408 HIGH RESOLUTION MELTING CURVE ANALYSIS (HRMCA) FOR THE RAPID DETECTION OF MUTATIONS OF TP53 GENE IN PATIENTS WITH B CHRONIC LYMPHOCYTIC LEUKEMIA (B-CLL)

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B chronic lymphocytic leukemia (B-CLL) is the most common leukemia in adults. B-CLL is a disease characterized by high biological and clinical heterogeneity. Analyses of large cohorts of patients have determined the most important markers, which help us to predict the course of the disease. Most valuable prognostic markers are mutational status of IgVH and chromosomal aberrations 11q-, +12, 13q-, and 17p-. Changes on chromosome 17 include also a tumor suppressor gene TP53. The loss of function of TP53 can be caused by deletion on chromosomal level or by point mutation. Direct sequencing is considered to be a gold standard in detection of point mutations. This approach is very expensive and time consuming. High resolution melting curve analysis (hrMCA) is based on comparison of melting temperatures (Tm) of PCR products of a wild type control and a tested sample. If Tm of the tested sample is different it is highly probable that a mutation is present in the TP53 gene in a patient's sample.

In our study was verified the suitability of hrMCA for rapid screening of mutations in TP53 gene. HrMCA was used to analyze our cohort of 30 B-CLL patients. All samples are characterized by molecular biologic and cytogenetic methods (mutational status of IgVH, cytogenetic panel of prognostic markers 11q-, 13q-,+12 a 17p- and expression of ZAP-70). All of these patients have 1 deleted allele on chromosomal level. DNA samples after isolation and amplification were subjected to hrMCA analysis. Each of exons 5 to 8 (comprises 94.2% of published mutations) were tested separately.

6 patients with atypical Tm in comparison to Tm of the wild type control was detected and subjected for direct sequencing to verify occurrence of the mutation. In all of these patients point mutations were detected (exon 5: 1 patient, exon 6: 3 patients, exon 8: 2 patients).

HrMCA is a very effective method to discover mutations in TP53 in CLL patients. One of the most promising advantages for routine application is that hrMCA is one tube procedure which means that it is a cost effective and a rapid method.

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409 IS THERE A FILIATION BETWEEN CHRONIC LYMPHOCYTIC LEUKAEMIA, HODGKIN LYMPHOMA AND DIFFUSE LARGE CELL LYMPHOMA? : CASE REPORT

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Chronic lymphocytic leukaemia (CLL) is a disease characterized by the relentless accumulation of CD5+ B lymphocytes in the peripheral blood, bone marrow and secondary lymphoid organs. Richter's transformation occurs in 5% of patients with CLL and denotes the development of high-grade non Hodgkin lymphoma, prolymphocytic leukaemia, Hodgkin disease (0.4%), or acute leukaemia. The large cells of Richter's syndrome may arise through transformation of the original CLL clone or represent a new neoplasm. We present a 67 years old Tunisian woman with CLL (Matutes score = 5) stage B of Binet classification, diagnosed on August 2002. She's treated with alkylant during 14 months. The splenomegaly disappeared after 4 months with persistence of axillary lymph node. She's received 7 cycles of COP without any changemen. On April 2005, she presented a rapidly enlarging of axillary lymph nodes with fever. The diagnosis of Hodgkin type 3 CD15-, CD30+, CD20+, EBV+ is confirmed by lymphadenectomy. Reed-Sternberg cells are presented in a typical polymorphous inflammatory background. The patient was staged as stage II according to the Ann Arbor classification. She was treated with combined chemo-radiotherapy. One year later she presented a splenomegaly, cervical and axillary lymph nodes. The biopsy of axillary lymph node revealed a diffuse large cell lymphoma CD20+.

This case demonstrates the possible filiation of three lymphoproliferative disorders in the same patient. The clinical course and the histologic and immunologic findings of this patient are presented, together with a review of the literature.

409 bis LYMPHOPENIA AT DIAGNOSIS IS THE MAJOR RISK FACTOR OF SEVERE INFECTIONS IN PATIENTS WITH HAIRY CELL LEUKEMIA: A LONG-TERM STUDY OF 73 PATIENTS

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Survival of pts with HCL has been improved since the use of effective treatments such as IFN and purine analogs, but severe infections (SI) and secondary (IId) neoplasia (Kc) remain considerable complications affecting results. In this long-term study, we tried to identify factors influencing pts' outcome. Between 1984 and 2003, 73 pts with HCL were evaluated. Median age at diagnosis (dg) was 53 yrs. 60 pts were symptomatic with splenomegaly, infection (INF), B-symptoms, lymphadenopathy. Median hgb, absolute neutro, lymphocyte (Ly), mono and platelet counts were 12 g/dL, 0.8 G/L, 1.3 G/, 0 G/L and 80 G/L, respectively. All but 2 pts received at least 1 line of therapy. At the time of analysis, median FU was 13 yrs. 8 pts died between 12 and 180 mo. from dg, including 2 of IId Kc, 1 of HCL and 5 of age-related complications. 27 pts developed INF of whom 11 developed SI one to 50 mo after dg. 19 pts developed IId Kc. Initial pts and disease characteristics and treatment modalities were considered for the analysis of OS, DFS, relapse, mild and SI incidence and incidence of IId Kc. Ten-yr OS, DFS and RR were 91±3%, 14±5% and 87±5%, respectively. In multivariate analyses, age >53 yrs was the only risk factor adversely influencing OS and IId Kc incidence with adjusted HR of 9.30 (95% CI, 1.15-76.6; p=.037) and 2.80 (95%CI, 1.05-7.71; p=.04), respectively. INF and SI were affected only by the absolute Ly count (<1 G/L) at dg with adjusted HR of 3.30 (95% CI, 1.42-7.67; p=.05) and 4.01 (95%CI, 1.47-11.20; p=.007), respectively. Eleven of the 25 pts with Ly less than 1 G/L at dg developed SI while only 13% of the other pts did (p=.007). Of note, we did not observe any significant association between either neutro or mono counts or the incidence of INF

Conclusion Unlike what has been reported by others, IId Kc did not seem to adversely affect outcome of pts. In accordance with the literature data, our results confirm the good prognosis of HCL but point out a high incidence of INF that could occurred even late in the course of the disease. The absolute Ly count at dg is the only predictive factor of developing SI and should be considered as an indicator for the initiation of treatment. Careful monitoring of pts with low Ly count at dg is warranted.

410 PROGNOSIS FACTORS IN CLL: IS SERUM FREE LIGHT CHAIN RATIO A NEW BIOLOGICAL MARKER?

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Introduction. The remarkable heterogeneity in clinical behaviour of CLL makes it very difficult to establish a reliable prognosis for an individual patient at the time of diagnosis. Some biological and genetic markers were recently identified that may help on refining the classical prognostic systems. We tested some of these markers as well as a new one, Serum-Free Light Chains (SFLC), for their prognostic value.

Methods. This non-interventional, cross-sectional study included 84 non-selected patients with CLL diagnosed between Mar87/Aug07. Based on clinical characteristics, 2 prognosis groups were established and compared with respect to: Rai / Binet staging, IgVH mutational status, chromosomal abnormalities, b2MCG and SFLC. These parameters were also analysed in relation with time to 1st treatment.

Results. Parameters statistically associated with prognosis were: RAI/Binet stages, IGVH mutational status, B2MCG and λ free light chain. Although not statistically significant, there is an association between the prognosis group and the presence of unfavourable cytogenetic changes. Time from diagnosis to first treatment was statistically higher in patients with: Rai 0/I, Binet A and IGVH status. An association of time to 1st treatment with presence of unfavourable cytogenetic abnormalities and k/λ was also observed. In our sample, the k/λ ratio is associated with IGVH status (p=0.05). According to a Cox regression model for the time to first treatment, with Rai at diagnosis and mutational status as covariates, patients with Rai 0/I have a risk reduction for treatment of 88% and IGVH mutated of 78%.

Conclusions. Our results confirm previously published data regarding the prognostic value of IGVH mutational status and B2MCG. The lack of statistical significance of the prognostic value of unfavourable cytogenetic changes most probably relates with sample size and short follow-up. The association between mutational status, time to treatment and prognosis with k/λ or λ suggests that these parameters may be useful as new prognostic tools in CLL and supports interest in further studies.

411 HUMORAL IMMUNE RESPONSES AGAINST THE IMMATURE LAMININ RECEPTOR PROTEIN SHOW PROGNOSTIC SIGNIFICANCE IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Chronic lymphocytic leukemia (CLL) is characterized by a highly variable clinical course. The role of an autologous tumor-specific immune control contributing to the variable length of survival in CLL is poorly understood. We investigated whether humoral immunity specific for the CLL-associated antigen oncofetal antigen/immature laminin receptor (OFA/iLR) has a prognostic value in CLL. Among sera of 67 untreated patients with CLL, 23 (34.3%) had detectable OFA/iLR-antibodies which were reactive for at least one specific OFA/iLR epitope. Patients with humoral responses compared to patients with non-reactive sera had a longer progression-free survival (PFS)($p = 0.029$). IgG subclass analyses showed a predominant IgG1 and IgG3 response. OFA/iLR-antibodies were capable of recognizing and selectively killing OFA/iLR-expressing CLL cells in complement-mediated and antibody-dependent cellular cytotoxicity (ADCC) assays. In the analysis of 11 CLL patients after allogeneic hematopoetic stem cell transplantation, eight showed high values for OFA/iLR-antibodies which specifically recognized the extracellular domain of the protein; suggestive for a potential role of anti-OFA/iLR-directed immune responses to the graft-versus-leukemia effect in CLL. Our data suggest that spontaneous tumor-specific humoral immune responses against OFA/iLR exist in a significant proportion of CLL patients and that superior PFS in those patients could reflect autologous immune control.

412 B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA FOLLOWED BY A COMPOSITE HODGKIN LIKE AND PERIPHERAL T-CELL LYMPHOMA. AN UNIQUE VARIANT OF RICHTER'S SYNDROME

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Richter's syndrome refers to the development of high-grade non-Hodgkin lymphoma in patients with chronic lymphocytic leukemia. We report an unusual transformation of CLL into a composite lymphoma consisting of a Hodgkin-like lymphoma and a peripheral T-cell lymphoma. A 76-year-old man was diagnosed in October 2000 with Binet stage A – CLL and treated between March 2004 and August 2007 by 6 cycles of chlorambucil/prednisone. In September 2007, he complained of repeated episodes of fever with weight loss. Blood analysis showed only a mild inflammatory syndrome (CRP 2.9 mg/dl), with normal lactate dehydrogenase (LDH). The PET-CT scanner showed a few non hypermetabolic lymph nodes. Because a previous history of prostatitis, the patient received 2 lines of broad spectrum antibiotics without effect. In November 2007, he was admitted for persistent fever, chills, weakness, and abdominal pain. He was febrile (38.2°C); ECOG performance score was 2; there were enlarged and firm axillary and inguinal lymph nodes. Repeated blood analysis showed a white blood cell count of 9900/mm^3 with 56% granulocytes and 36% lymphocytes, Hb 9.6 g/dl and platelets 99.000/mm^3. C-reactive protein was 4.9 mg/dl, and LDH were still in the normal range. Repetitive cultures of blood, urine, and expectorations remained negative. Bone marrow aspirate showed only a mild lymphocytic infiltrate. A second PET-CT scanner identified multiple hypermetabolic lymph nodes and high uptake of ^{18}FDG in the spleen. Lymph node biopsy revealed the presence of 3 lymphoid neoplasms: deposits of chronic lymphocytic leukemia cells (CD20+, CD5+), infiltrates of hypermitotic T lymphocytes (CD3+, CD5+), and Reed-Sternberg cells with expression of p53 and a high Ki-67proliferative index. The first courses of CHOP were followed by a rapid improvement of the performance status and disappearance of the symptoms. Only two patients with this composite lymphoma were reported and this would be the first case on a transformation in such a composite lymphoma.

413 CLINICAL AND LABORATORY PROFILE IN PATIENTS WITH T-CELL CHRONIC LYMPHOCYTIC LEUKEMIA (T-CLL)

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Background: T- CLL a rare disease. The clinical course is generally indolent, with lymphocytosis and hepatosplenomegaly. Lymphadenopathy is less common. T-CLL is associated with immunological abnormalities: RF with or without RA, AIHA, PRCA, positive ANA, ANCA.

Materials and methods: We analyzed 5 pts, diagnosed and treated at the Institute of Hematology, Clinical Center of Serbia, in the period of 2001-2007. The diagnosis was based on accepted morphologic criteria, immunophenotype and PCR method for detection of TCR gene rearrangement. We compared their clinical and laboratory profile and response to different therapies.

Results: All pts had lymphocytosis, splenomegaly and elevated serum LDH. Two pts had skin and liver infiltration, respectively, 1 had positive ANA. In 3 pts the treatment was initiated with FC regimen. One female patient received 6 FC cycles (cy) and achieved good therapeutic response. One of the male pts received 1 FC cy, after which he decided to discontinue the therapy while in other male patient the signs of disease progression were recorded after application of 2 FC cy. His treatment was continued with CHOP protocol, the patient completed 1 cy, however in spite of the applied measures he died. A female patient, diagnosed in 2001, was initially treated with 6 cy of CHOP protocol. She was in remission for 3 yrs, but when she relapsed therapy was continued with 2 cy of DHAP regimen. There was no effect and she died with signs of disease progression. The female patient, diagnosed in 2005, was initially treated with 3 cy of CHOP protocol, however in absence of good reasponse, her therapy continued with FC and DHAP regimen. There was no good therapeutic effect and she died during first year of disease.

Conclusions: 4 pts died. 2 pts who died during first year of disease had initially poor prognostic parametres (lymphadenopathy, liver and skin infiltration). It is important to establish initial prognostic scoring system and to define more appropriate therapy, maybe in combination with monoclonal Ab.

414 IMMUNOPHENOTYPIC CHARACTERIZATION OF PERIPHERAL BLOOD CELLS FROM RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS TREATED WITH LUMILIXIMAB IN COMBINATION WITH FCR

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Background: Lumiliximab is an anti-CD23 monoclonal antibody under investigation for the treatment of patients (pts) with relapsed chronic lymphocytic leukemia (CLL). A comprehensive immunophenotypic characterization of CLL cells obtained from pts treated with lumiliximab in combination with fludarabine, cyclophosphamide, and rituximab (L+FCR) was performed including an analysis of CLL cells ($CD5^+CD19^+$), and expression of CD23, CD38, CD55 and CD59 antigens.

Methods: Immunophenotypic characterization of peripheral blood cells was performed by four color flow cytometry analysis. CLL cells were identified by gating on viable CD45+ cells coexpressing CD5 and CD19. Antigen expression levels and their frequencies were reported in terms of mean fluorescence intensities (MFI) and fraction (%) of positive CLL cells.

Results: The analysis of peripheral blood samples from L+FCR treated pts indicated that a substantial decrease in CLL cells in 30 of the 31 evaluable pts. A majority of patients (90%) had CD23+ CLL cells and clinical activity was observed in pts with both high and low levels of CD38 and CD23 expression. Finally, clinical activity of L +FCR was independent of pre-treatment expression levels of CD55 and CD59 antigen and was observed in a few pts showing increased expression of CD59 receptor post therapy (potential factors of rituximab resistance).

Conclusions: Clinically, L+FCR is an effective regimen in decreasing tumor burden in the peripheral blood of pts with relapsed CLL. Moreover, clinical activity with this regimen is independent of the low and high levels of CD23 expression and CD38 expression (a poor prognostic factor) and thereby may provide clinical benefit to a subset of pts with a phenotype indicative of unfavorable clinical outcomes. Clinical activity was also observed in pts with CLL expressing high levels of CD59 antigen, thus, suggesting a different MOA than other mAbs active in this indication.

415 CLINICAL ACTIVITY OF LUMILIXIMAB IN COMBINATION WITH FCR IS INDEPENDENT OF ZAP 70 EXPRESSION ON CHRONIC LYMPHOCYTIC LEUKEMIA CELLS

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Background: Lumiliximab is a CD23 monoclonal antibody under investigation for the treatment of patients (pts) with relapsed chronic lymphocytic leukemia (CLL). Lumiliximab binds specifically to human CD23, a glycoprotein expressed on a majority of CLL cells. As ZAP70 is a poor prognostic factor of CLL, expression of the ZAP70 antigen by malignant B cells was analyzed in a subset of pts with relapsed CLL enrolled in a Phase I lumiliximab monotherapy study. Subsequently, pre-treatment ZAP70 expression was analyzed in pts treated with a combination of lumiliximab, fludarabine, cyclophosphamide, and rituximab (L+FCR). Additionally, the ability of lumiliximab to induce apoptosis *ex-vivo* was also evaluated in the monotherapy study.

Methods: In the lumiliximab monotherapy study, ZAP70 expression was quantified by Western blot assay using lysates from purified CLL cells and apoptosis was evaluated by flow cytometric assessment of Caspase-3 activation on pre-treatment and day 2 treated samples (*ex-vivo*). In the L+FCR study, frequencies of CLL cells and ZAP70 positive cells were estimated by four color flow cytometry using standard commercially available antibodies. CLL cells were identified by first gating on viable CD45+ cells and subselecting with antibodies to CD5 and CD19 receptors (CD5+CD19+ phenotype). ZAP70 expression was reported as % CLL cells.

Results: Analysis of data from the monotherapy study suggested induction of apoptosis by caspase-3 activation and decrease in CD5+CD19+ cells in pts expressing high levels of ZAP70. Moreover, apoptosis was also observed in a patient that expressed activated ZAP70. Results from the Ls+FCR study demonstrated clinical activity in pts having high or low levels of ZAP70 expression.

Conclusions: Lumiliximab potentially provides clinical benefit in CLL pts with both low and high levels of ZAP70, a characteristic associated with aggressive disease and poor prognosis.

416 HAIRY CELL LEUKEMIA: IMPACT ON THE DISEASE OF TWO DIFFERENT INTERFERON ADMINISTRATION SCHEDULES COMPARED TO PURINE ANALOGUES

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Background: The prognosis of hairy cell leukemia (HCL) has dramatically improved over the last decades after the introduction of a2-interferon (IFN) first and of purine analogues (PA), such as pentostatine and cladribine (2-CDA), subsequently. IFN can be administered for a definite period of time (usually 12 months) or until relapse. The aim of this study was to retrospectively compare the efficacy on treatment response and response duration of the different schedules of IFN administration in comparison to PA.

Methods: Data on 104 HCL patients observed between 1982 and 2005 at our Institution were retrospectively analyzed. Forty eight patients (46.2%) received as first line treatment IFN alone for 12 months (group A), 33 (31.7%) received PA alone (group B) and 23 patients (22.1%) received continuous IFN until relapse (group C). The clinical features of the 3 groups of patients are shown in the table.

	Age	Hb <10 (%)	WBC >10.000 (%)	PLTs <100.000 (%)	Splenomegaly (%)
A	54	33.3	12.5	81.2	83.3
B	57	12.1	24.2	45.4	75.7
C	61	21.7	8.6	78.3	78.3

Results: Group A: 8 patients (16.7%) achieved complete remission (CR), 34 (70.8%) partial remission (PR) and 6 (12.5%) were refractory. After 24 months 21 patients (43.7%) relapsed. Group B: 21 patients (63.6%) achieved CR, 11 (33.3%) achieved PR and 1 (3.0%) was refractory. Three patients (9.1%) relapsed at 2 years. Group C: 5 patients (21.7%) achieved CR, 17 (73.9%) achieved PR and 1 (4.3%) was refractory. Seven patients (30.4%) relapsed at 24 months. Irrespectively to the histologic response, a clinical complete response was obtained in 43.7%, 81.8%, 43.5% of groups A, B and C patients, respectively.

Conclusions: Despite some unbalances in basal features within the 3 groups, a significantly higher CR probability can be obtained with PA in comparison to IFN, irrespective of the administration schedule, as well as a lower relapse probability. Nevertheless, IFN still represents a good therapeutic option especially for patients ineligible for chemotherapy; the prolonged administration seems to reduce the relapse probability, although a longer follow-up is necessary to confirm these data.

417 COST OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) IN MEDICARE PATIENTS

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Background: About 15,000 new cases of CLL are diagnosed annually in the United States but the direct medical costs attributable to CLL have not been delineated.

Methods: We analyzed the CLL cost of care using SEER-Medicare data. Patients with CLL (including small lymphocytic lymphoma) as their first primary cancer were diagnosed from 1998 to 2002 with follow up through 2005. Patients had to have ≥1 year of prior non-HMO Medicare coverage. Costs were taken from claims for inpatient, outpatient and physician services. Control comparisons were made both to the pre-diagnosis 12 month period and to a 5% sample of Medicare patients without a cancer diagnosis. Linear regression models with robust standard errors were adjusted for age, co-morbidity score, diagnosis year, gender, and county of residence.

Results: There were 3,999 patients who met the inclusion criteria. The median time from diagnosis to first chemotherapy was 199 days. The unadjusted mean monthly cost was similar regardless of control groups (~$2,700). This cost declined over time but did not reach the pre-diagnosis level. Most costs were for inpatient and provider charges with chemotherapy representing 6.9% of 1st year and 8-10% of later year costs. After adjustment the incremental cost of CLL was $2,773/month for the first year compared to the 5% Medicare sample ($p<0.05$). Increasing age, male gender, and non-white race were significantly associated with increased monthly costs ($p<0.01$).

Conclusions: CLL is associated with increased costs of care in the Medicare population, particularly in the first year after diagnosis where it is over $33,000 per patient.

Mean monthly cost ($) relative to diagnosis date

Health Service	12 Months Before	12 Months After	12-24 Months After	24-36 Months After	Medicare 5% Sample
Inpatient facility	287	2244	1038	1005	227
Provider	172	901	573	753	133
Outpatient facility	11	25	20	23	5