotherapy followed by ASCT seems to improve the prognosis in a small fraction of them. We report here the preliminary results of standard CHOP therapy plus Campath-1H in a cohort of PTCL patients (p).

Methods:
Starting from January 2003, 12 consecutive pts were treated by CHOP for 8 courses, preceded on d. -1 by Campath 30 mg/m2 before the courses 1-4, for the last four patients accrued(Cohort-1: C1), and before all the 8 courses for the remaining patients (Cohort-2: C2). The diagnosis was PTCL-U in 8 p. and ALL-T in 4. 11/12 p. were in stage III-IVB, 7/12 had high LDH values, 5/12 bone marrow attainment. Nine p. completed the therapy and are available for the analysis.

Results:
after a median follow-up of 298 days (175–591), 59% are still alive. Two C1 p. progressed 115 and 66 days after diagnosis, and died of lymphoma, despite salvage treatment. 5/9 p. achieved CR, 1 PR and 1 MR; the latter, in C1 cohort, progressed and died 307 days after the end of the therapy. One patient of C2 cohort relapsed and died +25 days after CR. The median OS and DFS were 510 and 264 days respectively. No toxicity was recorded. WHO grade 4 neutropenia was seen in 32/70

ESHAP CHEMOTHERAPY REGIMEN AND 13-CIS-RETINOIC ACID IN ELDERLY PATIENTS WITH UNTREATED POOR-PROGNOSIS PERIPHERAL T CELL LYMPHOMA: A GELA PHASE II TRIAL OF FEASIBILITY AND EFFICACY

Introduction:
Peripheral T-cell lymphomas (PTCL) are associated with poor outcome after conventional chemotherapy including anthracyclines and alkylating agents. The aim of this study is to analyze the effects of alternating chemotherapy regimens and 13-cis-retinoic acids (RA) on a large series of elderly patients with PTCL.

Methods:
Patients with a non-cutaneous T-cell lymphoma had to be 60 years or older, with an age-adjusted international prognostic index (AIP-1) ≥ 1. Patients aged 60 to 69 years and those ≥ 70 years with a performance status (PS) of 0-2 received 6 monthly courses of ESHAP regimen with EP-16 40 mg/m2/d for 4 days, Ara-C 2 g/m2 intravenously over 2 hours on day 5, cisplatin 25 mg/m2/d for 4 days, and methylprednisolone 500 mg intravenously daily for 5 days. The doses were reduced in poor PS patients ≥ 70 years (cohort B) with Ara-C 1 g/m2, cisplatin 15 mg/m2, and methylprednisolone 250 mg. Patients simultaneously received continuous oral RA 0.5 mg/kg/d.

Results:
Complete data are available for 58 patients to date: 34 men and 24 women with a median age of 70 years (60–88). Cohort A comprised 41 patients, and cohort B, 17. Histology was: PTCL unspecified, 39 cases (67%); angioimmunoblastic T-cell lymphoma, 18 cases (31%); and null killer cell lymphoma, 1 case. Patients presented with a disseminated disease in 94% of cases, with an elevated serum LDH value in 84% of patients. Five p. had an Aa-IPI ≥ 2. 24/41 (59%) patients in cohort A received ≥ 4 courses of chemotherapy, and 17 (41%) completed chemotherapy. Treatment was discontinued after cycle 3 in 17 patients (41%): progression disease (PD), 9, partial response ≤ 50% (PR ≤ 50%), 2; toxic death, 6. In cohort B, 10/17 (59%) patients did not receive more than 3 cycles: PD, 3; PR ≤ 50%, 2; toxic death, 5. Only 5/17 (29%) patients completed treatment. Among the whole population, 38 (66%) could receive RA with a median dose delivered at 35 mg/d. The overall complete response rate was 33%, with 34% and 29% in cohorts A and B, respectively. With a median follow-up of 14 months, the 2-year overall survival and event-free survival of the series are 36% ± 17% and 21% ± 12%, respectively.

Conclusion:
Combination of ESHAP chemotherapy and RA is of high toxicity in elderly patients with poor-prognosis PTCL. Patients respond poorly to this therapy and have short survivals with no sustained remissions.

ALEMTUZUMAB, FLUDARABINE, CYCLOPHOSPHAMIDE, AND DOXORUBICIN (CAMPATH-FCD): AN EFFECTIVE FIRST-LINE TREATMENT IN PERIPHERAL T-CELL LYMPHOMAS

Introduction:
Peripheral (mature) T-cell lymphomas (PTCL) are represented by a group of lymphoma entities, mostly with an unfavourable clinical outcome.

Methods:
Treatment consisted of alemtuzumab 3, 10, 30, 30 mg, days 1–4, fludarabine (Flu) 25 mg/m2 days 2–4, cyclophosphamide (CP) 600 mg/m2 day 3, and doxorubicin (Dox) 50 mg/m2 day 4. Included were
patients with primary diagnosis, with first relapse, or with primary refractory disease.

Results: So far, 26 patients have been included, 21 are evaluable for response and toxicity: 12 PTCL-NOS, 6 AILD, 1 enteropathy-ass. PTCL, 1 NK-cell lymphoma, 1 T-PLL, 11 with primary diagnosis and 10 with relapse. The median age was 57 years (21–77); the median non-age adjusted IPI 2.5 (0–4). The overall response rate was 62% (13/21). In patients with primary disease the CR rate was 73% (8/11), 2 patients were primary progressive, 1 patient died from treatment as complications before response evaluation. Seven patients are in ongoing CR at 2+, 2+, 6+, 11+, 15+, 16+, and 17+ months. The patient with T-PLL relapsed after 20 months. In the group of relapsed or refractory patients one CR and 4 PR (50%) were observed. Grade III and IV toxicity: leukocytopenia (73%), anemia (15%), thrombocytopenia (39%), infections (15%), pruritus (9%), nausea/vomiting (7%), cardiac (6%, two patients with relapsed disease and pretreatment with CHOP-like regimens), and lung (3%) toxicity. Ten (56%) patients reactivated CMV, 9 without CMV-related disease and one patient with suspected CMV-pneumonia.

Conclusions: Campath-FCD is effective in the first-line treatment of peripheral T-cell lymphomas, however, regarding the general outcome a longer follow-up period of a larger patient population is required. Because the results were not convincing in relapsed disease and because of two heart failures in this group, the study was closed for relapsed patients, but is ongoing in primary disease.
11. Pediatric Lymphomas

NON HODGKIN LYMPHOMA (NHL) IN ADOLESCENTS: A 20-YEAR EXPERIENCE AT THE PEDIATRIC UNIT OF ISTITUTO NATIONALE TUMORI, MILAN

Methods: Since 1984, among 292 consecutive children with a newly diagnosed NHL, this analysis retrospectively considered 81 pts aged 14–21 yrs. Median age was 15 yrs (range 14–21); M/F ratio 2:5. Phenotype distribution was as follows: Burkitt’s (BU) 23 cases, diffuse large B-cell (DLBCL) 11 (variants: centroblastic 9, immunoblastic 1, anaplastic 1), mediastinal (thymic) large B-cell 3, anaplastic large cell (T or null) (ALCL) 14, precursor T lymphoblastic lymphoma (TL) 19, precursor B lymphoblastic 3, MALT 3, high-grade B cell not further specified 2. Three pts with a diagnosis of histiocytic sarcoma were excluded. Mediastinum was affected in 13/19 TL (8/19 had bone marrow involvement), while the ileum-cecum was involved in 14/23 BU. Other primary sites included: Waldeyer’s ring 3, lymph nodes, bone, liver, kidney.

Results: Mature B-cell neoplasm constituted 72% of histories in this age group (56/78), with BU representing 29% of all cases. Median Fup was 111 mos (range 5–277), 5-year DDFS for 56 mature B-cell lymphomas was 77.6% (SE: 5.7%), S 80.1% (SE: 5.4%); for 22 precursor T or B-cell neoplasm DDFS was 52.6% (SE: 11.6%), S 49.1% (SE: 11.7%), 5-year DFS for BU: 76.9% (SE: 9.1%), S 73.9% (SE: 9.2%); 5-year DDFS for all pts was 71% (SE: 5.4%), EFS 67% (SE: 5.4%), and S 72.1% (SE: 5.2%). S rates for mature B-cell without before (66.7%, SE 6.6%) or after (84.3%, SE 7.2%) 1996, were not significantly different (P = 0.11).

Conclusions: The histology-based approach to NHL that we adopted seemed to show less favourable outcome for adolescents in respect to children less than 14 yrs of age.

MYELOABLATIVE (MA) AUTOLOGOUS STEM CELL TRANSPLANTATION (AUTO SCT) FOLLOWED BY REDUCED INTENSITY (RI) ALLOGENIC SCT (ALLO SCT) IN CHILDREN & ADOLESCENTS WITH POOR RISK RELAPSED LYMPHOMA


Methods: We investigated MA AutoSCT followed by RI AlloSCT in poor risk relapsed/refractory pediatric HD/NHL. MA AutoSCT consisted of CBV, CD20+ lymphoma pts received Rituximab/GMCsf and all pts IFRT (2000–3000 cGy) post AutoSCT, 9/11 proceeded to RI AlloSCT to date with Bu/Flu ± ATG (unrelated only) (2 related PBSC, 1 8/10 MUD, 6 UCBC).

Results: 11 pts, 7 HD and 4 NHL, age 8–21 yrs, med F/U 666 d. 8/9 evaluable pts post AlloSCT. Median time to RI AlloSCT after MA AutoSCT was 130 d. GVHD: grade II-IV, aGVHD (208), cGVHD (208). All pts achieved 100% donor chimerism. 4/6 HD pts are NED d 1290, +1291, +610, +63 respectively; 2 pts died, 1 PO + 1 cGVHD. 2/2 NHL are NED day +972 and +87 respectively. The estimated 1 yr OS is 52.6%.

Conclusions: MA AutoSCT followed by IFRT, targeted antibody therapy, and AlloSCT is feasible and well tolerated in children & adolescents with poor risk if this approach will help reduce relapse and/or MDS and improve EFS.

WHOLE-BODY POSTIRON EMISSION TOMOGRAPHY USING 18F-FLUCODEXOXYGLUCOSE FOR POST-TREATMENT EVALUATION OF CHILDREN AND ADOLESCENTS WITH HODGKIN’S LYMPHOMA

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Introduction: After therapy approximately 40–60% of children with Hodgkin’s lymphoma (HL) have residual abnormalities with conventional imaging methods (CIM). However, only 10–20% of post-treatment residual masses are positive for lymphoma on biopsy. Metabolic imaging by 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) offers the advantage of functional tissue characterization and can differentiate between residual tumor and benign fibrosis. In our study, we evaluated prospectively the clinical value of FDG PET compared with CIM in detecting residual lymphoma and predicting relapse after first-line therapy in children with HL.

Methods: Forty children and adolescents (median age 15.2 years, range 4.1–18.1) with HL, who underwent FDG PET after completion of first-line chemotherapy and radiotherapy and chemotherapy were included. PET results were compared with results of histology, imaging, and/or follow-up.

Results: With a median follow-up of 31 months (range 6–42), 34/35 with negative post-treatment PET remained in CR, 43% of them had residual mass on CIM. Relapse occurred in 3/5 positive PET studies: 1/18 children with residual masses on CIM and 2/22 with negative CIM. Post-treatment PET studies had higher sensitivity (75% vs. 25%), specificity (94% vs. 53%) for characterization of residual masses than CIM. The positive and negative predictive values of PET were 60% and 97% versus 5% and 86% for CIM (P<0.05). The overall accuracy of PET for predicting disease-free survival was significant higher than that of CIM (93% vs.50%, P<0.05).

Conclusions: Post-treatment PET studies in children with HL had higher diagnostic and prognostic value than classical imaging. FDG PET predicted early progression but would not exclude the presence of minimal residual disease, leading to a later relapse.

Acknowledgements

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CDS2 AND CD25 ARE HIGHLY EXPRESSED IN CHILDHOOD NON-HODGKIN’S LYMPHOMA AND MAY BE EXCELLENT TARGETS FOR IMMUNOTHERAPY WITH ALEMTUZUMAB AND/OR DENILEUKIN DIFITIOX, RESPECTIVELY

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Introduction: There is little information on the expression of CD25 and CD25 in T-NHL and ALCCL. Use of humanized antibodies against CD25 (alectumab) and an immunotoxin to CD25 (denileukin difitox) have been approved for the treatment of adult NHL.

Methods: We evaluated 81 children and adolescents with NHL (central pathology confirmed) including 25 BL, 19 T-BL, 9 B-BL, 15 DLBCL and 13 ALCCL for CD25 expression and 12 children with ALCCL for CD25 expression. Paraffin sections from COG NHL specimens were stained for CD25 (Novocastro NCL, Santa Clara, CA) and CD25 (DAKO, Carpinteria, CA) by immunohistochemistry using protease 2 antigen epitope retrieval. Staining was recorded as 4+ (> 75% of cells+); 3+ (51%–75%+); 2+ (26–50%+); 1+ (1–25%+). Staining intensity was scored as weak (1+), moderate (2+), and strong (3+).

Results: 80/81 (99%) cases had CD25 expression including 4+ staining in 80% BL, 84% T-BL, 66% B-BL, 93% DLBCL and 93% ALCCL; in 54%, 2+ in 30% and 1+ in 20%. 91/125 (75%) patients with ALCCL had CD25 expression.

Conclusion: CD25 is uniformly expressed in 99% of childhood B and T NHL and CD25 is significantly expressed (75%) in childhood ALCCL. Future targeted immunotherapy studies with alectumab and/or denileukin difitox should be considered for subsets of poor risk childhood NHL.

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12. New Treatments

1D09C3, A NOVEL APOPTOTIC HUMAN MONOCLONAL ANTIBODY: MODE OF ACTION AFFECTS DOsing SCHEDULES

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Introduction: 1D09C3 is an HLA-DR-specific human IgG4 monoclonal antibody (mab) that induces rapid apoptotic death of lymphoid tumors. We have hypothesized that apoptosis once triggered by the mab can proceed in its absence, and thus, optimal in vivo effects may be achieved under "hit-and-run" kinetics. This hypothesis was tested in a xenotransplant model.

Methods: The half-life of 1D09C3 in mice was determined by ELISA. Down-regulation of HLA-DR in vivo was monitored on splenic B cells of HLA-DR-transgenic mice by FACS analysis. Xenotransplants: Granta-519 (B-NHL, ten million) cells were injected i.v. into SCID mice after elimination of NK cells. Disease was manifested in paraplegia and death 20–30 days after initiation.

Results: 1D09C3 had a short (<3h) half-life in mice. Transient down-regulation of the ligand (~80%) occurred at 24h, followed by re-expression at 48h after treatment. These observations suggested an optimal treatment schedule of every other day. However, comparison of treatments on days 5, 5+7, and 5+7+9 showed that frequent repeats were equivalent in potency to a single treatment. Increasing the treatment intervals to 4 and 7 days resulted in improved efficacy. Thus, despite re-expression of HLA-DR, tumor cells surviving the treatment gained temporary resistance to re-exposure. A similar resistance was demonstrated in vitro, with sensitivity to treatment reappearance gradually within several days.

Conclusions: Mab 1D09C3, despite a half-life of <3h, had optimal efficacy when applied at intervals as long as 7 days. Thus, sustained blood levels of mab may not be necessary. Treatment intervals of at least 4–7 days are dictated by the biology of tumor cells, since the latter show temporary resistance to antibody after surviving the first treatment. These findings may have relevance for the dosing schedules of 1D09C3 in phase I trials.

PROGNOSTIC FACTORS FOR TIME TO PROGRESSION (TTP) IN PATIENTS RECEIVING RITUXIMAB FOLLOWED BY IDIOTYPE IMMUNOTHERAPY

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Introduction: Idiotype immunotherapy represents a unique and promising approach for patients with B-cell malignancies. Prior studies suggest that idiotype immunotherapy following chemotherapy can result in an increase in TTP, at least in part, in a subset of patients. We have conducted a multi-center phase II study using Id/KLH (Favild) immunotherapy following cytoreduction with rituximab and have evaluated our patient population for prognosticators of clinical outcome as assessed by TTP.

Patients and methods: 103 patients (56 male, 47 female; median age 53 years) with treatment naïve (41) or relapsed/refractory (62) follicular NHL (FL) were enrolled in the study. Patients received rituximab for 4 weeks followed by idiotype vaccination with Favild (1 mg, subcutaneously) starting on week 12. Favild was administered monthly for 6 months, then every other month for 12 months, and then every 3 months until progression. Univariate analyses of potential prognosticators were performed, using as the predictive variable the TTP after the start of rituximab.

Results: Of the variables evaluated (age, sex, prior surgery, prior chemo, prior radiotherapy, prior rituximab, response to rituximab, number of relapses, WHO grade, stage, B-symptoms, albumin, hemoglobin and bulky disease), number of prior relapses (HR 1.8, P = 0.02) and prior rituximab (HR = 2.1, P = 0.05) were significantly associated with TTP.

Conclusion: In our patients with FL receiving rituximab followed by idiotype vaccination, only prior rituximab and number of prior treatment regimens are associated with TTP. Owing to the limited number of patients who have progressed to date (fewer than half of our patients have progressed), other associations may become apparent as the data matures.

The identification of number of prior regimens as a predictor for progression following idiotype immunotherapy supports the evaluation of this therapy in treatment naïve and less heavily pretreated patients.

THE ANTI-CD30 ANTIBODY-DRUG CONJUGATE SGN-35 IS A POTENT THERAPY FOR THE TREATMENT OF CD30+ MALIGNANCIES

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Introduction: CD30, a member of the TNF receptor superfamily, is highly expressed on the surface of Anaplastic Large Cell Lymphoma (ALCL) and Reed Sternberg Cells. Despite this expression, anti-CD30 based therapies have only achieved modest activity in clinical trials. A potent antibody drug conjugate using the anti-CD30 antibody cAC10, conjugated to a novel, synthetic anti-mitotic agent, monomethyl auristatin E (MMAE) has been developed.

Methods: The antibody cAC10 was mildly reduced to partially reduce the eight cysteines that comprise the antibody's four inter-chain disulfide bonds. MMAE was coupled to cAC10 using a protease cleavable Val-Cit peptide linker to yield SGN-35 with an average of four MMAE molecules per antibody. In vitro potency of SGN-35 was measured by incubating various concentrations of SGN-35 with CD30+ tumor cells and measuring cell viability in culture. SCID mice were implanted with the ALCL tumor cell line Karpas-299 and treated with either a single dose or multiple intra-necrotic intratumoral doses of SGN-35.

Results: SGN-35 had potent in vitro activity with IC50 ranging from 3.9 to 15.8 ng/ml against CD30+ cell lines, and an IC50 >1000 ng/ml against the CD30+ line WSU-NHL. In mice bearing subcutaneously implanted Karpas-299 cells, complete regressions were achieved at doses as low as 0.5 mg/kg, q4d x 4 and 1 mg/kg given as a single dose. Similar data have been obtained in other CD30 positive tumor cell models.

Conclusions: SGN-35 demonstrated activity in vitro against CD30+ cell lines while it had no effect on a CD30+ tumor cell line. SGN-35 was not only potent in vitro but also in Karpas-299 mouse model studies where SGN-35 produced complete regressions at low doses. Clinical trials are planned to begin in the near future.

HIGH DOSE CELECOXIB AND METRONOMIC "LOW DOSE" CYCLOPHOSPHAMIDE IS EFFECTIVE AND SAFE THERAPY IN PATIENTS WITH RELAPSED AND REFRACTORY AGGRESSIVE HISTIOCYTOSIS

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Introduction: Angiogenesis is increased in aggressive histiocyte non-Hodgkin's lymphoma (NHL) and may be a target with selective COX-2 inhibition and metronomic chemotherapy (MC). Methods: We assessed response, toxicity and biometers of angiogenesis to low dose cyclophosphamide (50 mg po OD) and high dose celecoxib (400 mg po bid) in adult patients with relapsed or refractory aggressive NHL. Results: 30 of 32 patients are evaluable for response. Median age 62. Patients were primarily relapsed diffuse large B cell (68%), heavily pretreated (median 3 regimens), high risk (77% IP3 ≥ 2) and 35% were relapsed post autologous stem cell transplant. With a median time to death or last follow up of 8.5 months, the overall best response rate (ORR) is 37% (2 CR, 9 PR, 9 NR) months, overall progression-free survivals are 8.5 and 4.7 months. Prolonged response durations were or continue to be observed in some responders (10–27 months). Serious toxicities were rare with no vascular complications or treatment related deaths. Circulating endothelial cells and their precursors declined and remained low in responders while serum VEGF and thrombospindolin levels did not correlate with response. Trough celecoxib levels achieved targeted "anti-angiogenic" levels. Conclusions: Low dose
cyclophosphamide and high dose celecoxib is safe and active in 37% of heavily pre-treated aggressive NHL. The anti-angiogenic activity of this regimen is being explored.

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RADIOIMMUNOTHERAPY (RIT) WITH LUTETIUM-177-DOTA-RITUXIMAB: A PHASE I/II – STUDY IN 11 PATIENTS WITH RECURRENT MANTLE CELL LYMPHOMA. AN INTERIM ANALYSIS

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Introduction: Pt with mantle cell lymphomas (MCL) may remain sensitive to radiation and immunotherapy. Many do not tolerate aggressive regimens.131Iodine or 90Ytrium labelled antibodies have been tested in MCL. Lutetium-177 may have better physical characteristics for small or diffusely infiltrating tumours. It also emits a smaller gamma component suitable for imaging.

Methods: In a Phase III study 11 pt (2f, 9m, med age 70y; 7 pt rituximab pretreated, 5 refractory) were treated with 20-40 mcg/m2 of Lu-177-DOTA-Rituximab on d 8 (250 mcg/m2 unlabelled Rituximab on d 1 and 8). Pt were PET and CT staged week (w) 1 + 4. Hospital stay was around 3d for logistic reasons.

Results: On w 8 2 CR and 2 PR were seen. Three were stable, 4 progressed. A pt with 1 CR progressed month 24. He received a 2nd Lu-177-DOTA-Rituximab and is in a 2nd CR. The 2nd pt with a CR on w 8 had been Rituximab refractory and relapsed month 7. One CR relapsed month 5 and then 3rd CR remains in PR in month 4+. Gr 2 arthritis, diarrhea and asthenia were seen in one pt each. Two Gr 3 TC perniciosa were seen.

Conclusions: Lu-177-DOTA-Rituximab is active in MCL. Further treatment in refractory cases to be possible and even retreatment may be an option. The accrual to this study is ongoing. (Supported by the Basel cancer league and the JP Obrecht foundation. Rituximab was provided by Roche Pharma Schweiz).

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ONGOING RESULTS OF A PHASE I TRIAL OF TWO SEQUENTIAL DOSES OF Y-90 BRITURIMOMAB TIIXETAN (ZEVALIN®) FOR PATIENTS WITH RELAPSED LOW-GRADE NON-HODGKIN LYMPHOMA (NHL)


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Purpose: To learn if patients can be safely retreated with Zevalin after an initial standard dose of 0.4 mcg/kg.

Patients and Methods: Patients were required to have measurable relapsed NHL; absolute neutrophil count >1,500; platelet count >150,000; bone marrow <25% tumor involvement, and stem cells harvested. All patients received 0.4 mcg/kg (capped at 32 mcg) as the first dose. Patients who achieved a CR/PR were eligible for the second dose (the Phase 1 dose) 3–6 months later.

Results: Eighteen patients were accrued and 83% (15/18) responded and received a second dose of Zevalin—9 received 0.2 mcg/kg and 6 received 0.3 mcg/kg. No patient was treated with prophylactic growth factors. Two of the 6 patients at 0.3 mcg/kg experienced a dose-limiting toxicity (thrombocytopenia) and thus 0.4 mcg/kg was considered the maximum tolerated dose for patients without prophylactic growth factors. No patient required stem cell reinfusion. Of the 15 responders, 7 achieved a CR and 9 achieved a PR. Six of the 18 patients (33%) remain in continuous remission, a median of 29 months (23–41 months) from the day of first treatment. The study was amended to allow prophylactic G-CSF (neupogen) and IL-11 (neumega). Seventeen patients have been accrued to this arm and 58% (10/17) responded and 5 patients received 0.2 mcg/kg as a second dose and 5 received 0.3 mcg/kg. Five of these 10 patients remain in continuous unmaintained remission, a median of 17 months (11–27+) from study entry. The trial continues to accrue with new patients being treated at 0.4/0.4 mcg/kg.

Conclusions: Retreatment with Zevalin is feasible and with prophylactic growth factors a second dose of 0.3 mcg/kg can be administered without the use of stem cells. The study continues to explore higher dose levels with growth factor support.

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TANDEM HIGH DOSE CHEMOTHERAPY AND MYELOABLATIVE RADIOIMMUNOTHERAPY WITH 131-I-ANTI-CD20 RITUXIMAB IN RELAPSED AND REFRACTORY B-CELL LYMPHOMA: INTERIM RESULTS OF A PHASE II STUDY OF THE GERMAN RIT STUDY GROUP

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Objectives: Radioimmunotherapy (RIT) has been shown to be effective in CD20+ B-cell lymphomas. Both non-myeloablative as well as myeloablative regimens have been employed for low grade and high grade lymphomas demonstrating objective response rates and long-lasting remissions. Recently, the Seattle group (Gopal et al., Blood 2003) and our group (Griesinger et al., Blood 2002) published data on myeloablative 131I-anti-CD20 RIT with high response rates and favourable long term survival, especially in follicular lymphomas and transformed FL. Therefore, this treatment approach is currently being studied in a prospective phase II feasibility study of the German Radioimmunotherapy Group that started in 2002/2003.

Methods: Patients were to receive R-Dexa-BEAM, followed by BEAM and a second high dose treatment with HD-RIT 2-6 months after BEAM. 131-I-Rituximab was administered with a maximum kidney and lung dose of 25 Gy. Results: 13 pts with relapsed (11) or primary refractory (2) B-cell lymphomas (FL/LII: 3pts; DLBCL: 3pts (all early relapses); transformed FL: 5pts; MCL: 2pts) were treated with 1 (12 pts) or 2 cycles (1 pt) of R-Dexa-BEAM. 10/13 pts achieving PR (3) or CR (7) were treated with BEAM, 2 pts with PD went off-study acc. to protocol. After BEAM, 7 pts were in CR, 1 in PR, 1 pt was in PD and 1 pt had lung toxicity prohibiting further treatment. 7/8 responding pts received HD-RIT (1 too early), 6/7 achieved CR, 1 remains in PR. 5/7 pts (4 CR, 1 PR) are alive for 6–27 months without progression of lymphoma, 2 pts died in CR, 1 of interstitial lung disease 2 months after HD-RIT, 1 pt of pneumonia 8 months after HD-RIT.

Conclusion: Tandem HD-chemotherapy followed by myeloablative RIT is a feasible and effective treatment strategy for relapsed poor prognosis CD20+ B-NHL offering the potential for long term relapse free survival. Further analyses of toxicity and outcome will be presented.

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A PHASE I TRIAL OF A NOVEL POLYMINE ANALOG, CGC-11047, IN PATIENTS WITH LYMPHOMA

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Introduction: The gene expression signatures of macrophages (MO) associated with follicular lymphoma are predictive of survival (Dave, 2004). We have previously shown that "pathogenic"(CD14+/16+) lymphoma -associated MO can initiate lymphomagenesis (Zengler,2002) and are found in tumor and peripheral blood in individuals with a variety of lymphomas.

Methods: CGC-11047, which is cytotoxic for tumor cells and proliferating MO but not normal MO, was administered to 6 patients(9) ((Hodgkins 2), SLL (2), follicular (1), ALC(L)1) at the first 2 dose levels of a dose-escalation study. SCGC-11047 was administered IV at 15 mcg/m2 or 25 mcg/m2 over 30 min on 5 consecutive days every 3wks. Blood for pK analysis, proliferating MO levels, and drug sensitivities was obtained.
Results: Toxicities included grade 3 neutropenia (2), grade 2 (2), grade 1 (1) thrombocytopenia, and grade 4 prothrombin time prolongation while on coumadin (1). Two to 7 cycles were administered. T/T2 for levels 1 and 2 were 0.1 and 0.59 hr, respectively with Cmax 291 and 400 ng/ml and AUC 254 and 210 ng hr/ml. ED 70% (70% in vitro killing) for abnormal peripheral blood macrophages: pt 1: 100m, pt 2: 10m, pt 3: 0m, pt 4: 0.1m, pt 3: >100m, pt 6: >100m. Controls (5): >100m. High baseline blood levels of proliferating MO returned to normal after cycle 1 without an associated minor anti-tumor response in pt 4. Pt 6 M0s responded after the first cycle with a minor clinical response. Pt 1,2,3,5 showed neither clinical nor blood MO responses. Pre- and post-treatment MO gene expression profiles will be presented.

Conclusions: CCG-11047 shows activity against both tumor and associated macrophages in vitro. In vitro sensitivities to drug can be determined and in the most sensitive patient tested to date (patient 4) clinical and blood MO responses were observed. T/T2 were short, as expected, and toxicities minimal. The study is ongoing.

PHASE 2 STUDY OF BORTEZOMIB AND RITUXIMAB IN PATIENTS WITH INDOLENT NON-HODGKIN’S LYMPHOMA (NHL)

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Introduction: Molecules targeting cell cycle proteins can play a role in the therapeutic approach of diseases large B-cell lymphomas (MCL) and mantle cell lymphomas (MCL). Sellecicib (Cyclacel Ltd.,Dundee,UK) is a purine analogue and selective inhibitor of cdk2/cyclinE as well as cdk7/cyclinH and cdk9/cyclinT. We evaluated in the in vitro kinetic activity of sellecicib in MCL and DLBCL cell lines and assessed the effect on the expression of cell cycle- and apoptosis-related genes, especially when deregulated as a result of translocations involving the 11q13 genes.

Methods: The effect of sellecicib was assessed on 4 human MCL and 9 DLBCL cell lines. To specifically evaluate the drug effect on lymphoma-specific genes, conventional and molecular cytogenetics, and Western blot experiments were performed.

Results: All MCL and DLBCL cell lines were sensitive to sellecicib. The IC50, assessed after 72-hour exposure, ranged between 15–50 μM in MCL and DLBCL. In MCL the drug induced cell cycle accumulation in G2/M and apoptosis. Down-regulation of various genes (e.g. CCND1, MCL-1 in MCL) was observed, possibly due to inhibition of daily activities, suggested by decrease in the phosphorylated and total forms of RNA polymerase II. Data on the expression of BCL2, BMY, BCL6 in DLBCL cells will be presented.

Conclusions: Our in vitro data suggest sellecicib as an active new compound for MCL and DLBCL therapy. A phase II clinical trial on MCL, chronic lymphocytic leukemia and multiple myeloma is on-going.

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PRELIMINARY EXPERIENCE OF ORAL ARSENIC TRIOXIDE BASED THERAPY IN THE TREATMENT OF REFRACTORY MANTEL CELL LYMPHOMA

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Background: Arsenic trioxide (As2O3) is an active agent in acute promyelocytic leukemia. We tested whether it might be active in lymphoma, either alone or in combination with chemotherapy or ascorbic acid (AA).

Material and methods: Mantle cell lymphoma (MCL) or chronic lymphocytic leukemia (CLL) patients with relapsed or refractory disease were recruited. Oral As2O3 (10 mg daily), ascorbic acid (AA 1 g daily) and chlorambucil (25 mg daily) were administered in the outpatient department until a response was obtained or the disease judged refractory. In cases of partial response, vincristine and steroids were added. Chlorambucil was omitted for cases with molecular evidence of residual disease only. In responding patients, maintenance treatment with the same regimen for 2 weeks was given every month for a planned two years.

Results: Nine men and one woman (MCL: 7, CLL: 3) at a median age of 58 (41–83) years were treated. The median time from diagnosis to treatment was 36 (3–85) months, and median number of previous treatment was 2 (range 1 to 4). Reversible liver enzyme derangement occurred in 4 cases. The CLL cases did not respond and two died subsequently. The median follow up in MCL cases was 8 (3–48) months. Molecular disease was cleared in two MCL cases. Among 5 MCL cases with frank disease, complete remission was obtained in 2 cases, and partial remission in 2 cases. One MCL case with static disease died at 17 months.

Conclusion: A combination of oral As2O3, AA and an alkylating agent is a feasible outpatient based option for relapsed and refractory MCL.

EFFECTS OF CARBOXYPEPTIDASE G2 (CPG2) RESCUE IN 30 LYMPHOMA PATIENTS WITH HIGH-DOSE METHOTREXATE (HD-MTX) INDUCED RENAL FAILURE

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Introduction: MTX-accumulation in patients (pts.) with HD-MTX induced renal failure is a life-threatening condition. CPG2 cleaves MTX into non-toxic metabolites. We have evaluated HD-MTX treated lymphoma pts. who received, in an emergency use protocol, CPG2 rescue treatment for delayed MTX-elimination/renal failure. Methods: Pts. with renal insufficiency (creatinine >1.5 upper limit of normal) were eligible for treatment with CPG2 at 1μmol/l at 42 h, or >0.4μmol/l at 48 h after start of HD-MTX. In addition, pts. with mMTX >5μmol/l at 42 h (+/- renal insufficiency) were also eligible. Serum concentrations of MTX and metabolites were measured by high-performance-liquid-chromatography (HPLC). Results: Overall, 30 lymphoma pts. (age: 19–78 years; 17 with CNS-involvement) were enrolled. At registration, mMTX ranged from 1.01–1187μmol/l (median: 10.02). Doses of CPG2, given i.v. at median 56 h (range 27–176 h) after start of HD-MTX, ranged from 10–56μmol/kg. CPG2 was well tolerated, except for fever (grade II) in a single pt. MTX serum levels, assessed by HPLC in 13 pts. with available serum samples, rapidly declined from a median of 5.75μmol/l (range 0.5–165.86) to 1μmol/l or less within 7–15 minutes after CPG2 administration. Serum creatinine levels remained normal in 1 pt. and returned to normal in 14 pts. after a median of 9 days. The remaining 15 pts. had a median peak serum creatinine level of 292μmol/l with subsequent decline to a median of 163μmol/l by days 1–55 after CPG2 therapy. Conclusions: CPG2 is a well tolerated and effective antidote for HD-MTX associated renal failure or delayed MTX-clearance resulting in a rapid reduction of circulating MTX.

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UPDATED ANALYSIS OF THALIDOMIDE PLUS RITUXIMAB IN RELAPSED MANTLE CELL LYMPHOMA

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Introduction: Stromal cells provide stimulatory signals to malignant B-cells supporting their proliferation and survival. This prompted us to evaluate thalidomide (THAL) in patients with mantle cell lymphoma (MCL), which showed promising antitumor activity in combination with rituximab (R) in the setting of relapsed/refractory MCL (Blood 2004;104:2269).

Methods: We present an updated analysis of 18 previously treated patients with MCL, who received R (one course with 4 weekly doses at 375 mg/m2) plus THAL (up to 400 mg concomitantly with R and as maintenance) at relapse. Median time between diagnosis and initiation of R+THAL was 21 months (range 4–52), and 8 patients had received ≥2 prior regimens (previous R in 5 patients).

Results: Overall response rate was 83% (15 of 18 patients), with a complete response (CR) in 5 patients (28%). Three of the 5 patients previously treated with R showed a response to R+THAL. Median progression-free survival (PFS) was 20.6 months, and median overall survival was 44.1 months (estimated 4-year survival 48%). PFS after R+THAL was significantly longer than PFS after the previous line of chemotherapy, which was particularly evident among the patients achieving a CR (2 patients in continuous CR at 46 and 38 months, respectively). Grade 4 neutropenia was observed in 2 heavily pretreated patients, and venous thromboembolism occurred in 2 patients. Gene expression analysis of lymphoma cells was performed prior to and 48 hours after administration of THAL, and significant up- or down-regulation of more than 40 genes was noted (2 patients studied to date).

Conclusions: THAL in addition to standard treatment shows marked antitumor activity in MCL, which provides the background of our current protocol (R plus CHOP plus THAL) in previously untreated patients with MCL.