# session 2 – mantle cell lymphoma

## 010 GENOMIC HYPERMETHYLATION CHARACTERIZES AN AGGRESSIVE SUBSET OF MANTLE CELL LYMPHOMA

T. Greiner[1], D. Klinkebiel[2], D. Weisenburger[1], W. Chan[1], J. Christman[2]
[1]Dept of Pathology and Microbiology, Univ of NE Med Ctr, Omaha, NE, United States, [2]Dept of Biochemistry and Molecular Biology, Univ of NE Med Ctr, Omaha, NE, United States

**Introduction/Background**: The average overall survival (OS) of patients with mantle cell lymphoma (MCL) is 3-4 years. However, an aggressive subset has been identified with OS of less than 2 years. Recently, gene expression profiling demonstrated a proliferation signature average value (PSAV) is associated with poor OS (Rosenwald, 2003). Structural abnormalities with mutation/deletion of p16 and p53 correlate with a high PSAV in MCL. Therefore, we hypothesize that hypermethylation in other genes may be associated with a high PSAV and poor OS.

**Materials and Methods**: DNA was extracted from 24 cases of MCL, from the Nebraska Lymphoma Study Group, and analyzed by methylation-specific PCR (MS-PCR) on the CpG islands of 12 genes. A 12,000 probe CpG island microarray (University Health Network Consortium, Toronto, Canada) was also used to examine the methylation status of the tumors.

**Results**: Of 12 genes examined by MS-PCR, the 4 genes with the most frequent methylation were CDH1 (71%), DAPK (71%), TIMP3 (66%), and RARB (54%). All four of these genes are methylated in 3 of 4 cell lines of MCL (Granta, Jeko1, Z138), and 3 of 4 genes are methylated in JVM2. A significant difference in OS was observed between MCL patients that had only 1-2 of 12 genes methylated (median survival of 5.2 years) compared to those that had 3-4 methylated genes (median survival of 1.8 years, p=0.04). Cluster analysis of the methylation data from the CpG island microarray demonstrated that two major groups could be delineated. One group with minimal methylation had a low mean PSAV of 0.08. A second group of 8 cases with hypermethylation had a mean PSAV of 0.47, which places the group in the worse survival category of MCL. A list of 15 known genes with hypermethylation in at least 4 of 8 cases and which best discriminate between the two groups includes CGI-48, DUSP-19, PER1, BHLHB5, SMCR5, EIF4A2, ABCF1, DUSP-10, KCNA4, HS2ST1, OSBPL5, SMUG1, PDCD2, CLSPN, and GPR88.

**Conclusions**: Both MS-PCR and CpG island microarray analysis demonstrate that hypermethylation of the genome is associated with an aggressive subset of mantle cell lymphoma.

## 011 INITIAL OBSERVATION WITHOUT THERAPY IN PATIENTS WITH ASYMPTOMATIC, NEWLY DIAGNOSED MANTLE CELL LYMPHOMA (MCL)

P. Martin[1], A. Chadburn[1], P. Christos[1], R. Furman[1], J. Ruan[1], R. Elstrom[1], R. Niesvizky[1], S. Ely[1], S. Chen-Kiang[1], M. Coleman[1], J. Leonard[1]
[1]Medicine, Weill Cornell Medical College, New York, United States

**Introduction**: Optimal treatment for MCL is undefined. Despite lack of evidence that aggressive therapies provide superior overall survival (OS), they are commonly applied immediately at diagnosis. We report outcomes from initial observation in asymptomatic patients with newly diagnosed MCL.

**Methods**: We used pathology records to identify all patients with a diagnosis of MCL at the Weill Cornell Medical Center since 1997. Patients were included if dates of diagnosis and first therapy could be determined. An online social security database was used to verify survival. Median OS was calculated by the Kaplan-Meier method. The observation group (OG) comprised those with time-to-first-systemic-therapy (TTT) of >3 mo from diagnosis. OS comparisons employed the log rank test. Potential predictors of treatment group were evaluated by logistic regression.

**Results**: Clinical information, and dates of diagnosis and first therapy were available in 97 patients. Median TTT was 1 mo (range 0-128 mo). Thirty-one patients (32%) comprised the observation group (OG). Of the OG, 14 (44%) went >1 year without requiring therapy, and 3 were observed for at least 5 years. Median age of the OG was 58 years (range 40-81 y), 25% had LDH > normal limit, and all had a WHO performance status (PS) 0-1. IPI was ≥ 3 in 36% and 18% had elevated WBC. Of age, stage, WHO PS, extranodal status, and LDH, only PS predicted early treatment (OR 9.9 p=0.006 for PS>0), but this difference disappeared on multivariate analysis. Median OS of all 97 pts is 68 mo (95% CI 61-101 mo), and that of the early treatment group 64 mo (95% CI 45-85 mo). With median 55 month followup the median OS for the OG is not reached and is statistically superior to that in the early treatment group (p= 0.0038).

**Conclusions**: We provide the first report of results with observation in patients with newly diagnosed MCL. Prognostic factors are limited in correlation with TTT. Our data support an approach of a clinical observation period of >3 mo in selected, asymptomatic patients as a substantial proportion may go months to years before requiring treatment with no apparent negative impact on OS.

## 012 IMMUNOCHEMOTHERAPY (R-MCP) IN ADVANCED MANTLE CELL LYMPHOMA IS NOT SUPERIOR TO CHEMOTHERAPY (MCP) ALONE - 50 MONTHS UP DATE OF THE OSHO PHASE III STUDY (OSHO#39)

M. Herold[1], A. Haas[2], B. Doerken[3], S. Neser[4], K.H. Al Ali[5], A. Neubauer[6], G. Dölken[7].
[1]Hematology/Oncology, HELIOS Klinikum Erfurt, Erfurt, Germany, On Behalf of East German Study Group Hematology and Oncology (OSHO), [2]Hematology/Oncology, Klinikum Ernst von Bergmann Potsdam, Potsdam, Germany, [3]Hematology/Oncology, Charite, Berlin, Germany, [4]Hematology/Oncology, Klinikum Chemnitz, Chemnitz, Germany, [5]Hematology/Oncology, Universitätsklinikum Leipzig, Leipzig, Germany, [6]Hematology/Oncology, Universitätsklinikum Marburg, Marburg, Germany, [7]Hematology/Oncology, Universitätsklinikum Greifswald, Greifswald, Germany

**Introduction**: Rituximab plus chemotherapy has been proven to be the standard in treating advanced follicular lymphoma. However in mantle cell lymphoma (MCL) the results are still controversial.

**Methods**: In a prospective randomised trial (OSHO#39) we compared the efficacy and toxicity of MCP chemotherapy (mitoxantrone 8 mg/m$^2$ d 1+2, chlormabucil 3x3 mg/m$^2$ d 1-5 and prednisolone 25 mg/m$^2$ d q 4 weeks) versus MCP plus rituximab (375 mg/m$^2$ d -1) in advanced indolent (FL, LPL) and mantle cell lymphoma. Here we present the results of the MCL subgroup (n=90). Study endpoints included overall and complete response rate (RR + CR), progression free survival (PFS), event free survival (EFS), overall survival (OS) and toxicities.

**Results**: with a median follow-up of 50 months for the MCL subgroup (n = 90) we can provide relatively mature data. The treatment results for the MCL patients are as follows:

| | R-MCP n=44 | MCP n=46 | p value |
|---|---|---|---|
| Resp. rate | 71% | 63% | .5074 |
| CR | 32% | 15% | .0822 |
| PFS median | 20 mo | 18 mo | .2400 |
| PFS 50 mo | 26% | 11% | |
| EFS median | 18 mo | 13 mo | .1383 |
| EFS 50 mo | 23% | 9% | |
| OS median | 56 mo | 50 mo | .5176 |
| OS 50 mo | 56% | 52% | |

**Conclusions**: Concerning all end-points R-MCP is not superior to chemotherapy alone in advanced mantle cell lymphoma. Immunochemotherapy is obviously not the solution for this poor prognosis lymphoma entity.

## 013 RESULTS OF SEQUENTIAL CHEMOTHERAPY FOLLOWED BY HIGH DOSE THERAPY AND AUTOLOGOUS STEM CELL RESCUE FOR MANTLE CELL LYMPHOMA: ROLE OF RITUXIMAB AND FUNCTIONAL IMAGING

A.D. Zelenetz[1], D. Persky[1], R.D. Rice[1], J. Maragulia[1], S.A. Weaver[1], C.S. Portlock[1], C.H. Moskowitz[1]
[1]Lymphoma Service/Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, United States

**Introduction**: Optimal management of mantle cell lymphoma (MCL) remains undefined. Addition of rituximab (R) to conventional CHOP chemotherapy failed to demonstrate an improvement in PFS or OS in a phase III study (Lenz et al). In contrast R appeared to improve outcome when combined with the dose intense HyperCVAD chemotherapy regimen in a historical comparison of phase II studies (Romaguera, et al). Since 1994 we have treated patients (pts) with MCL with sequential chemotherapy followed by high dose therapy with autologous stem cell transplant (HDT/ASCR); after R became available it was added to induction and as post transplant maintenance (RM). Early functional imaging (FI) with gallium or FDG-PET has not been previously studied in MCL. The current analysis is a retrospective review of our treatment program focused on the role of rituximab and FI in the outcome of patients (n=79) with MCL.

**Methods**: Pts were treated with 4 cycles of induction with CHOP-14 without (n=20) or with (n=59) R.FI (gallium or FDG-PET) was performed after 4 cycles of induction treatment. Pts with a positive scan (n=16) received 3 cycles of consolidation with ICE with R; pts with a negative scan (n= 43) (or did not have FI, n=20) received 2 cycles of consolidation with ICE without (n=20) or with R (n=42). Pts underwent transplant

conditioning with either TBI/Cy/VP16 or BEAM.In this era-sequential cohort, 28 pts did not receive and 51 did receive RM following the HDT/ASCR.Outcomes were analyzed by the method of Kaplan-Meier and comparisons were by log-rank.

**Results**: The median EFS was 4.75 years and the median OS has not yet been reached for the study group as a whole. The conditioning regimen (TBI/Cy/VP16 vs BEAM) had no impact on outcome. We found that patients who never received R (n=20) had similar outcomes to the patients who received R (n=59). Similarly, there was no impact of RM (n=51) compared to the patients who did not receive RM (n=28). The FI status (positive versus negative) after the induction with four cycles of CHOP±R was correlated with both EFS (p=0.04) and OS (p<0.001).

**Conslusions**: Uniquely among the CD20+ B cell lymphomas, rituximab does not appear to have a signficant role in improving outcome of MCL. However, the FI data suggest that the quality of early remission is important and may suggest new strategies for pre-HDT/ASCR therapy.

## 014 NON-MYELOABLATIVE ALLOGENEIC STEM CELL TRANSPLANTATION (NST) VS. AUTOLOGOUS TRANSPLANTATION (ASCT) IN PATIENTS WITH MANTLE CELL LYMPHOMA (MCL)

I.F. Khouri[1], C.S. Tam[1], C. Ledesma[1], R.E. Champlin[1]
[1]*Stem Cell Transplantation and Cellular Therapy, M. D. Anderson Cancer Center, Houston, United States*

**Background**: MCL remains incurable with cytotoxic therapy alone. Since the availability of NST(1997) and rituximab(1999), we have employed the following risk-adapted strategy: patients in first remission after one chemotherapy (REM1) were offered ASCT with high-dose rituximab (R), and patients beyond REM1 were offered NST if a donor was available, and ASCT+R if not. In order to assess the success of this strategy, we analyzed the results of transplantation in 123 patients with MCL at our center, including ASCT patients transplanted without R as historical controls.

**Methods**: 52 patients in REM1 (ASCT1) and 36 patients beyond REM1 (ASCT2) received ASCT with (43%) or without (57%) R, and 35 patients beyond REM1 received NST. NST patients were more heavily pretreated (p=0.01) and were further from initial diagnosis (p=0.02).

**Results** {ASCT}: ASCT1 patients experienced superior median PFS (42 v 27 months, p=0.009) and OS (94 v 52 months p=0.01) than ASCT2. B-symptoms and B2 m ≥ 3.0 mg/L adversely affected OS in both ASCT groups. There was a trend to improved PFS for the 20 ASCT1 patients who received R, with no events in 10 patients followed between 24 to 94 months, compared with a continuous pattern of progression in non-R patients (p=0.06). {NST}: 94% of patients were in CR after transplantation, and the 42 month current-PFS was 57%. In contrast to the ASCT patients, OS following NST was not affected by high B2m. Despite all patients being transplanted beyond REM1, a plateau in survival was evident with no deaths occurring among 11 patients followed between 46 to 98 months. Actuarial non-relapse mortality (NRM) at 90 days, 12 months and 2 years were 0%, 13% and 20% respectively.

**Conclusions**: These results suggest that ASCT is most effective in patients transplanted in REM1, in whom the addition of R may have improved PFS. NST is effective in overcoming the adverse impact of prior chemotherapy and high B2m, and remains the modality of choice for patients beyond first remission.