that an improvement of function and adaptation to daily life routine took place during the second half year following completion of treatment.

Conclusions: Preoperative ILP combined with an aggressive surgical approach results in an excellent local control rate in high grade soft tissue sarcomas. Long-term limb salvage can be achieved in the overwhelming majority of our patients. Ranked by the patients themselves, functional results allow to maintain greater than 80% of preoperative routine activities.

Hematological malignancies

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Long-term follow-up of patients with newly diagnosed adult Acute Lymphoblastic Leukemia (ALL): A single institution experience of 378 consecutive patients over a 21-year period

X. Thomas[1], C. Danaïla[1], Q.H. Le[1], C. Sebban[1], J. Troncy[1], C. Charrin[2], V. Lhéritier[1], M. Michallet[1], J.P. Magaud[2], D. Fiere[1]. [1] *Service d'Hématologie Clinique;* [2] *Laboratoire d'Hématologie et de Cytogénétique, Hôpital Edouard Herriot, Lyon, France*

Purpose: Although the prospect of long-term leukemia-free survival (LFS) after treatment for adult ALL is widely accepted, few studies have reported long-term survival data. 378 ALL patients (pts), referred to our hospital from 1978 to 1999, were reviewed for long-term follow-up data.

Methods: The analysis included data on 351 pts treated by standard chemotherapy according to 11 different successive regimens.

Results: Complete remission (CR) was achieved in 299 pts (79%). Initial performance status, LDH level, immunophenotype, age, and risk group at diagnosis were of significant prognostic value for CR achievement. Median LFS was 14 months with a 3-year (y), a 5-y, and a 8-y LFS at 30%, 26%, and 24% respectively. LFS was better in T-lineage ALL than in B-lineage ALL ($p = 0.05$). Younger age was also a favorable prognostic factor for LFS ($p = 0.001$). Philadelphia-positive (Ph+) ALL displayed a poor outcome since median LFS was 7 months with only 13% of survival at 3 ys. Median overall survival (OS) of the entire cohort was 18 months with a 3-y, a 5-y, and a 8-y OS at 32%, 24%, and 22% respectively. Favorable prognostic factors for OS were younger age ($p < 0.0001$), and T-lineage ALL ($p = 0.001$). Among non T-lineage ALL, standard-risk ALL displayed a significant better outcome than high-risk ALL ($p = 0.0003$). All pts relapsing after 3 ys of CR were B- or non B non T-lineage ALL. Long-term survivors (LTS), defined as survival in CR $\geq$ 3 ys, represented 23% of evaluable pts. 83 pts remain alive in initial CR at >3 ys, while only 3 were LTS after a second CR. Regarding survival, a significant improvement was demonstrated in T-lineage ALL ($p = 0.03$). Furthermore, pts (aged less than 50 ys) transplanted while in first CR did significantly better than those receiving only chemotherapy as post-remission therapy ($p < 0.0001$). The 3-y OS, after allogeneic transplantation in first CR, was 74% in T-lineage ALL, while it was less than 50% in B-lineage ALL.

Conclusion: This single center study on a large cohort of unselected ALL pts reflects the degree to which ALL treatment remains unsuccessful in adults. Only T-lineage ALL outcome has improved over the ys. The results suggest a time (3 ys) at which it becomes reasonable to speak of potential cure, provided the pt is in CR.

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Treatment of patients with refractory, C-KIT positive, acute myeloid leukemia with SU5416, a novel receptor tyrosine kinase inhibitor

W. Fiedler[1], P. Staib[2], R. Kuse[3], U. Dührsen[4], M. Flasshove[5], V. Spataro[6], S. Kelsey[8], P. Scigalla[8], D.K. Hossfeld[1], W.E. Berdel[7]. [1] *University Hospital Hamburg-Eppendorf, Oncology/Hematology, Hamburg, Germany;* [2] *University Hospital, Oncology/Hematology, Cologne, Germany;* [3] *AK St. Georg, Hematology, Hamburg, Germany;* [4] *University Hospital (GHS), Hematology, Essen, Germany;* [5] *University Hospital (Cancer research), Oncology, Essen, Germany;* [6] *University Hospital, Oncology/Hematology, Bellinzona, Switzerland;* [7] *University Hospital, Oncology/Hematology, Münster, Germany;* [8] *Sugen Inc., South San Francisco, USA*

In acute myeloid leukaemia (AML) increased microvessel densities have been detected on bone marrow histologies. Endothelial cell (EC) proliferation is driven by VEGF released by AML blasts. Stem cell factor (SCF) secreted by activated ECs or AML blasts may promote AML growth. SU5416 represents a small molecule inhibitor of phosphorylation of VEGF receptor-1 and -2 and of c-kit, the SCF receptor. This possible mechanism represented the rationale to initiate a phase II trial of SU5416 in patients with refractory AML.

Thirty-two patients (pts) with c-kit positive AML which was either refractory or occurred in patients older than 60yrs not judged medically fit enough for induction therapy, were treated twice weekly with 145 mg/m² SU5416 as a 60-minute infusion via a central venous device. From July 2000 to April 2001 15 female and 17 male patients with a median age of 68yrs (range 27-79) were enrolled. Treatment was generally well tolerated and toxicity was mild. Side effects included severe bone pain in 3 pts, liver failure with gastric hemorrhage and fatal shock (1 pt), grade IV pancreatitis (1 pt). Leukemia related side effects were: fatal thrombocytopenic hemorrhage (2pts), pneumonia/pyrexia/sepsis (6pts). 19 patients are evaluable for response: one patient with morphological remission (absence of blasts in peripheral blood and in bone marrow <5% without normalisation of peripheral blood thrombocytes and granulocytes), 7 pts with PR (reduction of blasts in blood and bone marrow by at least 50%) with a duration of 1-5 months, 11 pts were Non-responders after 4 weeks of therapy. 10 patients were non evaluable due to a treatment of less than two weeks caused by rapid disease progression after one infusion or serious adverse events due to underlying disease. 3 pts are too early to assess.

Treatment of c-kit positive AML with SU5416 represents a novel therapeutic approach. Administration of SU5416 was fairly well tolerated and toxicity was mild. Morphological and partial remissions were observed in a subgroup of patients. Future research is necessary to further identify the subgroup of AML patients where SU5416 shows activity.

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Troxatyl is effective in non-lymphoid blastic phase chronic myeloid leukemia (CML-BP)

F. Giles[1], M. Talpaz[1], C. Bivins[1], J. Jolivet[2], H. Kantarjian[1]. [1] *University of Texas MD Anderson Cancer Center, Departments of Leukemia and Bioimmunotherapy, Houston, USA*

Troxatyl(TM) (troxacitabine) is the first dioxolane nucleoside with potent antitumor activity. In a Phase I study of Troxatyl in patients (pts) with refractory acute myeloid or lymphocytic leukemia, myelodysplastic syndromes or CML-BP, mucositis and hand-foot syndrome were DLTs (Giles et al, JCO 2001). The Phase II single agent dose was defined as 8 mg/m2/day daily for 5 days. Seventeen pts (10 F, 7 M; median age: 52 years, range: 23-80) with CMLBP have been treated at the recommended dose. Nine pts had failed prior therapy for CMLBP which included topotecan-based therapy - 5 pts, allogeneic SCT - 3 pts, 6 thioguanine - 1 pt, homoharringtonine - 2 pts, mitoxantrone/ara-C - 1 pt, STI571 - 6 pts, donor lymphocyte infusions - 1 pt, 2-CDA/cyclophosphamide/VP16 - 1 pt, hCVXD - 1 pt, clofarabine/decitabine - 1 pt, liposomal daunorubicin/ara-C - 1 pt, CVAD - 1 pt. Toxicities included Grade 2 skin rash - 5 pts, hand-foot syndrome Grade 2 - 4 pts, Grade 3 - 3 pts, Grade 2 mucositis - 1 pt, Grade 4 mucositis - 2 pts. Six pts (35%) have returned to a second chronic phase. The durations of 2nd chronic phase in these pts are 3 to 18 plus months. In a recent analysis of results in 162 pts following first salvage therapy for non-lymphoid CML-BP treated at MDACC between 1986 to 1997 (Sacchi et al, Cancer 1999), 36 pts (22%) had an objective response and the median overall survival was 22 weeks. The median survival in the Troxatyl-treated CML-BP patients is 52+ weeks at the present time ($p < 0.01$). Troxatyl is being studied as a single agent in a multicenter Phase II study of pts with CML-BP including STI571 (Glivec) failures. Initial data from this study will be presented.

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Zevalin radioimmunotherapy offers safe and effective therapy for relapsed or refractory, B cell non-Hodgkin's lymphoma (nhl)

M. Saleh[1], C.A. White[2], T.E. Witzig[3], L. Gordon[4], G.A. Wiseman[3], C. Emmanouilides[5], J.L. Murray, J. Lister, R. Landin[2], P.S. Multani[2]. [1] *UAB Cancer Center and Georgia Cancer Specialists, Birmingham/Atlanta, USA;* [2] *IDEC Pharmaceuticals, San Diego, USA;* [3] *Mayo Clinic, Rochester, USA;* [4] *Northwestern Univ, Chicago, USA;* [5] *UCLA, Los Angeles, USA*

Zevalin consists of the anti-CD20 murine monoclonal antibody ibritumomab covalently bound to tiuxetan, which chelates 90Y for therapy. Zevalin therapy includes pretreatment with 2 doses of rituximab (250 mg/m2) 1 week apart to clear peripheral blood B cells and provide improved targeting. A total of 349 patients with relapsed or refractory low grade, follicular, or CD20+ transformed or intermediate grade B-cell NHL were treated with 90Y Zevalin on five clinical trials: a Phase I/II dose finding trial, a

Phase II trial of reduced dose 90Y Zevalin (0.3 mCi/kg) in patients with mild thrombocytopenia, a Phase III randomized trial of 90Y Zevalin (0.4 mCi/kg) versus a standard course of rituximab (375 mg/m2 weekly x 4), a Phase III nonrandomized trial of 90Y Zevalin (0.4 mCi/kg) in patients with rituximab-refractory follicular NHL, and an expanded access trial in patients with relapsed or refractory NHL. All patients had < 25% bone marrow involvement, ANC > 1500/mm3, platelets > 100K/mm3, and no prior high-dose therapy. These patients are a refractory population with advanced disease: median age 60 yrs (range: 24 ñ 85 yrs); 10% splenomegaly; 42% with bone marrow involvement; 16% intermed/high or high IPI risk groups; 31% with => 4 prior therapies. Overall response rates (ORR) for the two Phase III trials, using the International Workshop response criteria for NHL [JCO 1999;17(4)1244-53], were determined by an independent panel, blinded to investigator assessment of response. The ORR for the randomized trial was 80% (34% CR/CRu) in the Zevalin arm and 56% (20% CR/CRu) in the rituximab arm. The ORR in the nonrandomized, rituximab-refractory trial was 74% (15% CR/CRu). Toxicity was primarily hematologic. Median nadirs: ANC = 800/mm3; platelets = 40K/mm3; and Hgb = 10.3 g/dL. Grade 4 neutropenia and thrombocytopenia occurred in 30% and 10% of patients, respectively. The median duration below an ANC of 1000 cells/mm3 or platelets of 50K/mm3 was 13 days and 14 days, respectively, for all patients, and 22 and 25 days, respectively, for those patients with a Grade 3 or 4 nadir. 7% of patients were hospitalized with infection or febrile neutropenia. Myelodysplasia or AML was reported in 5 patients (1.4%) from 8 to 34 months after Zevalin treatment, which is below the 4-8% cumulative background incidence reported for such heavily-pretreated patients. In summary, Zevalin therapy is effective and well tolerated, even in this refractory population at risk for toxicity.

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Histiocyte-rich, T cell rich B cell lymphoma. A distinct clinicopathological entity

R. Achten[1], G. Verhoef[2], L. Vanuytsel[3], C. De Wolf-Peeters[1]. [1] *University Hospitals K.U.Leuven, Department of morphology and Molecular Pathology, Leuven, Belgium;* [2] *University Hospitals K.U.Leuven, Department of Haematology, Leuven, Belgium;* [3] *University Hospitals K.U.Leuven, Department of Oncology, Leuven, Belgium*

Background: Although it has proven difficult to delineate diagnostically reproducible and clinically relevant subgroups, the heterogeneity of diffuse large B cell lymphomas (DLBCL) is widely acknowledged. In 1992 we reported on six cases that suggested that histiocyte rich, T cell rich B cell lymphoma (HRTR-BCL) may be identified as a separate clinicopathological entity within DLBCL.

Methods: In a retrospective study of 60 cases, the clinicopathological features of HRTR-BCL were analyzed in order to provide a precise disease definition and to suggest reliable differential diagnostic criteria. In addition the clinical relevance of recognizing HRTR-DLBCl as a distinct lymphoma entity was evaluated and the predictive value of several phenotypic markers in TRHR-BCL was assessed.

Results: HRTR-BCL is easily distinguished from other B cell lymphomas rich in stromal T cells by (1) a diffuse or vaguely nodular growth pattern, (2) the presence of a minority population of CD15-, CD20 large neoplastic B cells, (3) a prominent stromal component composed of both T cells and nonepitheloid histiocytes, and (4) the absence of small reactive B cells. These diagnostic criteria also allow one to differentiate HRTR-BCL from lymphocyte-rich classical Hodgkinzs disease, from lymphocyte-predominant Hodgkinzs disease, paragranuloma type and from peripheral T cell lymphoma. HRTR-BCL typically affects middle-aged male patients who present with advanced-staged disease that is not adequately managed with current therapeutic strategies. Whereas proliferation fraction and p53 overexpression, in addition to the clinical variables incorporated in the IPI, significantly correlated with response to treatment and survival in a univariate analysis, only the IPI score identified relevant prognostic HRTR-BCL subpopulations in a multivariate model.

Conclusion: These results confirm that HRTR-BCL constitutes a morphologically identifiable and clinically distinct diffuse large B cell lymphoma subtype. Based on the morphological aspect and the immunophenotypic profile of the neoplastic B cells, we speculate that HRTR-BCL may be derived from a progenitor cell of germinal centre origin. On the analogy of germinal centre-derived lymphomas in SJL/CD57L mice, reverse immune surveillance phenomena may determine the peculiar histologic features of the disease as well as its aggressive biologic behaviour.

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Gastric MALT lymphomas prospective LY03 randomised cooperative trial: preliminary results of the molecular follow-up

F. Bertoni[1], A. Conconi[1], C. Capella[1], T. Motta[1], R. Giardini[1], M. Ponzoni[1], E. Pedrinis[1], F. Cavalli[1], A.C. Wotherspoon[1], E. Zucca[1]. [1] *International Extranodal Lymphoma Study Group (IELSG)*[2] *Istituto Oncologico della Svizzera Italiana, Oncologia Medica, Bellinzona, Switzerland;* [3] *Barts and The London, Experimental Haematology, London, United Kingdom*

Purpose: Gastric extranodal marginal zone lymphoma of MALT-type can regress after anti-Helicobacter pylori treatment. The IELSG, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) and the United Kingdom Lymphoma Group (UKLG) have conducted a trial to ascertain whether the addition of chlorambucil is of benefit after anti-H. pylori therapy. At the last interim analysis, 105 patients out of 189 (55%) had achieved a complete histologic remission after antibiotics. In order to further assess the ability of treatment to eradicate the lymphoma clone we analysed the gastric biopsies from a subset of the patients by PCR targeted to the immunoglobulin heavy chain genes, an established molecular marker for molecular residual disease assessment.

Methods: At diagnosis, DNA extracted from paraffin-embedded tumour tissues were first analysed using FR3A primers. Polyclonal cases were analysed with FR2A primer. DNA samples from gastric biopsies performed during the follow-up were analysed for the presence of residual disease. Patient-specific oligonucleotides were designed to increase the specificity and sensitivity of the PCR assay. Results: Fifty-seven cases were analysed at diagnosis. Forty-nine cases were monoclonal by PCR. Forty-six out of the 57 achieved histologic complete remission (hCR): 34 cases underwent molecular follow-up. Ten had not been randomised, thirteen had been randomised to chlorambucil, 11 to observation alone. Fourteen (41%) patients failed to achieve molecular complete remission (mCR), as a whole. At one year after hCR, 17 patients were in mCR and a further 3 were in mCR by 2 years (mCR 59%). After a median follow-up of 2 years (6-57 months), 13 (38%) patients are still in mCR at the last follow-up biopsy. mCR was persistent in 5/6 of patients randomised to chlorambucil, and in 5/9 of the ones randomised to observation alone. However, to date those with persistent molecular disease do not show a higher rate of histologic relapse.

Conclusion: About half of the patients with MALT lymphoma can achieve molecular remission after antibiotic therapy. The presence of molecular disease in the absence of histologic disease, apparently not associated to histologic relapse, could be due to the persistence of lymphoma - related terminal differentiated plasmacells. However, since the indolent nature of MALT lymphomas, a longer follow-up might be needed.

Supported by the Swiss National Science Foundation and the Schweizerische Krebsliga/Krebsforschung Schweiz

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Consolidation radiotherapy to bulky disease in aggressive non Hodgkin's lymphoma. Results of the NHL B-94 trial of the German high grade NHL study group (DSHNHL)

T.P. Nguyen[1], M. Kloess[2], M. Loeffler[2], L. Truemper[4], M. Pfreundschuh[3], C. Ruebe[1]. [1] *Department of Radiotherapy, Saarland University Hospital, Homburg/Saar, Germany;* [2] *Med. Statistics and Epidemiology, Leipzig University, Leipzig, Germany;* [3] *Clinic for Internal Medicine I, Saarland University Hospital, Homburg/Saar, Germany;* [4] *Clinic for Internal Medicine, Goettingen University Hospital, Goettingen, Germany*

Purpose: The role of radiotherapy (RT) in the treatment of high grade NHL ist not very well defined. In the study design of the DSHNHL radiotherapy was added after chemotherapy (CT) in patients with bulky disease. The presented data analyse patients with bulky disease only treated in the NHL B-94 trial.

Methods: Patients with an initial tumor size larger than 7.5 cm were defined to have "bulky disease". An irradiation to the bulk area had to be given after 6 cycles of CT. Total dose was 36 Gy given in single fractions of 1.8-2 Gy 5 times per week. Out of the total of 959 pts.included in the study 323 (33.9%) had bulky disease, 170 of them had additional extranodal lymphoma; therefore, the incidence of bulky disease in patients without extranodal disease was 15.9% (153/959). To evaluate the impact of radiotherapy after chemotherapy, we analysed the group of 366 patients with nodal disease only, who completed therapy according to the protocol. Out of this group 91 pts. had bulky disease, 84 were treated with RT, 7 patients were not irradiated because of prior surgery.