Results. After first line treatment 35/55 (64%) pts achieved CRm, 13 pts (24%) CR+, 9 (16%) PR+ (partial response). After SCT (81.8%) pts attained CRm (100% receiving rituximab in the 1st line). Median follow up is 50 months (mo). 23/55 (41.8%) pts relapsed or progressed (median PFS 30 mo), 11 pts died - one in CRm due to acute graft versus host disease, the other due to progression of the disease. At present 32/35 CRm pts are still in CRm, whereas 6/11 pts in CR+ relapsed. Median disease free survival (DFS) was longer in CRm pts than in CR+ pts (median EFS 33 mo vs not reached, p 0.0024). Median DFS in patients with or without autologous stem cell transplantation was not significantly different. Patients in CRm have longer overall survival (64 mo vs not reached, p 0.05) compared to pts in CR+ and PR. *Summary.* Molecular remission after first line treatment have an impact on disease free and overall survival in all risk subgroups of FL patients. Persistent PCR bcl-2/IgH positivity is asociated with high risk of relapse and additonal (maintenance) treatment should be considered.

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0215

CLINICO-BIOLOGICAL CHARACTERISTICS OF PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA AND HEPATITIS C VIRUS INFECTION

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Background. The infection with Hepatitis C Virus (HCV) is involved in the etiology of some subtypes of non Hodgkin's lymphoma (NHL) as diffuse large B cell lymphoma (DLBCL). *Aims.* We tried to analyze the clinico-biological characteristics of a group of 82 patients with DLBCL associated with HCV infection. *Methods.* We did a retrospective analysis of the clinical and biological profile of 82 patients hospitalized in the Hematology Clinic during 1993-2003. All patients were HIV negative and they were positive at diagnosis for the HCV antibodies Elisa method. The statistical analysis was performed with the special programs EPI INFO 6 and INSTAT. *Results.* The characteristics of the diffuse large cell lymphoma group that we studied were: medium age - 52,2 years; males/females=1/1; extranodal determinations - 48 cases (58.5%)- primitive extranodal 25 cases (30.5%) and secondary extranodal 23 cases (28%); B signs - 66 patients (80,5%); IK < 70 - 40 cases (48,8%); IPI at diagnosis was 16% low, 24% int.low, 35% int/high and 25% high; Bulky disease - 35 cases (42,7%); clinical stage I, II/III, IV=40/41; medullar determination - 14 cases (17,2%); LDH = 672,024±598,128 U/l; ESR = 50,45±37,73 mm/h; Ki67 = 51,90±22,16. The transformation from a low grade lymphoma in a DLBCL was 10% and primary mediastinal DLBCLwas 5%. The most important extranodal determinations were the stomach, the spleen, the liver, the skin. The treatment was CHOP or CHOP-like regiments. A small number of cases received CHOP and Rituximab. 11% of patients with severe liver dysfunction received monochemotherapy or radiotherapy only. In 5% of DLBCL and HCV positive patients the chemotherapy was discontinuous because of the hepatic failure. Medium follow-up was 48 month for the survivors and the overall survival at 5 years was 59%, while failure free survival at 5 years was 34%. *Conclusions.* It is important to recognize the clinical and biological features of DLBCL with HCV positive patients for bigger groups, which could clarify the connection between HCV infection and aggressive non Hodgkin lymphomas. It is also necessary to continue the study in order to evaluate the differentiate survival of nodal and extranodal types of lymphomas.

0216

RITUXIMAB IN INDUCTION TREATMENT AND IN HIGH DOSE CHEMOTHERAPY PRIOR TO AUTOLOGOUS STEM CELL TRANSPLANTATION AS FIRST LINE THERAPY IN STAGE III-IV DIFFUSE LARGE B-CELL LYMPHOMA AT POOR PROGNOSIS

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Background. We investigated efficacy and safety of adding Rituximab (R) to induction and intensified HDC as part of first line treatment in pts with aa-IPI at Intermediate-High (IH) or High (H) risk with B-DLCL at diagnosis, comparing two groups of pts enrolled in two non-randomized phase II clinical trials with up-front HDC and ASCT with or without R. Aims and *Methods.* 118 previously untreated pts <61 years with B-DLCL, stage III-IV at aa-IPI IH or H risk were treated: 41 pts were enrolled into HDC trial (control group; August 1991-August 1995) and 77 pts into R-HDC trial (study group; January 2001-December 2004). Treatment in R-HDC study group consisted in an induction treatment lasting two months with four courses of R-MegaCEOP chemotherapy (R 375 mg/m^2 day1, CTX 1200 mg/m^2 + EPI 110 mg/m^2 + VCR 1.4 mg/m^2 day3 and PDN 40 mg/m^2 days3-7) every 14 days with G-CSF support; then two courses of intensified chemoimmunotherapy R-MAD (Mitoxantrone 8 mg/m^2 + ARAC 2000 mg/m^2 /12h + Dexamethasone 4 mg/m^2 /12h for 3 days and R 375 mg/m^2 day4 and before PBSC harvest) followed by ASCT with BEAM as conditioning regimen. Treatment in HDC control group was an induction treatment lasting two months with MACOPB x 8 weekly infusions followed by the same intensified and HDC regimens (MAD x 2 courses + BEAM and ASCT). IF RT was given to areas of previous bulky disease in both trials. *Results.* Pts characteristics in both trials were comparable with no statistically significant differences: median age was 45 years (19-60); 51% were at H risk; 36% had bone marrow (BM) involvement, 80% LDH>normal and 42% extranodal sites>1. Complete Response at the end of the treatment was: 60 pts (78%) in R-HDC group and 28 (68%) in HDC group (p=.25). Failures (17% vs 25%) and toxic deaths (5% vs 7%) were comparable between the two groups (R-HDC vs HDC). Short-term toxicity appeared similar. NO MDS or ANLL or solid tumours were reported in both arms. No differences were observed in neutrophils >500/mm^3 and platelets >50000/mm^3 engraftment; median times in R-HDC vs HDC were: 9 vs 10 and 15 vs 16 days. Median follow-up was 36 months in study group and 72 months in control group. Three-year failure-free survival (FFS) and 3-yr overall survival (OS) rates in R-HDC group vs HDC group were: FFS 64% vs 46% (p=.016); OS 80% vs 54% (p=.004). A better outcome for pts treated with R-HDC was confirmed in both IPI groups (IH and H risk). A Cox's model was performed to adjust the effect of treatment for competing risk factors (age, IPI, BM involvement, number of extranodal sites). In this multivariate analysis the risk of failure and death was confirmed as significantly reduced in R-HDC group: adjusted hazard ratio (R-HDC vs HDC) was 0.56 (95% CI=0.30-1.01, p=.05) for FFS and 0.42 (95% CI=0.21-0.88, p=.02) for OS. *Conclusions.* these results suggest that the addition of Rituximab to induction and intensified chemotherapy before BEAM and ASCT is effective and safe in B-DLCL at poor prognosis.

0217

EFFECTS OF PRE-TRANSPLANTATION TREATMENT WITH RITUXIMAB ON OUTCOMES OF AUTOLOGOUS STEM-CELL TRANSPLANTATION FOR DIFFUSE LARGE B-CELL LYMPHOMA

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Background. Rituximab (R) in combination with chemotherapy (CHT) has become standard treatment for patients (pts) with diffuse large B-cell lymphoma (DLBCL). However, there are limited data concerning the comparison of the use of R-CHT and CHT alone before high-dose therapy (HDT) either as a part of induction regimen or as a part of salvage treatment. *Aims.* We retrospectively analysed the efficacy of R-CHT versus CHT without R followed by HDT and autologous stem cell transplantation (ASCT) in patients with DLBCL. *Methods.* Out of 127 pts with DLBCL who underwent HDT with ASCT, 59 pts received R as part of chemotherapy regimen (R-CHT group): 32/59 (54%) received HDT in 1st CR. 68 pts received CHT without R (CHT group): 14/68 (21%) received HDT in 1st CR (p<0.0001). Patient characteristics were comparable in both groups with the exception of status at HDT, indi-

cation to HDT (induction vs salvage therapy) and type of salvage regimen. Higher proportion of patients received HDT as a part of induction therapy in R-CHT 69,5% vs 48,5% in CHT group (p=0.01). The majority of pts in R-CHT group received salvage regimen ICE. Regimens ESHAP and IVE were mostly used as a salvage therapy in CHT group. Median follow-up is 2.2 y (range 0.5-4.0) in R-CHT group and 7.3 y (range 2.1-11.0) in CHT group. *Results.* At 2 years from the date of transplantation, the estimated overall survival (OS) was 81% in R-CHT group vs 60% in CHT group (p=0.03) and the event-free survival (EFS) was 75% vs 56% (p=0.02). The results remain significant while analyzing data for pts transplanted in 1st CR in R-CHT vs CHT group, OS 87% vs 57% (p=0.04), EFS 84% vs 57% (p=0.04) at 2 years. The differences were however not significant for pts who underwent HDT for relapse in R-CHT vs CHT group: OS 69% vs 55% and EFS 53% vs 48% at 2 years. *Conclusion.* Our analysis suggests that rituximab plays a significant role in pretransplant therapy in pts with poor risk factors treated with HDT in 1st CR (EFS, p=0.04, OS, p=0.04). Rituximab seems to improve the outcome of CR pts, it might be important how is the CR reached (with or without antibody). The difference is not however significant for pts treated with HDT in relapse or progression. The role of rituximab in this subset of pts could be in the improvement of salvage therapy results in order to increase the number of pts who are able to undergo HDT and ASCT.

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0218

COMPARATIVE ANALYSIS OF TREATMENT OUTCOMES WITH CHOP REGIMEN, ETOPOSIDE PLUS CORTICOSTEROID AND PREDNISOLONE IN ADULT PATIENTS WITH HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS: BASED ON UNDERLYING DISEASES

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Background. The outcome of CHOP treatment in the case of lymphoma-associated hemophagocytic lymphohistiocytosis (LAHLH) and EBV-associated HLH (EBV-HLH) has rarely been reported. *Aims.* The present study analyzed the treatment outcomes for CHOP chemotherapy as well as etoposide combined with corticosteroid (Eto-CS) and prednisolone (PRS) in adult patients with EBV-HLH and LAHLH. *Methods.* 46 adult patients older than 16 years of age were diagnosed with HLH. Among these patients, 30 treated with CHOP chemotherapy (n=18), Eto-CS (n=6), and PRS (n=6) were reviewed retrospectively. *Results.* With CHOP chemotherapy, complete remission (CR) was achieved in 5/18 patients (27.8%), partial remission (PR) in 5/18 (27.8%), and the overall response rate was 55.6%. With Eto-CS therapy, PR was achieved in 3/6 patients (50%), however no CR was achieved. With PRS therapy, CR was achieved in 1/6 patients (16.7%) and PR in 1/6 (16.7%). The median response duration (RD) was not reached and the 3-year estimated RD was 68.57% for the CHOP chemotherapy, while the median RD was three weeks for the Eto-CS therapy and one week for the PRS therapy, with a median follow-up of 132 weeks. The median duration for the overall survival (OS) was 16 weeks and the 3-year estimated OS rate 40.63% for the patients treated with CHOP therapy, yet only four and two weeks for the patients treated with Eto-CS and PRS, respectively (p=0.0016). *Conclusions.* CHOP chemotherapy seemed to be useful in adult patients with LAHLH and EBV-HLH. Additional treatment including stem cell transplantation may also be needed, especially for patients with poor prognostic factors.

Myeloma and other monoclonal gammopathies I

0219

PP2500 MRNA, A SPLICE VARIANT OF THE MULTIPLE ANKIRIN REPEAT SINGLE KH DOMAIN (MASK), IS HIGHLY EXPRESSED IN PLASMA CELLS OF MULTIPLE MYELOMA

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Background. The Ankyrin (ANK)-repeat is one of the most common protein sequence motifs, which leads itself to variation in overall domain size by simple sequence duplication or deletion. The Mask (Multiple Ankyrin Repeats Single KH domain) gene, which codifies an ANK-repeat protein, is located in chromosome 5(q31.3) and it is composed of 39 exons . It generates isoforms by alternative 3'splicing. The first splice variant (hMask) lacks the 10A exon of the Mask gene, generating a mRNA containing 34 exons. The other, Mask-BP3ARF, results from fusion of splice variant hMask, with the two last exons of the gene Eif4Ebp3 (exons B and C) and an intermediate exon (exon 0), generating 36 exons. Recently, a new splice variant, denominated PP2500, was deposited in the data base GeneBank, it presents the first 10 exons, homologous to Mask mRNA with a poly(A+) signal and it is a new splice variant of Mask. In Drosophila, MASK protein seems to interact with members of the Receptor Tyrosine Kinase (RTK) signalling pathway and loss of this interaction increases programmed cell death, reduces cell proliferation, inhibits photoreceptor differentiation, affects RTK dependents processes but does not affect MAPK (Mitogen Activated Protein Kinase) activation. However, the biological functions of these proteins in humans remain still unknown. Aim:The aim of this study was to investigate the expression of Mask splice variants in multiple myeloma (MM).*Methods.* Fifteen patients with MM and 3 normal donors participated in this study. Total RNA was extracted from positively selected plasma cells in magnetic column, by Macs Microbeads antibody anti-CD138 and the percentage of purity of plasma cells varied from 78.38% to 96.02% (average 87.95%). We used as control, total RNA from positively selected plasma cells, from a culture of B normal lymphocytes of bone marrow donors (purity 88.69%). The complementary DNA (cDNA) was analyzed by Real-time detection of amplification, performed in an ABI 5700 Sequence Detector System using SybrGreen PCR Master Mix (qPCR). The b-actin gene was used as endogenous control of the reaction. *Results.*The mean expression of the mRNA of the hMask and Mask-BP3ARF genes were 3 and 4 times increased, respectively, compared with control. The mean expression of the PP2500 mRNA was 14 times increased, compared with control. Quantification of hMask, Mask-BP ARF and PP2500 mRNA was not influenced by age, gender, ethnic origin, stage of the disease, B2-microglobulin, serum creatinine and lactate dehydrogenase values (Fisher´s exact test, p>0.05). Previously we demonstrated that MASK is associated with SHP2, a protein tyrosine-phosphatase. *Conclusions.*In MM, SHP2 mediates the anti-apoptotic effect of Interleukin-6 (Chauhan *et al.* JBC 275: 27845, 2000). Interleukin-6 triggers proliferation of MM cells via the MAPK cascade, which includes SHP2 activation. Thus, the increased expression of Mask splice variants in plasma cells of MM suggests that their proteins may be involved in this signaling pathway and provide an insight for novel treatment approaches in MM.

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0220

A PHASE II STUDY OF THALIDOMIDE, DEXAMETHASONE AND PEGYLATED LYPOSOMAL DOXORUBICIN (THADD) FOR UNTREATED PATIENTS WITH MULTIPLE MYELOMA AGED OVER 65 YEARS

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Background. No standard therapy have been yet identified for elderly patients with multiple myeloma (MM) despite two third of cases affected by this incurable malignancy are older than 65 years. The combination melphalan-prednisone yelds unsatisfactory results and high-dose therapy, despite feasible also in elderly patients, can be an unavailable option because of pre-existing medical comorbidities. Improvements in the outcome of elderly MM patients have been obtained using thalidomide as single agent or in combination with dexamethasone or conven-