9. Extraneural Lymphomas

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REACTIVE PERIVASCULAR T-CELL INFLTRATE IS AN INDEPENDENT FAVORABLE PROGNOSTIC FACTOR IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMAS (PCNSL) IN IMMUNOCOMPETENT PATIENTS


Introduction: No clear-cut histopathologic prognosticators have been identified so far in PCNSL.

Aim: To assess the prognostic role of reactive perivascular T-cell infiltrate (RPVI) in 120 immunocompetent patients (pts) with available histologic specimens included in the context of IELSG retrospective study on PCNSL (IELSG#7).

Methods: Thirty-five cases are pending because of needing for additional clinical information or completion of basic immunohistochemistry. Eighty-five were patients were evaluated (25% of the IELSG#7 cohort). Pathologic variables considered were: presence of tumor necrosis (TN), (conglomerate type) and presence of RPVI. The latter was defined as a perivascular rim of small reactive T-lymphocytes occurring alone or at least intermingled between vessel wall and neoplastic cells. Fifty-nine cases were assessable for TN and RPVI, while 26 were assessable only for presence of TN. Results: REAL histotypes were: 12 diffuse large B-cell lymphomas, 10 Ki-1-ALK-1- anaplastic. REAL histotypes were: DLBCL, 18 (20%) cases. RPVI was present in 19 (22%) cases. RPVI was inversely correlated with cerebrospinal-fluid protein concentration, which was elevated in 17 (94%) of 24 RPVI-negative cases and in 5 (23%) of 13 RPVI-positive cases (p < 0.05). Patients with RPVI-positive lesions exhibited a trend to improved survival, with a 2.2-year OS of 48% and 35% (p = 0.07), respectively. Multivariate analysis confirmed an independent association between RPVI (p = 0.0006, Odds ratio: 3.15, 95% CI 1.60-6.12) and survival. No association was found with TN.

Conclusion: Our preliminary results suggest an independent prognostic role for RPVI in PCNSL. Additional investigations are ongoing in order to assess whether this attitude could be related to distinct immunophenotypes or biologic properties carried by neoplastic cells.

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A Phase II Study of High-Dose (BD) Methotrexate And HD Cytarabine Followed By Radiotherapy in Primary CNS Lymphomas (PCNSL)


Purpose: The optimal therapy of PCNSL is controversial and to date no study has evaluated the role of the combination of HD-MTX/HD-Ara-C as induction treatment. Methods: We treated 28 unselected BD-negative patients aged 34-72 (median 57) with DLBCL lymphoma. Order neurologic performance status was 3-4 in 43% of the cases. Chemotherapy consisted of MTX 1 g/m² iv over 24 hours (8) with leucovorin rescue followed by four doses of ara-C 2 g/m² every 12 hours (4-2-3-2) at 3 week interval. In the 15 pts younger than 60, the doses of MTX and ara-C were escalated to 2 g/m² and 3 g/m² respectively. Pts in CR or CR i.e. (i.e. response ≥90%) after the 1st cycle received two cycles and those in PR/SD 3 cycles. Chemotherapy was followed by whole brain irradiation (mainly 30 Gy plus 10 Gy boost). Results: Median follow-up was 22 mo (range 1.7-151). Overall, 63% were assessable: 13 pts received 2 cycles, 11 received 3 cycles and 4 pts (all over 60) received 1 cycle (2 toxic deaths, 2 infectious complications). Grade 4 neutropenia and thrombocytopenia were of short duration (median 3 and 3 days respectively). 27/28 pts are evaluable for response to chemotherapy (1 pt radially corrected). CNSCR rate was 52% after chemotherapy and 75% after RT. Survival was as follows: (table)

<table>
<thead>
<tr>
<th>time (yr)</th>
<th>median (mo)</th>
<th>2-yr</th>
<th>3-yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>all</td>
<td>28</td>
<td>30</td>
<td>59</td>
</tr>
<tr>
<td>&lt;60y</td>
<td>15</td>
<td>not reached</td>
<td>79</td>
</tr>
<tr>
<td>&gt;60y</td>
<td>13</td>
<td>18</td>
<td>36</td>
</tr>
</tbody>
</table>

Of the recurrences, 4 were outside the CNS.

Conclusion: This intensive treatment obtained a high rate of CNS CR also in unselected pts (including 3/13 of cases over 65), however, to improve long-term survival, consolidation or maintenance with different drugs may be indicated.

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PRIMARY ORBITAL LYMPHOMA:

CLINICAL OUTCOME OF DIFFERENT TREATMENT MODALITIES


Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong

Purpose: To retrospectively analyze the clinical outcome and complications (Cs) associated with different treatments (Ts) modalities used in the management of primary orbital lymphomas in a single institution.

Materials and methods: Thirty-eight patients (pts) with primary orbital (lymphomas were assessed in our institution between January 1984 to May 2001. Four pts defaulted Ts after initial assessment and thirty-four pts were available for Ts outcome analyses. There were 18 males and 16 females with a median age of 55.5 years (range, 14-88). All pts had low-grade tumors (majority of them had MALT lymphoma). Thirty-two pts had Ann Arbor stage I while only two pts had stage II disease. Disease occurred in the conjunctivae only in 9 pts, lid only in 8 pts (terminal gland only in 2 pts), subcutaneous site only in 8 pts and involved more than one site in 7 pts. Primary definitive Ts modality was radiotherapy (RT) in 16 pts, chemotherapy (chemo) in 14 pts and surgery alone in 4 pts. Depending on the tumor location and extent of disease, RT ranged from a single exterior field to CT planned 3-field technique. Majority of pts treated with chemo received either chlorambucil or CVP regimen.

Results: Median follow-up time was 37.5 months (range, 5 to 156 months). RT dose ranged from 21 to 40 Gy, given over 6 to 20 fractions. Local control of disease was achieved in all 16 pts (100%) in the RT group. One (5%) of the 16 pts in the RT group had narrow timeapse but was successfully salvaged by chlorambucil. Nine (64%) out of 14 pts in the chemo group achieved local control of disease but 7 (50%) of them had local and/or distant progression of disease. Pts who received chlorambucil had higher local control and lower disease progression rate than those who received CVP scheme. Two (14%) out of 4 pts in the surgery alone group had disease progression. The disease-specific survival and progression free survival for the whole group at 5 yrs was 100% and 62% respectively. The difference in progression free survival for pts in RT group and chemo group was statistically significant (p=0.002). Chemo was generally well tolerated with no life threatening Cs seen. Acute Cs of RT were mild. Late Cs of RT included dry eye, cataract formation and rarely retinopathy. Cataract formation was not seen in these patients who had their lens shielded.

Conclusion: Treatment of choice for primary orbital lymphoma is RT but it is important to give it with good technique, possibly with less shielding if feasible. Appropriate radiotherapy (30-35Gy in 20Gy) should be given in order to avoid significant late Cs while securing local control.
DETECTION OF CHLAMYDIA PNEUMONIAE DNA IN NEOPLASTIC LESIONS OF PATIENTS WITH MYCOSIS FUNGOIDES AND SEZARY SYNDROME.

R. Zambello, E. Bonoldi, M. Russi, S. Cazzavillan, M. Zoppellaro, P. Betto, L. Trentin, P. Bevilacqua, F. Roderighi, G. Semenzato

Dept of Clinical and Experimental Medicine, Padua University, San Bartolo Hospital, Vicenza, Italy.

Introduction: The concept that chronic antigenic stimulation could be related to the pathogenesis of cutaneous T cell lymphomas has been postulated for many years. Recent data suggest that Chlamydia pneumoniae (CP), an intracellular pathogen which replicates in the cytoplasm of infected cells, might be detected in some cutaneous T cell lymphomas.

Methods: Using PCR analysis we investigate the presence of C. pneumoniae DNA in skin samples from a large series of patients suffering from mycosis fungoides at the time of diagnosis (n: 69; 69 in erythrodermic stage, 11 in plaque stage and 6 in tumoral stage) and Sézary syndrome (SS)(11 cases), diagnosed in a single centre in the period 1986-2001. In 6/86 cases of MF, cells obtained in peripheral blood and from nodal biopsies were analyzed. In all 5 patients with SS, cells obtained from skin, peripheral blood lymphocytes and bone marrow biopsies were studied. A nested primer set specific for the ompA gene of CP was used.

Results: The presence of CP DNA was detected in the skin samples of 44/46 cases (51.5%) of MF and 6/11 (54.5%) of SS cases. In this last group of patients, when present, CP DNA was detected in all the different samples analyzed, i.e. skin lymph node and peripheral blood lymphocytes. On the other hand, CP DNA was detected in 4/15 cutaneous samples (26.6%) of non-cutaneous cutaneous disorders and 1/6 cases (16.6%) of cutaneous lymphomas other than MF/SS. No correlation was shown between the detection of CP by genes monoclonal rearrangements and the presence of CP DNA.

Conclusions: Our data indicate that CP DNA may frequently be demonstrated within the neoplastic lesions of patients with MF and SS. These results suggest a role for Chlamydia pneumoniae infection in the pathogenesis of Mycosis Fungoides and Sézary syndrome.

PRIMARY CUTANEOUS NON-HODGKIN'S LYMPHOMA WITH AGGRESSIVE HISTOLOGY: INFERIOR OUTCOME IS ASSOCIATED WITH PERIPHERAL T-CELL TYPE AND ELEVATED LDH, BUT NOT EXTENT OF CUTANEOUS INVOLVEMENT.


The University of Texas M.D. Anderson Cancer Center, Houston, USA.

Background: The association between the extent of cutaneous involvement, presenting features, and progression-free survival (PFS) in patients with primary cutaneous non-Hodgkin's lymphomas (PC-NHL) of aggressive histology remains controversial.

Methods: Retrospective review of previously untreated patients with localized or extensive PC-NHL of aggressive histology, treated with combination chemotherapy, but excluding lymphohistiocytic lymphomas and mycosis fungoides and its variants.

Results: We identified 53 patients, of whom 38 received doxorubicin-based regimen. Median age was 52 years (range 22-81), gender was male in 35, and disease was localized in 15 and extensive in 16 patients. According to the REAL classification, 24 patients had diffuse large B-cell lymphoma, nine grade 3 follicular lymphoma, 13 peripheral T-cell lymphomas not otherwise specified (PTCL), and seven mycosis fungoides large cell lymphomas. With a median follow-up of 104 months (range 2-237 months) for survivors, the 10-year PFS was 65 ± 7% and overall survival 72 ± 8%. The first failure involved the skin in 33% of B-cell and in 91% of relapsing T-cell lymphomas. Univariate analysis revealed that PTCL (p=0.005), lymphomas (p=0.01), and high serum level of D-dimer (p=0.0006) and LDH (p=0.002), but not extent of skin involvement, were associated with inferior PFS. Multivariate analysis revealed that only PTCL and high serum LDH were independently associated with inferior PFS.

Conclusions: PTCL and elevated serum LDH level, but not the extent of cutaneous involvement, is associated with inferior PFS in aggressive PC-NHL treated with combination chemotherapy.

INTERFERON ALPHA-2b (IFN-A) COMBINED WITH PHOTOCHEMOTHERAPY (Pauta) FOR MYCOSIS FUNGOIDES (MF) AND SEZARY SYNDROME (SS): A NATIONAL PHASE II STUDY.

D. Bruns, M.L. Geerts, A. Bosy, A. Ferrari, C. Dubois, M. Lapierre, M. Raus, V. Robo, L. Mathieu.

For the Belgian CTG Group, Belgium.

Background: Cutaneous T cell lymphomas (CTCL) remain an incurable subtype of lymphoma. At advanced stages, the prognosis is poor and severe systemic symptoms interfere with quality of life. Kuzel et al reported promising results (70% OR combining IFN-A and PUVA therapy. We thus prospectively investigated this therapeutic approach in terms of efficacy and tolerance.

Population: Between November 91 and December 00, 42 patients (pts) with MF (35) and SS (7) were enrolled in the trial. Median age was 63 (range 38-86) yrs. Stages II to IV were included in first line (3 IIIA-6 IIIB-7 IIIB-2 IIII-11 IVA-1 IVB-2). 10 pts with stage IA and IB were included in first relapse. Disease was staged according to the TNM classification. Assessment of response was performed every three months. Treatment consisted of IFN-A SMX35ug/week for three months (induction followed by SMX35ug/week for 9 months in case of CR. In PR and SD IFN-A doses was increased to 100MU/PUVA therapy consisted 8 methoxypsoralen 10mg/kg/h body weight followed by UV A exposure times 3 times weekly and adapted to patient tolerance. The maximal UV A dose was 83cm2. PUVA was gradually decreased according to response and stopped after 1 year. IFN-A related toxicity grade 2 resulted in a 70% reduction with discontinuation in case of grade ≥3 toxicity.

Results: 35 patients were evaluable showing 30% of CR (45% for stage 1 to 28% for stage IV) with a duration of CCR of 26 (10-72) mos. Overall response was 65%. Progressive disease during treatment occurred in 5/35 pts. The median FU is 54mos and overall survival is 58% 5 yrs are still in CR.

Conclusion: Low dose IFN-A (LD IFN-A) combined with PUVA is an effective and relatively well tolerated treatment. Advanced stage is a predictive factor for poor response. The beneficial role of a longer maintenance therapy with LD IFN-A requires further investigation.

CLINICAL OUTCOME OF PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA AND BREAST INVOLVEMENT.


Introduction: Clinical data concerning non-Hodgkin’s lymphoma with breast involvement are limited, and no consensus exists on its optimal treatment. We report here the clinical outcomes of all 22 women with diffuse large B-cell lymphoma of the breast treated at the Milan Cancer Institute from 1980 to 1999.

Patients and Methods: Main patient characteristics were as follows: median age 50 years (range 24-80); P.S. (ECOG) 0-1; 22 pts; B symptoms: 2 pts; right breast involvement: 11 pts; left breast involvement: 10 pts; bilateral breast involvement: 1 pt; Stage I-IIIE: 13 pts; Stage III: 1 pt; Stage IV: 8 pts (BM: 3; lung: 1; liver: 1; massive breast involvement: 2); bulky disease (≤ 5cm): 10 pts; high LDH: 5; IPI: 0-1: 17 pts. Twenty pts received conventional CHOP or MACOP-B for a median number of 4 cycles (range 1-12), and two patients received high dose chemotherapy with ABMT or PBSC as first line chemotherapy. All but four pts received local radiation therapy. Six pts had surgical resection of the involved breast.

Results: Overall, 18 pts achieved a CR (82%), 12 with chemotherapy, and 6 after surgical resection. Four pts progressed while on chemotherapy. After a median time of 8 months (range 3-144), 7 of the 18 complete responders have relapsed. Second line therapy consisted of high-dose sequential chemotherapy with autologous bone marrow or PBSC transplant in 2 pts, conventional 2nd line chemotherapy in 7 pts, and whole brain RT in 2 pts. The clinical characteristics of both refractory (4 pts) and relapsed (7 pts) patients were as follows: median age: 46 yrs (24-62); stage IV: 5 pts; bulky disease: 7 pts; high LDH: 5 pts; IPI: 0-1: 7 pts; IPI: 2-4: 2 pts. After a median follow-up of 10 years (2-21), 10 pts (45%) have died: 8 with progressive disease (including 4 at the CNS), one for cardiovascular event, and one for unknown reasons: DFS 51%, OS 51%. Conclusions: Primary diffuse NHL of the breast appears a distinct clinical entity, with increased susceptibility to CNS and possibly BM involvement. More effective therapies, including CNS prophylaxis, are warranted.
I1ELS G PHASE II STUDY OF RITUXIMAB IN MALT LYMPHOMAS.


on behalf of the International Extranodal Lymphoma Study Group (I1ELS).

This phase II study aimed to evaluate tolerability and activity of the monoclonal anti-CD20 antibody rituximab in either untreated or relapsed, biopsy-proven extranodal marginal-zone lymphomas (MALT lymphomas). Treatment consisted of rituximab 375 mg/m² i.v. weekly for 4 weeks; responses were assessed at 2, 6 and 12 months after treatment start. Between January 2000 and May 2001, 35 patients (pts) (24 females and 11 males were registered; 11 of whom had been previously treated with chemotherapy. Median age was 57 years (range 27-85). Fifteen pts had a primary gastric lymphoma, 2 of them had no evidence of prior H. pylori (HP) infection at diagnosis, 13 pts progressed, after the eradication of HP, after a median time of 25 months (range 5-89). Twenty pts had a primary non-HP gastrointestinal localisation (7 skin/subcutaneous, 4 lung, 4 salivary gland, 3 orbit, 1 breast and 1 liver) in 7 of these cases multiple mucosal sites were involved. At entry study 12 pts had Ann Arbor stage I, 3 stage II and 20 stage IV disease; bone marrow involvement was documented in 9 pts, 2 pts had B symptoms; LDH was elevated in 3 cases. All pts had ECOG PS 0-1.

Thirty-four patients entered the treatment program; one pt refused to receive the third and fourth planned doses and was lost to follow-up. At a median follow-up of 12 months, the overall response rate was 72% (95%CI: 60%-87%) with 16 CRs and 10 PRs. The median time to best response was 2.2 months (range 1.5-6) from treatment start. Three pts progressed immediately after treatment, 3 pts relapsed after a CR and 3 after a PR. The favourable toxicity profile of rituximab was confirmed in most adverse events were of mild to moderate severity. Our results show the antineoplastic activity and safety of rituximab as single agent in MALT lymphomas, a study of combination with chemotherapy is planned.

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CLINICOPATHOLOGIC COMPARISON BETWEEN THE API2-MALT1 CHIMERIC TRANS-SCRIPT-POSITIVE AND -NEGATIVE GASTRIC LOW-GRAD B-CELL LYMPHOMA OF MALT TYPE.

T. Nakamura1, S. Nakamura1, T. Yokoi1, H. Suzuki3, and M. Seto1

1 Aichi Cancer Center Hospital, Nagoya, Japan.
2 Aichi Cancer Center Research Institute, Nagoya, Japan.

Purpose: Little is known about the clinicopathological differences between API2-MALT1 chimeric transcript-positive and -negative gastric low-grade B-cell lymphomas of MALT type. The aim of this study was to clarify these differences in gastric MALT lymphomas.

Patients and methods: Twenty-three patients with gastric MALT lymphoma were enrolled in a uncenter study. H. pylori infection status and clinical stages were investigated. Antibacterial treatment was performed for every patient. Responsiveness of MALT lymphomas to this treatment was assessed by means of regular follow-up endoscopy combined with biopsy. All cases were examined for API2-MALT1 chimeric transcript by means of RT-PCR and sequencing analyses.

Results: H. pylori infection status was assessed as positive in 20 patients and negative in three. With regard to responsiveness to antibacterial treatment, complete remission was observed in 2 patients, partial remission in 12 and no change in nine. API2-MALT1 chimeric transcript was detected in seven patients, all of whom showed no change against antibacterial treatment. API2-MALT1 positivity was found to be significantly correlated with responsiveness to antibacterial treatment (P=0.001); absence of H. pylori infection (P=0.0198), and gross cobblestone mucosa observed endoscopically (P=0.0198). For the other factors (age, sex, dominant site of lesion, high-grade component, infiltrated layer of gastric wall, nodal involvement or clinical stages), there were no differences between API2-MALT1 chimeric transcript-positive and -negative cases.

Conclusion: Gastric API2-MALT1 chimeric transcript-positive MALT lymphoma features unresponsiveness to antibacterial treatment, and is thought to be unrelated to H. pylori infection as its pathogenesis. Our findings indicate the presence of different clinical subtypes in gastric MALT lymphomas.

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RADIATION THERAPY HAS CURATIVE POTENTIAL IN STAGE I & II MALT LYMPHOMAS.

R.W. Tsang, M. Gospodarowicz, M. Plint, W. Wells, D. Hodgson, A. Sun, B. Patterson, and M. Cram.

Princess Margaret Hospital, University of Toronto, Toronto, Canada.

Purpose: We analyzed the outcome of patients with stage I/II MALT lymphoma treated with involved field radiation therapy (RT) over an eleven year period.

Methods: 98 patients (pts) with stage IE (86) and IIE (12) disease were referred between 1988-2000. Transformed MALTomas (diffuse large B-cell lymphomas) were excluded. The median age was 59 yrs (range 22-83 yrs). E.M. ratio 1:1.8. Presenting sites included: stomach 17, orbital adnexas 26, salivary glands 24, thyroid 13, other head and neck sites 4 (nasopharynx 2, sinus 1, larynx 1), lung 5, urinary bladder 3, skin 2, breast 1, and 12 patients 1. Staging included site-specific imaging, CT abdomen in 92% and bone marrow biopsy in 79%. Eighty-eight pts received RT, 80 RT was chemotherapy and RT. Five pts had complete surgical excision alone, 2 pts with gastric lymphomas received antibiotics alone, and 3 other pts refused any treatment. The analysis focused on 88 pts who received RT; the median follow up was 4.3 yrs (range 1.0-9.8 yrs). Common RT prescriptions were 25Gy (59% of treatments), 30Gy (4%), 35Gy (2%), and 40Gy (1%).

Results: A complete response (CR/CRu) to RT was achieved in 87/88 pts; 1 pt had no response (nR). To date, 3 pts have died (1 due to lymphoma, 2 from unrelated causes). The 5-yr disease-free survival (DFS) was 74%, and overall survival (OS) 97%. No relapses were observed in 26 pts with stomach and thyroid lymphomas, while 13/26 pts relapsed in the other sites. The 5-yr DFS for gastric and thyroid lymphomas was 93% in contrast to 67% for other sites (P = 0.009), although OS was the same. Among 87 pts with CR, 13 relapsed (4 salivary, 5 orbit, 2 nasopharynx, 1 larynx, 1 breast). Relapse sites: the untransformed cribriform-paired-organ only, 4 pts (2 orbit, 2 parotid), distant sites, 7 pts; and both local (both parotid) and distant sites, 2 pts. The overall local control rate with RT was 97% (85/88 pts). All 4 patients with paired-organ relapse were radiated with complete response.

Conclusions: Moderate-dose RT achieved excellent local control in localized MALT lymphomas. Relapses were observed in non-irradiated paired-organs or distant sites. Gastric and thyroid MALT lymphomas had better outcomes, as compared to the other sites where distant failures were more common. However, with an indolent course of disease, longer term follow-up is required to determine the curative potential of local therapy.

SEREX ANALYSIS IN LOW GRADE GASTRIC MARGINALZONE B-CELL LYMPHOMAS OF MALT TYPE.

M. Almeida1, A. C. Girão, M. Scardini, B. Willman1, L. Neuber1, L. J. Old1, Y. -T. Chen1

1 Weill Med College of Cornell Univ, New York, USA, 1 Ludwig Institute for Cancer Research, New York Branch, New York, USA, 1 Philips University - Department of Hematology, Oncology, Immunology, Marburg, Germany.

Introduction: Primary gastric B-cell lymphomas of the mucosa associated lymphoid tissue (MALT) is associated with chronic Helicobacter pylorus (HP) infection. It is unknown whether specific antigen exist on MALT lymphomas cells that elicit both humoral and/or cell-mediated immune responses. We have analyzed MALT lymphomas by SEREX to establish a list of serologically reactive epitopes to identify antigens that have elicited high-titer IgG responses in these patients. MATERIALS AND METHODS: A, ZAP-70 transduction expression library was constructed from a reactive specimen of a 20-yr-old patient with low grade MALT lymphoma. Results: 18 clones derived from 16 genes were identified, many previously identified by SEREX. The following table summarizes the clones.

<table>
<thead>
<tr>
<th>clone number</th>
<th>corresponding gene</th>
<th>mRNA tissue expression</th>
<th>previous SEREX database entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>MALT-1</td>
<td>p53</td>
<td>ubiquitous</td>
<td>y6s</td>
</tr>
<tr>
<td>MALT-17</td>
<td>B-cell receptor 1A</td>
<td>ubiquitous</td>
<td>y6s</td>
</tr>
<tr>
<td>MALT-37</td>
<td>F4/100 hypotetial</td>
<td>protein</td>
<td>y6s</td>
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<td>CD5</td>
<td>protein</td>
<td>y6s</td>
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<td>protein</td>
<td>y6s</td>
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<tr>
<td>MALT-12-11</td>
<td>Golgi matrix protein</td>
<td>protein</td>
<td>y6s</td>
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<td>y6s</td>
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<td>kidney</td>
</tr>
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<tr>
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<td>y6s</td>
</tr>
<tr>
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<td>MALT-16-36</td>
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Conclusions: Several potentially interesting genes were identified from the MALT lymphoma library screening. In addition to a variety of antigenic epitopes, the Nibrin protein appears to be upregulated in cancer. The mRNA expression pattern for MALT-16-26 is being analyzed.
POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD): A MONOCENTRIC CLINICOPTHOLOGIC STUDY OF 67 CASES
S. Chabot, V. Levy, F. Davi, F. Charlotte, M. Raphael, R. Dore, B. Barou, V. Leblond
Hôpital Pitié-Salpêtrière Paris, France

Introduction: Organ transplantations can lead to PTLD as a result of immunosuppressive therapy. Several studies tried to identify characteristics and prognostic factors in PTLD but the size of these series and the heterogeneity of the data often hinder the results. We present a monocentric analysis of 67 PTLD and try to identify prognostic factors for the overall survival.

Methods: Since 1987, 67 patients have been followed for a PTLD in our center. Clinico pathological data of each patient have been analysed in order to characterize PTLD and to find relevant prognostic factors for survival. Treatment consisted first in a decrease of the immunosuppressive therapy (IT) and, in case of failure, in monoclonal antibodies (mAb) and or chemotherapy.

Results: Among the 67 patients, 47 were male and 20 females; the mean age was 46 (15 to 72). PTLD arised in a mean of 1490 days (23 to 10.002) after transplantation (24 hearts, 28 kidneys, 7 lags, 5 livers and 3 combined heart-lung). Majority of the PTLD were of B phenotype (60) and were clonal (63/68). Tumors were EBV positive in 45 out of 64 analysable PTLD. 5 patients died before any treatment, 4 have been cured tapering the IT, 42 received mAb and 3 chemotherapy.

The overall survival's median is 36 months (7.9-NA), 55.5 months (0-NA) without central nervous system localizations (SNL). In monoclonal analysis, prognostic factors for a prolonged survival are: B phenotype (p=0.02), monoclonality (p=0.03), EBV positivity (p=0.01), only one localization (p=5.10^-7), personal status (PS) ≤ 2 (p=3.10^-7) and absence of SNL. Neither the IT, the LDH nor the Ann Arbor classification were significantly linked with survival. The International Prognostic Index (IPI) is less accurate to predict survival than a score using the PS and the number of involved sites.

Conclusion: PTLD is a severe complication of organ transplants. Evolution, treatment and prognostic factors are clearly different from immunocompetent patient's aggressive lymphoma. A score using PS and number of involved sites is more accurate than IPI as a predictive tool for survival. Search for other predictive values and the analysis of results of mAb versus chemotherapy are ongoing.


Objective: to evaluate the pathologic findings, clinical course and outcome of patients who developed lymphoma after solid organ or bone marrow / peripheral blood transplantation.

Patients and Methods: retrospective study of adult patients transplanted in 7 reference hospitals in Spain. Fifty-two patients who developed lymphoma were identified. Patients with polyclonal lymphoproliferative disorders were excluded. Survival curve was constructed by the Kaplan-Meyer method, comparisons were made by the log-rank test.

Results: 34 (65%) patients were males. The median age was 51 y (range: 19-75). The organs transplanted were kidney (n=23), heart (n=13), liver (n=11), bone marrow (n=4) and lung (n=1). Lymphoma was diagnosed at a median time of 59 months post-transplantation (range: 1-185). Lymphomas was of B-cell origin in 44 cases, T-cell in 4 cases and Hodgkin in 4 cases. EBV detection was performed in tissue in 20 cases and was positive in 12 (60%), all of B-cell origin. The clinical presentation was as follows: stage IE/II in 25/52 (48%), extramedullary disease in 34/51 (68%), bi-symptoms in 17/51 (33%), ECOG 2-4 in 24/50 (48%), IPI ≥ 2 in 24/43 (56%), high LDH in 23/43 (54%), and high BSG in 23/43 (57%). Immunosuppression was modified in 41/43 (96%) patients (3 patients were not receiving immunosuppression at diagnosis of lymphoma), and 43/49 (88%) received further treatments, the most frequent being chemotherapy (n=30), surgery (n=15) and local radiotherapy (n=8). Complete remission was achieved by 24 (49%) patients. Median overall survival was 23 months (CI 95% 1.4-5.3). Median event-free survival was 11.4 months (CI 95% 0.04-22.5). In the univariate analysis, clinical variables influencing overall survival were: stage III-IV (p<0.015), B-symphomes (p=0.002), ECOG 2-4 (p=0.006).

Conclusion: most post transplant lymphomas were of B-cell origin and EBV was detected in tissue in a significant proportion of them. Therapy was heterogeneous. These patients who presented with disseminated disease and bad performance status had significantly worse outcome.

PRIMARY BONE LYMPHOMAS: EXPERIENCE WITH 52 PATIENTS
Institute of Hematology and Medical Oncology “L. e A. Seraglini”, University of Bologna, Bologna; *Operative Unit of Anatomic Pathology, Cardarelli, Napoli, Italy.

Introduction: A retrospective analysis was performed to assess the efficacy of various treatments of primary non-Hodgkin’s primary bone lymphomas (PBL). Methods: Fifty-two consecutive, previously untreated PBL patients were seen between the years 1982 and 1998. Information was obtained regarding each patient’s presentation and clinical course. Histology was reviewed in all cases. Modern immunohistochemical stains were performed on each case.

Results: Regarding therapeutic approach, we observed CR in 35/41 (85%) patients treated with chemotherapy without radiation therapy and in 7/11 (64%) patients who received radiation therapy. Relapses were observed in only 2/35 (6%) patients after chemotherapy (without radiation therapy), as compared with 4/7 (57%) patients after radiation therapy alone (p=0.004). The RFS curves of these two subsets were significantly different. At both univariate and multivariate analysis, only type of front-line therapeutic approach (chemotherapy without radiation therapy vs. radiation therapy alone) turned out to have a significant prognostic influence.

Conclusions: Our data indicate that in PBL use of chemotherapy or combined-modality therapy seems to provide more durable CRs than radiation therapy alone.

EARLY STAGE NASAL NK/TL CELL LYMPHOMA: PRELIMINARY RESULT OF INTENSIFYING TREATMENT WITH CONCURRENT CHEMIO-RADIATION AND HIGH DOSE CHEMOTHERAPY
Department of Clinical Oncology and Department of Pathology*, Queen Elizabeth Hospital, Hong Kong, China.

Introduction: The prognosis of early stage nasal NK/T cell lymphoma treated by conventional therapy is poor with common local and distant failure. The purpose of this study is to analyze the preliminary result of intensifying treatment with concurrent chemio-radiation (CCR) and high dose therapy (HDT) in a single institution.

Materials and methods: Twenty consecutive patients (pts) received primary treatment for early stage nasal NK/T cell (CD56 positive) lymphoma in the period January 1998 to January 2003 in our institution from the basis of this analysis. There were 16 males and 4 females. The median age was 58.5 (range 35-81). Nineteen pts had stage I disease while 1 had stage II disease. Seven pts had B lymphomas. Combined Modality Treatment (CMT) with conventional chemio-radiation (CCRP or ProMAC/CYtoBOM regimen) and radiotherapy was intended for 15 patients while 5 pts were given radiotherapy (RT) alone because of old age and significant medical co-morbidities. CCR with cis-platinum was given in 11 pts and HDT using the CBV regime with peripheral stem cell rescue was given as consolidation therapy in 6 patients.

Results: Treatment was moderately well tolerated. Grade 3 mucositis occurred in 14.3% (RT alone as local treatment) and 27.3% (CCR) of pts. The latter treatment also resulted in 18.2% grade 3 vomiting. Forty percent of pts receiving conventional chemiotherapy developed grade 3 or more neuropathy with 33.3% neuropathy at 6 months. One pt (6.7%) died of neutropenic sepsis. Although 5 of 6 pts receiving HDT developed neutropenic fever, the duration was brief (median 2 days, range 2 to 6 days) and there was no treatment-related mortality. Sixteen pts (80%) attained CR after primary treatment of whom 4 (25%) developed recurrence. After a median follow-up of 26.5 months in the survivors (range 12.2 to 48.1months), 7 pts were dead with 3 died of disease. The actuarial 2 year local control rate, distant control rate, disease free survival and overall survival are 79.6%, 68.2%, 63.3%, and 64.3% respectively. These results compare favorably with that of a cohort of 59 patients treated before 1998 in our institution for the same disease but the differences do not reach statistical significance.

Conclusions: Intensified treatment with CCR and HDT in early stage nasal NK/T cell lymphoma was well tolerated. The added treatment morbidity was manageable. However, the efficacy of such treatment in improving disease outcome has to be evaluated in a randomized trial setting.
PHASE-I STUDY OF THE AZA-ANTHREACINONE BBR 2778 IN PATIENTS WITH RELAPSED AGGRESSIVE NHL


Purpose: BBR 2778 is a newaza-anthracinone with superior activity compared to doxorubicin and mitoxantrone against disseminated murine YB-lymphoma and leukemia. In contrast to anthracycines, BBR 2778 re

nealed cardiotoxicity in animal models. A phase-I study in patients (pts) with Non-Hodgkin’s lymphoma (NHL) showed promising anti-tumor activity particularly in high-grade NHL. Thus, a multicenter phase-II study in pts with relapsed aggressive NHL was initiated. Methods: Primary objective was to determine the efficacy of 85 mg/m² BBR 2778 for a q2w x 3 treat

ment schedule (day 0, 7, 14, repeat on day 28). Secondary objectives included the evaluation of response duration and safety. This was an open

label, non-randomized, international, multicenter phase-II trial. Pts with relapsed aggressive NHL according to the REAL-classification were included. Results: 12 centres in France and Germany enrolled a total of 33 pts between 02/00 and 03/01, of which 32 are evaluable. Pts had a median of two prior regimens (range 0-5). The median prior cumulative exposure to doxorubicin was 300 mg/m² (range 110-600 mg/m²). The median age was 56 years (range 24-81 y; 22/33 aged ≥ 65). The majority of patients had diffuse large-B-cell lymphoma (24), or mantle-cell lymphoma (7). 8 pts were treated with the first relapse, 12 with the second, 7 with the third, 3 with the fourth, 2 with the fifth relapse and one pt was treated naïve. Tumor re

sponse included 5 complete remissions, 4 partial remissions (PR), and 4 PRs. The main acute toxicity was neutropenia, necessitating dose reduc

dion in 6 pts. There was only one episode of neutropenic fever, that was associated with a fatal outcome. Decrease of the left ventricular ejection fraction of at least 15% measured by MUGA-scan was documented in three pts, of which three showed clinical signs of cardiac insufficiency. Follow up of response and safety will be presented. Conclusions: These results indicate that BBR 2778 using the q2w x 3 treatment schedule with 85mg/m² is effective as a single agent in heavily pretreated elderly patients with relapsed and advanced aggressive NHL. Neutropenia is the main toxicity. On the basis of these results, efficacy of BBR 2778 is currently investigated in a polychemotherapy-regimen.

IDENTIFICATION OF NOVEL TUMOR-ASSOCIATED ANTIGENS IN CLL - IMPLICATIONS FOR IMMUNOTHERAPY IN CLL

Angela M Krakhardt, Mathias Witzens, Jason Zaula, Patrick Barrett, Morgan Chessa and John G Gribben

Adult Oncology, Dana Farber Cancer Institute, 44, Binney Street, Boston, MA 02115

Introduction: Although patients with CLL have a number of immunological disturbances, CLL is an attractive candidate to examine immunotherapeutic approaches. We have previously shown that cytotoxic T cell responses can be generated against naturally presented and immunoglobulin derived peptides, however, these responses are mostly weak.

Methods: We therefore sought to identify additional candidate tumor antigens in this disease using SEREX (Serological identification by recombinant expression cloning). cDNA expression libraries were constructed from tumor cells from 5 untreated CLL patients with different disease stages.

Results: After screening of over 30 million clones, 25 independent clones were detected by patients’ sera representing 14 different antigens designated as KW-1 to KW-14. Seven of these antigens are novel antigens. Three of these antigens have only been detected by serum from patients with CLL. Seven antigens have been additionally recognized by lymphoma patients but only three by healthy donors. Of note, patients with hypogammaglobulinemia or immunosuppressive therapy appeared to have less humoral responses against SEREX antigens. Novel antigenic peptides were detected in six clones. Several clones showed restricted expression patterns in normal tissue. Moreover, distinctive expression of splice variants was detected and several clones show aberrant expression in a malignant tissue. In addition, cytotoxic T cell responses could be generated in an HLA-class I dependent manner against peptides derived from 2 clones so far.

Conclusion: These findings demonstrate that humoral and cellular immune responses against CLL-associated antigens are present and identified antigens might be useful for the development of immunotherapy strategies in this disease.
ALLO-RESTRICTED EPITOME-SPECIFIC T CELLS: POTENTIAL FOR THERAPEUTIC INFUSION

N. Steven, A. Tranter, S. Davies, S. Lee, A. Rickinson. Institute for Cancer Studies, University of Birmingham, Birmingham, UK

Introduction: T cell precursors specific for humour associated antigens (TAA) are typically rare in peripheral blood and may be anergised because of self-presentation of antigen. This has limited the development of an experimental therapeutic infusion programme using autologous TAA-specific T cell clones. An alternative approach, by-passing self-tolerance, uses T cell clones from other individuals existing cross-recognition of epitopes from TAA presented on non-self MHC alleles. For therapeutic use, allo-restricted TAA-specific T cells should exhibit high avidity and specificity for the target epitope-MHC to enable effective and selective killing of malignant cells. In this pilot study we compare the functional properties of self- and allo-restricted T cells recognising an immunogenic virus-encoded TAA. This work is being extended to study the properties of allo-restricted T cells specific for a wide range of non-viral TAA.

Method: Self- and allo-restricted T cell cultures were generated from peripheral blood samples from HLA A2+ and A2- individuals by co-culture with HLA A2+ cells loaded with the epitope CLGGLTMV from Epstein-Barr virus (EBV) LMP 2. Specific T cells were labelled with phycoerythrin (PE)-conjugated HLA A2-CLG tetramers followed by anti-PE microspheres, positively selected in a magnetic column and cloned by limiting dilution.

Results: Specific clones were identified by positive HLA A2-CLG tetramer staining and recognition of CLG in killing assays. In FACS analysis, the mean fluorescence intensity of allo-restricted T cell clones stained with the HLA A2-CLG tetramer was lower and more readily blocked by anti-CD8 antibody than that for self-restricted clones. However, both allo- and self-restricted clones recognised EBV+ lymphoblastoid cell lines (LCL) judged by interferon-y release and inhibition of LCL growth.

Conclusion: Despite a relatively low affinity for the MHC-peptide, allo-restricted T cells are able to recognise LMP 2-positive target cells. The fine specificity of and functional avidity of the allo-restricted CLG-specific T cells is being studied.

THE BISPECIFIC MOLECULE H22xKi-4: PHASE-I RESULTS AND IMMUNOLOGICAL FINDINGS IN PATIENTS WITH HODGKIN'S LYMPHOMA

P. Borrmann, R. Schnell, T. Davis, L. D Lewis, V. Diehl, A. Engert

Purpose: CD30 is an excellent target for immunotherapy of Hodgkin's lymphoma (HL) due to its overexpression on the malignant Hodgkin-Steinberg-reed cells (H-RS). Therefore, we developed a novel bispecific molecule (BSM), that consists of chemically linked Fab' fragments of the murine CD30 antibody (Ab) KI-4 and the humanized CD64-specific Ab H22. This BSM acts by binding the H-RS cells to CD64 positive immune effector cells (monocytes) and by mediating antibody dependent cellular cytotoxicity through activation of these cells. Methods: Patients (pts) with refractory CD30 HL were treated with escalating doses up to a maximum dose of 80mg/m^2 per cycle of BSM using an accelerated titration design. H22xKl-4 was administered on days 1, 3, 5 and 7 i.v. using daily doses of 1, 2.5, 5, 10 and 20 mg/m^2, respectively. Primary objective was the determination of dose limiting toxicities (DLT) and the maximum tolerated dose (MTD). Secondary objectives included the analysis of the pharmacokinetic profile, immune response against H22xKl-4 and the documentation of any clinical response. Results: A total of 10 pts were enrolled and are evaluable for toxicity and response. All were heavily pretreated with a median of 4 (range 1-7) prior therapies, including RT and AIIMT in 10/10. The mean age was 34.6 years (range 21-53). 10/10 pts had advanced disease (stage III/IV). 6/10 pts were treated on the highest dose level with 20mg/m^2/d. Side effects were transient and mild with hypotension (4/10), tachycardia (6/10), fatigue (10/10), and fever (3/10 grade II, 2/10 grade I). Symptoms were accompanied by the release of cytokines (IL-6, IL-15, G-CSF, TNF-α) and CD64-saturation on monocytes. PK data revealed an elimination half-life of 11.1 hours resulting in significant accumulation of H22xKl-4. Immunohistochecmical studies showed binding of the BSM to the H-RS cells in vivo. Response to H22xKl-4 included one CR and 3 PR. Conclusions: The BSM H22xKl-4 can be given to pts with refractory CD30 HD in doses up to 20 mg/m^2 without DLT. Although this dose is not the MTD as defined by toxicity criteria, surrogate parameters suggest a biological effective regime. In addition, H22xKl-4 shows very promising activity in heavily pretreated HD patients warranting further investigation.

A PHASE 2 TRIAL TO EVALUATE THE EFFICACY OF RECOMBINANT IDO TYPE WITH ABBREVIATED COURSE OF GRANULOCYTE- MACROPHAGE COLONY-STIMULATING FACTOR ADJUVANT IN FOLLICULAR NON-HODGKIN'S LYMPHOMA

J. Yousef, P. Berman, M. Hollingsworth, D. Ingoliff, D. Denney, and L. Kunkel
1. University of Nebraska Medical Center, Omaha NE, USA.
2. Genetope Corporation, Redwood City, CA, USA.

Introduction: Tumor-specific variable regions of the clonal immunoglobulin (Id)otype or Id) expressed by B cell Non-Hodgkin's Lymphoma (NHL) can be exploited as a target for active immunotherapy. In follicular (f) NHL patients previously treated with chemotherapy, immunization with custom-made tumor-derived protein products has shown clinical benefit. This has resulted in anti-Id immune cellular and humoral immune responses (IR) that correlate with improved disease-free and overall survival (Blood, 1997). These studies have included adjuvant agents to potentiate immune recognition of the Id protein. Immunizations with Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) as an immune adjuvant achieves an effective anti-tumor response (Nat. Med., 1999). The dose and schedule of GM-CSF employed was based on murine models. We have previously demonstrated that treatment consisting of sub-cutaneous injections (s.c) of recombinant Id (produced by HIGET™ technology) conjugated to Keyhole Limpet Hemocyanin (KLH) on day 1 along with 250 µg of GM-CSF (s.c. days 1-4 at the same site), given at 0, 4, 8, 12, and 24 weeks elicited an IR in 14 of 21 patients (67%). The optimal dose of GM-CSF for adjuvant use in human vaccine therapy has not been determined.

Methods: A Phase 2 study in fNHL patients in 1st clinical remission was designed to assess whether an abbreviated course of GM-CSF would induce anti-Id IR. The treatment schedule was identical to our previous study, however a single s.c. dose of 500 µg of GM-CSF was administered on day 1 of each immunization series. Results: Eighteen patients enrolled in the study are evaluable for IR testing. Four of these patients (22%) have demonstrated specific anti-Id humoral responses.

Cellular immune responses appear non-specific.

Conclusions: This study has demonstrated that humoral IR can be elicited with an abbreviated course of GM-CSF, however further investigations into the strength and duration of the IR are ongoing.

ANTI-CD80 ANTIBODY (IDEC-114) THERAPY FOR NON-HODGKIN'S LYMPHOMA


IDEC Pharmaceuticals Corporation, San Diego, California, USA.

IDEC-114 is a PRIMATIZED® antibody with human IgG1 constant regions and macaque variable regions. IDEC-114 specifically binds human CD80, a costimulatory molecule expressed transiently on the surface activated B lymphocytes and constitutively on B-lymphoma cells. Preclinical experiments were performed to assess the potential of IDEC-114 as a targeted therapy for lymphoma. Flow cytometry confirmed IDEC-114 binding to all lymphoma lines evaluated. 13 follicular lymphomas, 3 small noncleaved lymphomas, 2 mantle cell lymphomas, and 2 small lymphocytic lymphomas. Additional flow cytometry performed on CD80+ lymphoma cell lines (SKW, SB, Raji, and Daudi) demonstrated an average of 4400 IDEC-114 binding sites per cell (range: 1300 to 6700). In vitro assays of antibody dependent cellular cytotoxicity (ADCC) demonstrated a dose-dependent increase in cell lysis at IDEC-114 concentrations between 0.1 and 10 µg/mL. When IDEC-114 was combined with rituximab (Rituxan®, MabThera®), ADCC activity was higher than that observed with rituximab alone. In SCID mice with SKW lymphoma xenografts, IDEC-114 and rituximab were similar in their ability to prevent tumor progression and improve mouse survival. The combination of IDEC-114 and rituximab extended survival beyond that seen with either antibody alone. In summary, preclinical evidence demonstrates that IDEC-114 binds B-lymphoma cells, induces ADCC, has in vivo antitumor activity, and could potentially be used with rituximab to increase efficacy. Clinical trials have been initiated in patients with non-Hodgkin's lymphoma.
Introduction: Over recent years, monoclonal anti-CD20 antibody (Mab) is available for the treatment of B-cell non-Hodgkin’s lymphoma. Despite a relatively high response rate, a few patients appear to remain resistant to Mab therapy. In order to identify patients in whom rituximab therapy could be beneficial, we evaluated the influence of various clinical and laboratory parameters of patients with B-cell NHL on response to rituximab.

Methods: Thirty rituximab cycles (four consecutive weekly intravenous infusions of 375 mg/m² Mab) in 25 consecutive patients were screened for this study. Twenty cases received one course of rituximab and 5 received 2 courses. The tumors consisted of 19 follicular lymphomas (FL), 3 cases of Waldenstrom macroglobulinemia or marginal zone B-cell lymphoma, 4 mantle cell lymphomas, and 4 diffuse large B-cell lymphomas. Twenty-four cases were classified as stage III or IV. Rituximab was administered during the first course of the disease in 8 patients (27%), the second in 14 cases (47%), and during greater than 2 courses of the disease in 8 patients. Before starting Mab, 16 patients had disease sensitive to conventional chemotherapy, 6 had refractory disease, and 8 patients relapsed at least 3 months after completion of all treatment modalities.

Results: The overall response rate to rituximab was 50%, with 33% of complete responses and 17% of partial responses. On univariate analysis, the absolute lymphocyte count (ALC) before starting monoclonal antibody was the only factor found to influence the overall response rate, with rates of 73% and 27% when ALC was greater than or less than 1000/µL, respectively (p = 0.01). No other clinical or laboratory parameters significantly influenced response to rituximab.

Conclusions: ALC appears to be a strong predictive factor for response to monoclonal anti-CD20 antibody therapy. This may suggest a tumor-specific immune response. Further studies should explore this hypothesis in order to improve lymphomatous-directed immunotherapy.

IL-2 plus rituximab results in clinical responses in advanced patients with non-Hodgkin’s lymphoma related to the degree of NK expansion.

PHASE II STUDY OF ALEMTUZUMAB (CAMPATH-1H) IN PATIENTS WITH ADVANCED MYCOSIS FUNGUNOSIS / SEZARY SYNDROME

Introduction: Alemtuzumab (Campath-1H), a humanized anti-CD52 monoclonal antibody, binds to normal and malignant B- and T-cells and has significant activity in chronic lymphocytic leukemia. The number of CD52 receptors are particularly high on malignant T-cells and tumor regression has been reported in a few patients with cutaneous T-lymphoma cells (CTCL) including mycosis fungoides/Sézary syndrome (MF/SS). The aim of this phase II study was to evaluate the safety and efficacy of alemtuzumab (dosage escalated rapidly from 3 mg to 10 mg to 30 mg, three times per week, for up to 12 weeks) in patients with advanced, symptomatic MF/SS. To date, response and toxicity data are available on 19 and 20 patients, respectively. The median age was 61 years (range 38-77). Most patients had chemotherapy-refractory disease and the median number of previous anti-tumor treatment regimens was 2 (range 1-5). All but stage III or IV disease and most patients had severe eczema due to disseminated cutaneous involvement. Result: The overall response rate was 63% (42% complete response and 21% partial response). Severe itching was reduced or eliminated in all but 1 responding patient. The median time to treatment failure was 10 months.

Toxicity: Mild to moderate first-dose reactions (fever, rigour, muscle pain) were observed in most patients but disappeared during continued therapy. Transient grade IV neurotoxicity with a febrile episode was recorded in four (20%) patients and grade IV thrombocytopenia in 1 (5%) patient. Cytomegalovirus (CMV) reactivation (causing fever without pneumonia and promptly responding to i.v. ganciclovir) occurred in four patients (20%).

RITUXIMAB AS SINGLE AGENT AND IN COMBINATION WITH INTERFERON-α2a AS TREATMENT OF UNTRATED AND FIRST-RELAPSE FOLLICULAR OR OTHER LOW-GRADE LYMPHOMAS. A RANDOMIZED PHASE II STUDY.

Introduction: The anti-CD20 monoclonal antibody rituximab is effective and well-tolerated as single agent in the treatment of indolent lymphoma, but the majority of patients relapse. In order to increase the efficacy of rituximab, interferon-α2a (IFN), which has multiple immunomodulatory effects and is well-known as therapy for FL, was added as "priming". Method: Pts with symptomatic advanced stage previously untreated or first relapse (<6 months of chemoablation and/or local radiotherapy) CD20+ low-grade lymphoma were included in a multicentre randomised phase II study. After a first cycle of rituximab (Mabthera®), 375 mg/m² wk x4 (IV infusion), response was assessed at wk 9 and 14. Pts in CR at wk 14 got no further treatment. Pts with SD or PD went off study. Pts with PR or MR were randomized to a second cycle: rituximab, 375 mg/m² wks x4 (wk 1-4), or IFN (Roferon®) 3 MIU/day x wk (wk 1), 3 MIU/day x wk (wk 2-5) + rituximab 375 mg/m² wks x4 (wk 3-6). Results: 127 pts were included (126 intention-to-treat) 91/99 to IFN: median age: 54 yrs (26-75), 70 males, 56 females, 81 previously untreated. Most had FL. Response rate (wk 14, cycle 1): 14 CR (11%), 56 PR (44%) and 13 MR (10%). Wks 16 after 1st cycle, 28/36 pts (78%) randomized to rituximab were responders (CR+PR) vs 31/33 pts (94%) with rituximab+IFN (p=0.087). CR rate was higher with the combination. Other 12 pts went off study (from intentification to randomization) was 28 mo in the rituximab group. With the combination 70% were still failure-free at this time point. Toxicity was mild and mostly related to the first infusion in both cycles. Reversible thrombocytopenia and leukopenia (WHO grade 3) were seen in 1 and 6 pts, respectively in the rituximab+IFN group. Conclusion: Two cycles of rituximab is an efficient and well-tolerated treatment for patients with symptomatic low-grade lymphoma. The effect of rituximab seems to be augmented with IFN with a prolonged failure-free survival. A phase III trial with two cycles rituximab +/- IFN will test this hypothesis.
INTERFERON ALPHAs FOR 18 MONTHS VERSUS NO TREATMENT AFTER INTENSIVE THERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR RELAPSING-LYMPHOMA. AN INTERNATIONAL RANDOMIZED STUDY ON 221 PATIENTS.

High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) prolongs survival in relapsing lymphoma in comparison with standard chemotherapy. Immunotherapy with interferon was chosen in this prospective multicentric (Europe, Australia-New Zealand and South Africa) randomized trial because of its efficacy in phase II trials. Since October 95 to November 00, 221 patients (pts) were randomized to receive either IFN alpha 2b 3.0 (0000000) U ITW for 18 months (104 pts) or no further treatment (117 pts) after HDT ASCT for patients in second remission. Fifty-four pts had low-grade lymphoma (NHL-LO); 8 small lymphocytic, 37 follicular, 9 mantle; 113 pts had high-grade lymphoma (NHL-HG); 90 diffuse large B cell, 20 peripheral T cell, 1 Burkitt's, 2 anaplastic; 54 pts had Hodgkin's disease (HD). At the time of relapse, 12/54 in NHL-LG, 50/113 in NHL-HG and 4/25 in HD had high-intermediate or high-risk in the IPI score. After HDT ASCT, 51/54, 94/113, 38/54 are in CR or CRu. No difference between the 2 arms was observed. Early progression was seen in 20 pts during the first 3 months and in 23 pts between 36 and 60 months in NHL-HG pts. Interferon treatment was not given in 4/25 in NHL-LG, in 13/54 in NHL-HG and in 4/25 in HD and was interrupted in 14/25, 22/54 and 42/75 respectively for progression (23 pts), toxicity (25 pts), or other (2 pts). Event-free survival (EFS) at three-years (3-y) was 45% ± 10.2 for IFN arm and 51% ± 10 for treatment arm (p = 0.94). 3-y overall survival (OS) was 62% ± 10 for IFN and 61% ± 10 for no treatment (p = 0.91). According to histological grade, EFS and OS were significantly different (p = 0.001) for NHL-LG (51% ± 14 and 72% ± 13 respectively), NHL-HG (37% ± 9 and 48% ± 10 respectively) and HD (68% ± 14 and 78% ± 13 respectively), but no statistically significant difference was observed according to interferon or no treatment arm. In this study, Interferon can only be given after HDT ASCT for a total of 18 months in 24% of the pts, and only 33% of the total planned dose could be effectively given. As intent-to-treat, it does not improve EFS or OS.

RADIOIMMUNOTHERAPY WITH IODINE-131 ANTI-CD20 CHIMERIC MONOCLONAL ANTIBODY (RITUXIMAB) FOR RELAPSING OR REFRACTORY LOW GRADE NON-HODGKIN'S LYMPHOMA: AN AUSTRALIAN PHASE II TRIAL.
M.F. Leahy, J.H. Turner, J. Seymour*, Fremantle Hospital, Western Australia and Peter MacCallum Cancer Institute, Melbourne, Australia.

Radioimmunotherapy of relapsed or refractory low grade lymphoma using murine anti-CD20 monoclonal antibodies (Mab) has demonstrated objective response rates (ORR) of 75-80% and complete remission (CR) in 15-40% of patients. These results are significantly better than anti-CD20 immunotherapy with rituximab (ORR 45% and CR 5%). The chimeric Mab have enhanced cytotoxicity with less immunogenicity than murine Mab. We have radiolabeled chimeric IgG, anti-CD20 Mab in an ongoing physician-sponsored multicentre phase II Australian clinical Trial of 121 rituximab radioimmunotherapy of relapsed/refractory low grade non-Hodgkin's lymphoma in 40 patients (median age 66 years) followed up for 6 months to 2 years. Eligibility included at least one prior course of chemotherapy, ECOG performance status 0-2 and adequate hematopoietic function defined as neutrophils >1.5x109/ml and platelets >100x109/ml. A tissue biopsy (other than bone marrow) confirming low grade disease (REAL classification) and CD20 expression was required within 12 months of entry to the study. Tracer dosimetry studies in each patient limited whole body radiation absorbed dose to 0.75 Gy. Thirty two (80%) patients responded. Nineteen (48%) achieved a complete clinical response, median duration yet to be determined. In 5 of these patients a molecular CR has been confirmed. Self limited myelosuppression occurred in all cases with a mean time to radio of 6 weeks. One patient developed grade IV neutropenia/thrombocytopenia requiring G-CSF and platelets and one transient grade IV neutropenia resolving without G-CSF antibiotherapy. There was no other toxicity. Repeat treatments in 3 relapsed patients showed similar therapeutic responses without significant myelotoxicity. Radiolabelled chimeric Mab showed an improved CR rate compared with studies using murine anti-CD20 Mab.

NON-MYELOABLATIVE RADIO-IMMUNOTHERAPY WITH AN IODINE-131 TAGGED ANTI-CD20 ANTIBODY IN PATIENTS WITH Hodgkin's LYMPHOMA.
1. Department of Internal Medicine I, 2. Department of Nuclear Medicine, University of Cologne, Germany.

Introduction: Despite Hodgkin's lymphoma (HL) has demonstrated to be an excellent target for immunotherapy due to the expression of CD25 and CD30 clinical trials using antibody-based strategies like native antibodies (Mabs), immunotoxins or bispecific Mabs demonstrated only moderate efficacy. Thus, we developed a new radio-immunonoconstruct consisting of the murine anti-CD25 Mab Ki-4 labeled with iodine-131 (131I).

Methods: To assess Mab distribution we performed a dosimetry with a preinfusion of 5mg native Ki-4 to block soluble CD20 followed by 185 MBq 131I labeled Ki-4. Whole body counts were done on days 1-2-3 and 7. The therapeutic dose was given on day 8 after preinfusion of unlabeled Mab. Escalating individual total body doses of 0.25 Gy and 0.35 Gy were administered.

Results: We enrolled from 11/01 - 01/02 eight heavily pre-treated patients (pts) (age: 15 to 37 years) with relapsed or refractory CD30-positive HL. Imaging demonstrated enhancement of involved areas in 3 of 8 patients. Treatment was tolerated well with fatigue in 6/8 pts and nausea in 3/8 pts. Two patients experienced a JTV hematotoxicity 3-4 weeks after treatment. Three pts are evaluable for response demonstrating a partial remission, 1 minor response and 1 stable disease.

Conclusions: Treatment of pts with our 131I labeled anti-CD20 radioimmunoconstruct is feasible and further evaluation is needed. Updated results will be presented in detail.
BEXXAR™ OVER FIVE YEARS EXPERIENCE IN TWO UNITED KINGDOM CENTRES.
St Bartholomew's Hospital, London, and Christie Hospital, Manchester, UK.
Between March 1996 and March 2001, 99 patients (pts.) aged 27-90 (median 53 years) with recurrent or refractory follicular lymphoma (FL) 64 pts., mantle cell lymphoma 3 pts., lymphoplasmacytic lymphoma (LPL) 4 pts., small lymphocytic lymphoma 3 pts. and a further 20 pts. who had transformed (Tx) to large B cell lymphoma (LBCL), 19 pts. previous FL, 1 pt. LPL were enrolled to be treated either in an open phase II trial (61 pts.) or on a compassionate basis (35 pts.) with Bexxar™ (tosotinomab and 131I tositumomab). Forty patients had bone marrow infiltration (all <25%). The median number of previous therapies was 2 (range 1-9). Eleven pts. had progressed following high-dose therapy (HDT), Rituximab (Rix) 13 pts., or Bexxar™ 3 pts. Administration, after dosimetry, was as previously described, delivering a whole body dose of 75 Gy if the planetae (pt.) count was >150x10^9, 65 Gy for pts. with a pt. count of 100-140x10^9 and 45 Gy following HDT. Seven pts. did not receive therapy; 3 because of human anti- mouse antibodies, 1 pt. withdrew and 3 progressed after dosimetry. Response was first evaluated 7 weeks post therapy and repeated 3 monthly. Further disease regressions were observed for up to 1 year, although regressions occurred in other pts. during this time. Toxicity was principally mucositis. Median neutrophil and plt. counts occurred at 7 and 6 weeks respectively. Grade 3 or 4 toxicity: neutropenia in 38% of pts. and thrombocytopenia in 31%. With a median follow up of 2 years, the median duration of response was 2 years (95% CI:1.1 to not reached) for those in CR/CRs (7) and 7 months (3 mo. to not reached) for those in PR. Overall response rate at first evaluation declined with successive number of previous therapies: 73%, 66% and 46% respectively for 1, 2 or 3 more treatments. The efficacy of Bexxar™ has been demonstrated in a range of clinical settings with the longest remission duration in those who achieved CR/CRs.


Introduction: Bexxar™ (tosotinomab), an antiCD20 antibody and iodine 131I tositumomab, has resulted in high response and CR in patients with Rel & Ref LG-NHL. Methods: From 1995-2000, 2 clinical trials enrolled 229 patients with Rel & Ref LG or TG-LG NHL onto Bexxar treatment protocols. Baseline patient characteristics: 31% >60 years of age; 60% male; 46% positive HIV; and 34% bulky disease (>50mm). Bexxar treatment has been previously described (J Clin Oncol 2001:19:3918). All responses were confirmed by at least 2 evaluations >4 weeks apart. A panel of independent medical oncologists and radiologists conducted a masked review of efficacy for three of the studies and for ongoing responders for all five studies. Results: The panel's blinded re-evaluations were as follows.

EFFICACY BASED ON MASKED INDEPENDENT REVIEW


Hyperuricemia and tumor lysis syndrome are well-known complications of NHL treatment. Classical prophylaxis or treatment consists of allopurinol. Rambucil, a recombinant urate-oxidase, has been shown to be superior to allopurinol in a randomized trial in pediatric patients with acute leukemia and lymphoma (Goldman Blood 2001). GRAAL 1 study was designed to analyze Rambucil effects in 100 adult patients with aggressive NHL with at least one adverse prognostic factor according to the International Prognostic Index. Rambucil was given at the dose of 0.20 mg/kg/day for 3 to 7 days, started either the day before chemotherapy or at initiation of chemotherapy. Uric acid (UA) levels were measured 4 hours after Rambucil injection and repeated during treatment. Out of the 71 patients enrolled, we report the 53 first patients included in 13 centers in France, Belgium and Switzerland with diffuse large B-cell lymphomas (39), anaplastic large cell lymphoma (5), peripheral T-cell lymphoma (5), transformation of indolent lymphoma (3), Burkitt's lymphoma (1). 37 out of 52 patients had elevated LDH at baseline, including 16 with LDH above 1000 IU/L, and 9 patients had UA level >450 μmol/L before initiation of chemotherapy. Chemotherapy regimens were ACVBV (21), CHOP (19), CHOP + Rituximab (7). All patients responded to Rambucil treatment, as defined by UA levels normalized and maintained under chemotherapy. No patient suffered renal insufficiency or required dialysis. In 41 of the 53 patients, 3 days of treatment with Rambucil were sufficient to control hyperuricemia while 8 patients were treated for 4 days and one received 5 days of treatment (1 missing information). Three patients stopped their treatment earlier because of an increase of liver enzymes, attributed to chemotherapy. One patient discontinued Rambucil after 2 days because of underlying disease. Tolerance of Rambucil was excellent. These interim results show that Rambucil allows an effective control of uric acid in adult lymphoma patients treated with intensive chemotherapy.
ONCE-WEEKLY (QW) EPOETIN BETA (NEORECOMRON®) 30 000 IU IS EFFECTIVE FOR THE TREATMENT OF ANAEMIA IN LYMPHOPROLIFERATIVE MALIGNANCIES: RESULTS OF THE NOW (Neorecomron® Once Weekly) STUDY

M Cazzola, I B Coiffier, J Kloczko, I Spieka on behalf of the NOW Study Group. 1IRCCS Policlinico San Matteo, Pavia, Italy; 2Centre Hospitalier Lyon-Sud, Pierre-Bénite, France; 3Medical Academy, Białystok, Poland; 4General Faculty Hospital, Prague, Czech Republic.

Introduction: Epoetin beta is effective in increasing haemoglobin (Hb) levels, reducing transfusion requirements and improving quality of life in anaemic patients with malignant disorders when administered three times weekly (twi) subcutaneously (sc). With the aim of increasing patient compliance and convenience, the NOW study was initiated to investigate if a once weekly (qw) dosage regimen is effective in the treatment of anaemia.

Methods: This open-label, randomised, parallel-group, multicentre study compared the efficacy and safety of sc epoetin beta 30 000 IU qw versus 10 000 IU twi for 16 weeks in anaemic patients (Hb 9-11 g/dL) with low-grade non-Hodgkin's lymphoma, multiple myeloma or chronic lymphocytic leukaemia, and a relative serum erythropoietin deficiency (sEPO ≤100 mIU/ml). The primary analysis (per protocol population) was comparison of the time-adjusted area under the Hb concentration-time curve (Hb-AUC) between the two treatment groups during weeks 5 to 16. Secondary variables (intent-to-treat analysis) comprised among others response to treatment (increase in Hb of 2g/dL vs baseline and no transfusion in the 6 weeks before the last available Hb value), Hb nadir at 4-weekly intervals, percentage of patients with corrected anaemia and transfusion requirements.

Results: 241 patients, in 52 centres, were randomised to epoetin beta treatment (n = 119 qw; n = 122 twi). The difference in the Hb-AUC was -0.20 g/dL (CI: -0.52, 0.11). Response rates during the study were 72% and 75% in the qw and twi groups, respectively. Hb nadir at 4-weekly intervals was similar in the two treatment groups. Correction of anaemia (defined as Hb nadir ≥11 or ≥12 g/dL at 4-weekly intervals) was achieved in 83 (65%) and 86 patients (68%) in the qw and twi groups, respectively. Eleven patients (9%) in the qw and 17 patients (14%) in the twi group received blood transfusions. The frequency of adverse events was comparable in the two study groups.

Conclusion: Epoetin beta 30 000 IU administered qw is an effective treatment for anaemia in patients with lymphoproliferative malignancies.

EPOETIN BETA DECREASES TRANSFUSION REQUIREMENTS IN PATIENTS WITH RELAPSED LYMPHOMA TREATED WITH THE COLOGNE HIGH-DOSE SEQUENTIAL CHEMOTHERAPY REGIMEN PRIOR TO AUTOLOGOUS STEM CELL SUPPORT.


Introduction: Patients treated with aggressive chemotherapy and stem cell support usually develop severe anaemia requiring multiple red blood cell (RBC) transfusions. rhEpoetin beta (rhEPO) has been shown to reduce the number of transfusions in chemotherapy-induced anaemia. This study evaluated the ability of rhEPO to decrease the need of RBC transfusions in patients with relapsed lymphoma treated with an aggressive high-dose sequential chemotherapy (HDSTCT) regimen. Patients and methods: Sixty patients (pt) with early or late relapsed Hodgkin's lymphoma (HD) or first relapse of aggressive Non-Hodgkin's lymphoma (NHL) were treated in a randomised multicentre study involving 21 centres. Patients were stratified according to gender, age (<40 vs. ≥40y), and hemoglobin (hb) level before therapy (<10 vs. ≥10 g/dL). Pts in both study arms received two cycles DHIAP; pts with PR or CR then received cyclophosphamide 4g/m2, followed by FISH harvest, melphalan 8g/m2 plus vincristine 1,4mg/m2 and etoposide 2g/m2. The final myeloablative course was BEAM followed by autologous stem cell support. Pts in the experimental arm additionally received 10000 IU rhEPO (Neorecomron® 3x/wk) from the start of therapy until the end of VP-16. Primary end-point of the study was number of RBC units needed during HDSTCT. In addition, hb levels and quality of life were measured. Mean values were compared using t-test. Results: The median age of the 29 male and 31 female pts was 49y (19y - 66y). Thirty-nine pts (65%) had HD, 21 pts (35%) had NHL. Eighteen pts had stage III/IV disease vs. 42 pts with stage I/IIV. There was no difference in terms of age, gender and hb level between the two groups. The mean number of RBC units given in the rhEPO arm was 4.5 compared to 8.9 in the control arm (p = 0.0049). Five pts (25%) in the rhEPO arm and 1 patient (5%) in the control arm needed no transfusion. Twelve pts (55%) in the control arm received 8 RBC units compared to 4 pts (20%) in the rhEPO arm. The mean hb levels during therapy were 10.4 g/dL in the rhEPO arm and 9.7 g/dL in the control (p = 0.022). Quality of life (QOL) and fatigue (MF1) assessment, however, showed no significant difference. Conclusion: This prospectively randomised study indicates that rhEPO is effective in decreasing RBC transfusion re-requirements in patients with relapsed lymphomas undergoing aggressive chemotherapy and stem cell support. Quality of life and fatigue of pts appear not to be affected.