sis of B-cell NHL in our area. 2. The high number of cases of B-cell NHL (12 of 54) who associate chronic liver disease produced by HCV infection. 3.The two deaths related to chemotherapy indicate hepatotoxicity in the cases of B-cell NHL associated with chronic liver disease produced by HCV. 4.We consider that antiviral therapy is required in all this cases to avoid the hepatotoxicity and possibly to induce by itself a regression of the lymphoma (based on the references in literature).

1203

CYTOMEGALOVIRUS REACTIVATION DURING ALEMTUZUMAB THERAPY FOR CLL: SAFETY AND EFFICACY OF VALGANCICLOVIR

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Background and Aims. Several study described a variable incidence of cytomegalovirus (CMV) reactivation in patients treated with alemtuzumab. No prospective reports currently provide results of oral valganciclovir as pre-emptive therapy in patients with CMV reactivation during alemtuzumab treatment. We explored the efficacy and safety of oral valganciclovir as a therapy of CMV reactivation and of prophylaxis of CMV disease. *Methods.* Starting from May 2004, we treated 10 patients (9 males and 1 female; median age 57). Six patients were in partial response after previous chemotherapy regimen containing fludarabine, and 4 were refractory to previous treatment (range 1-7). All patients received alemtuzumab at 10 mg as target dose, 3 times weekly for a prolonged period of 18 weeks. The drug was delivered subcutaneously and, in order to further minimise adverse local therapy-related effects and make the treatment more manageable, were associated with 50 mg of hydrocortisone s.c. for the first two weeks. At baseline all patients had undetectable CMV DNA but were positive by serology. Prophylaxis with oral acyclovir 800 mg bid was given during therapy and for a months after alemtuzumab therapy. CMV reactivation was detected weekly in peripheral blood mononuclear cells by PCR and was considered positive if >200 copie/mL. CMV disease was diagnosed from the association of clinical symptoms with virologic confirmation of a CMV infection of an organ. *Results.* During the treatment 4 patients (40%) showed CMV reactivation. 2 out 4 patients showed fever but no clinical evidence of CMV disease. CMV reactivation appeared after a median of 5 weeks (range 4-6) of treatment. The alemtuzumab and acyclovir prophylaxis were discontinued and the patients were treated immediately with oral valganciclovir 900 mg bid. Only one patients required hospitalization for fever. After a median of 14 days (range 9-21) of antiviral therapy all patients had achieved negative CMV PCR assays; oral valganciclovir was reduced at 450 mg bid and alemtuzumab treatment were resumed. No myelotoxicity or other side effects were observed during the treatment with oral valganciclovir. None of the 4 patient showed other episode of CMV reactivation after reintroduction of alemtuzumab. *Conclusion*: We successfully use valganciclovir in all patients with CMV reactivation. The response was prompt and there was no progression to CMV disease, no relevant clinical toxicity and unnecessary hospitalization for drug administration. Valganciclovir is effective and safe as CMV prophylaxis in CLL patients treated by alemtuzumab, allowing an easy management of a therapy previously difficult to be routinely used.

1204

MUTATED OR NON-MUTATED? WHICH DATABASE TO CHOOSE WHEN DETERMINING THE IGVH HYPERMUTATION STATUS IN CHRONIC LYMPHOCYTIC LEUKEMIA?

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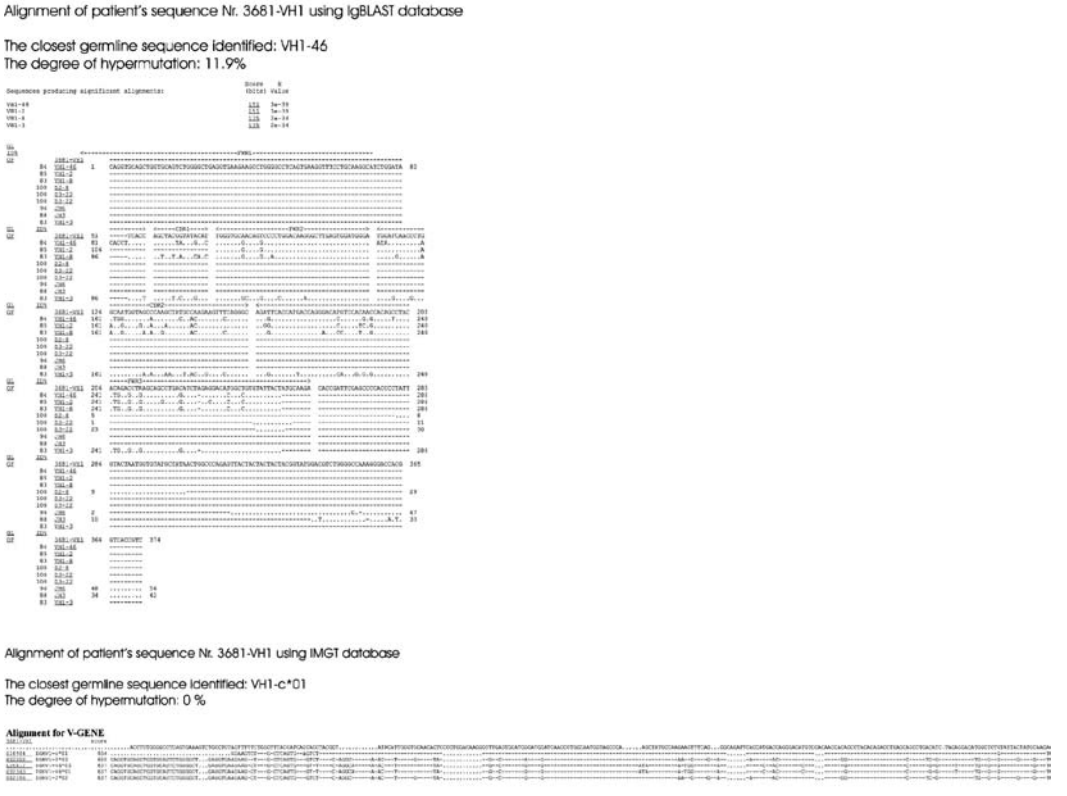
Backgrounds. It has been accepted that the hypermutation status of immunoglobulin heavy chain genes (IgVH) is one of the most important independent prognostic factors in chronic lymphocytic leukemia (CLL). According to the degree of IgVH hypermutation, CLL patients can be stratified into prognostic groups, with favorable or unfavorable prognosis. Aims. Given the impact of IgVH mutation status on clinical setting, it has become highly desirable to standardize the laboratory methodologies used for IgVH mutation status determination. To check the reliability of our laboratory results, we performed an interlaboratory testing, carried out at Homolka Hospital and Hôpital Avicenne. Methods. IgVH hypermutation status was determined in 10 randomly selected CLL patients, according to the Biomed-2 Study protocols. *Results.* From 10 CLL samples tested, in 9 cases identical results were obtained in both laboratories. In one case, the result was discordant. It turned out that the discrepancy was caused not by a technical obstacle, but by the IgVH database used. This finding prompted us to double-check our cohort of 624 CLL patients, using IgBLAST and IMGT databases. The results showed 7.5% (47/624) discrepancies between both databases. In 21 out of 47 cases, the degree of hypermutation has changed in regard to the database used, resulting in major changes in the prognostic subgroup (Figure 1 below). Other irregularities between both databases were identified, with yet to be determined significance. *Conclusions.* In the light of



presented data we would like to stress the necessity to identify/compile the most comprehensive IgVH database to be used for the determination of IgVH mutation status in CLL.

1205

ALLOTRANSPLANTATION FOR CHRONIC LYMPHOCYTIC LEUKEMIA A SINGLE CENTRE EXPERIENCE IMPLYING ITS APPLICABILITY AND CURATIVE POTENTIAL

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It is increasingly clear that allogeneic hematopoetic cell transplantation (alloHCT) offers currently the only curative option for chronic lymphocytic leukemia-CLL, but the relatively high transplant related mortality has limited its application. The recent experience following both the use of newer first line treatment with purine analogues and less toxic pre-transplant preparative regimens appeal for wider trials evaluating alloHCT early in the CLL course in younger patients. *Materials*. Ten patients (F/M=5/5), median age 44,5y (36-53), time from diagnosis to alloHCT 3 years (1-7,5). After diagnosis patients were treated using 1-5 different chemotherapy regimens, all obtained purine analogues and all displayed treatment resistant and progressive course. Other treatments included radiotherapy (n=2), anti-CD20 MoAb (n=2), anti-CD52 MoAb (n=1) and repeated 2 autologous HCT (n=1). The disease status at alloHCT was as follows: CR; n=4, PR;n=3, NR;n=3. AlloHCT characteristics: HLA matched Sibling Donor HCT (n=8), HLA single allele mismatched SibDHCT (n=1), matched Unrelated Donor-HCT (n=1). Stem cell source for SibD transplant: bone marrow -2, peripheral blood -6 (two using positive selection of CD 34+ cells and CD3 cell add back), BM+PB -1, for URD-HCT 'bone marrow in 1 pt. Conditioning: myeloablative Ctx+TBI: n=2; Ctx+TBI+alemtuzumab: n=1; reduced intensity: alemtuzumab (20 mgx5)+fludarabine (30 mg/m 2x5)+melphalan (140 mg/m^2): n=7. The number of transplanted cells: nucleated cells 4,25×10^8 (0,043-12) ; CD34(+) cells 4,34×10^6 (1,6-9,6) ; CD3(+) cells 35×10^6 (15-314) / kg recipient body weight. All transplantations were performed in intensive care, sterile HEPA units. GVHD prophylaxis consisted of cyclosporine A and methotrexate. *Results.* All patients engrafted. Hematopoetic recovery was as follows: granulocytes to 0,5 G/l -22 d (11-55) ; PLT to 50 G/l '24d (13-40). One patient died on day 92 after transplantation of pulmonary Aspergillosis and hepatitis after LPD due to EBV infection transmitted from the donor. The remaining 9 patients achieved CR after transplantation. All 3 patients after myeloablative conditioning acquired full donor chimerism. Among RIC conditioned patients at 6 months 2 displayed full donor chimerism, 3 mixed chimerism and one presented autologous recovery. Acute GVHD grade I was observed in 3/10 patients, limited cGVHD in 3 patients and extensive cGVHD in 2. Six patients developed CMV reactivation, one VZV, and one HBV. Two patients (both after ablative conditioning) died due to late complications: on day 180 (cGVHD with obstructive bronchiolitis) and on day 720 (chronic hepatitis). No patient relapsed with CLL suggesting efficacy of GVL mechanism. At 53 months after transplantation the probability of OS and DFS equals 60% with median observation time of 13 months (7-53). This observation compares well with recent other data (Toze CL et al 2005; 5y OS 39%) and suggests that allotransplantation offers an effective treatment with curative potential for progressive CLL patients who are in good biological condition.

1206

SIGNIFICANCE OF SOME FACTORS IN THE ERA OF MODERN CLL THERAPY

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Background. Expression of CD38, high level of Bcl-2 and β2-microglobulin and absence of CD95 expression are well-known unfavourable prognostic factors (UPF) for overall and progression free survival (OS and PFS, respectively). It is uncertain whether they retain their significance in the time of fludarabin (F) and mabthera (Rituximab (R) therapy. *Aim*. To evaluate the influence of the above mentioned prognostic factors on clinical course of CLL in patients (pts) treated with modern therapy. *Patients and methods*. Sixty nine pts with B-CLL were included in this study (median age 59,5 years; Binet stage A - 1, B - 41, C - 27; median follow up was 143 mo, median follow up after the start of treatment was 43 mo). Thirty four pts received FC treatment - F 25 mg/m^2 and cyclophosphamide (C) 300 mg/m^2 for 3 days; 35 pts received RFC treatment - R 375 mg/m^2 on day 1, FC regimen on days 2-4. All pts received 6 cycles of therapy. The multivariate analysis with Cox's regression model was used. *Results*. 18,5% of pts had all factors investigated, 27,7% had 3 and 21,5% 2 unfavourable factors in different combinations. One factor was found in 26,2% and none in 6,1%. In pts without UPF median OS was 107 mo; in pts with Bcl-2 expression, 97 mo; with Bcl-2 and CD38 expression, 70 mo. High β2-microglobulin level as well as absence of CD95 expression had no prognostic significance. The multivariate analysis showed that expression of CD38 (Relative Risk-RR=0,57, p= 0,3) and high level of Bcl-2 (RR=0,61, p=0,3) had the most pronounced negative influence on OS. For PFS lack of CD95 expression (RR=0,83, p= 0,099) and especially expression of CD38 (RR=1,26, p=0,059) were the most unfavourable factors. Median PFS was not achieved in pts with any UPF combinations without CD38 expression whereas in pts with all 4 UPF it was only 20 mo. *Conclusion*. Modern therapy with FC and RFC allows overcome the negative influence of high level of β2-microglobulin and Bcl-2 and lack of CD95 expression. CD38 expression retains its unfavourable significance.

1207

INFLUENCE OF CLADRIBINE ON BONE MARROW ANGIOGENESIS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

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Backgrounds. Angiogenesis is the process of formation of new blood vessels. The process is increased in many neoplastic diseases, including chronic lymphocytic leukemia (CLL). The purine nucleoside analogues, fludarabine and cladribine, represent a novel group of cytotoxic agents with high activity in low grade lymphoid malignancies. Fludarabine decreases bone marrow vessels density in CLL patients. The influence of cladribine on bone marrow angiogenesis in CLL was not studied so far. *Aims.* The aim of the study was to evaluate the influence of cladribine on angiogenesis in bone marrow of CLL patients. *Methods.* Parafin-embaded trephine biopsies were prepared and stained with antibody to CD34 for endotelial cells in patients with CLL before and after treatment with cladribine. Number of microvessels were counted in hot spot places, the areas, with highest vessels density under the microscope in 200x magnification. *Results.* Trephine biopsies from 14 previously untreated progressive CLL patients were evaluated before and after treatment with cladribine. Female/male ratio was 8/6 and median age of the patients 59 years (range 44-73). Staging according to Rai : Rai 0'2 8 patients, Rai 3-4 6 patients. All of the patients received cladribine alone (4 patients), in combination with cyclophosphamide (7 patients) or in combination with cyclophosphamide and mitoxantron (3 patients). All of the patients responded to the therapy and were in complete remission (4 patients) or partial remission (10 patients) according to NCI sponsored Working Group criteria. Median vessels number in hot spot places before treatment was 105 (range 45-238) and after treatment 65 (range 35-1600, p=0,02). There were no differencences between different regimens containing cladribine. *Conclusions.* Number of vessels in bone marrow of CLL patients was decreased after treatment with cladribine containing regimens.

1208

MATURE B-CELL AND T-CELL NEOPLASMS PRESENTING WITH LYMPHOCYTOSIS: A SYSTEMATIC DIAGNOSTIC APPROACH BASED ON CLINICAL, MORPHOLOGIC, IMMUNOPHENOTYPIC AND PATHOLOGICAL FEATURES IN 373 CONSECUTIVE CASES

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Background. Various types of mature B- and T-cell malignancies may involve the peripheral blood (PB) and bone marrow (BM) at presentation. However, among patients requiring an hematological diagnostic work-up because of persistent lymphocytosis, information on the pattern and proportion of the different diagnoses is scanty. *Aims*. To analyze the results of a systematic approach carried out for the differential diagnosis of cases consecutively referred to our center because of persistent