

# Session 3: mantle cell lymphoma

## 015 DIFFERENTIAL EXPRESSION OF SOX11, HDGFRP3, AND DBN1 IDENTIFIES TWO SUBGROUPS OF MCL WITH DIFFERENT CLINICAL OUTCOME AND GENETIC FEATURES

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Mantle cell lymphoma (MCL) is an aggressive disease characterized by the overexpression of cyclin D1 and a poor outcome with frequent relapses, but some patients have a very indolent clinical behavior with long survival. We have recently reported that both subgroups of MCL share a common gene expression profile but can be distinguished by the differential expression of a gene signature highly expressed in conventional MCL but absent in the tumor with an indolent clinical course. However, this signature was identified using microarrays, a technology not readily applicable in the clinical practice.

We have analyzed peripheral blood samples of 76 MCL and 37 leukemic B-cell neoplasms, including 19 CLL, 8 SMZL, 5 HCL, and 5 FL. Seven of 13 genes from the previous signature and Cyclin D1 were analyzed by quantitative RT-PCR. The IGHV mutational status was examined and copy number alterations were assessed by SNP array.

The three genes (SOX11, HDGFRP3, DBN1) with the highest correlation coefficient between the mRNA levels detected by microarrays and RT-qPCR were selected. Two subgroups of MCL were identified based on the expression levels of these genes using ROC curves. One group (52 cases) had high expression of SOX11, HDGFRP3 and DBN1 whereas the other subgroup (24 cases) had low expression of at least 2 of the 3 genes. MCL patients with high expression of these genes had a significant shorter survival than patients with lower expression (4-year OS: 50% vs. 95%;  $P < 0.001$ ). These two groups also differed in their IGHV mutational status. The majority of cases with low expression had mutated IGHV genes ( $\geq 2\%$  mutations-22/23 cases assessed). In contrast 33/41 cases with high expression in which mutational analysis was performed had unmutated IGHV ( $P < 0.001$ ). Cases with high expression had significantly higher number of genomic imbalances than cases with low expression (9.2 vs. 2.6, respectively,  $P = 0.02$ ). Cyclin D1 expression levels were similar in both subgroups of MCL. Cyclin D1, SOX11, HDGFRP3, and DBN1 mRNA was not expressed in the 37 non-MCL samples.

In conclusion, the low expression of SOX11, HDGFRP3, and DBN1 combined with Cyclin D1 determined by qRT-PCR identifies a subgroup of leukemic MCL with predominantly mutated IGHV genes, few genomic alterations and a very indolent clinical outcome. This assay may be useful to guide the selection of therapy in leukemic MCL.

## 016 R-CHOP VERSUS R-FC FOLLOWED BY MAINTENANCE WITH RITUXIMAB OR IFN: FIRST RESULTS OF A RANDOMIZED TRIAL FOR ELDERLY PATIENTS WITH MANTLE CELL LYMPHOMA

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**Introduction:** R-CHOP is a widely accepted induction regimen for elderly patients with mantle cell lymphoma (MCL), but achieves only low rates of complete remissions (CR). Fludarabin-containing regimens have appeared promising. In the European MCL Elderly trial we studied both induction regimens and the role of maintenance. Here, the results of the induction regimens are reported.

**Methods:** Patients with stage II-IV MCL >60 yrs not eligible for high-dose therapy were randomized between 8 cycles of R-CHOP-21 or 6 cycles of 4-weekly R-FC (rituximab 375 mg/m<sup>2</sup> day 1, fludarabin 30 mg/m<sup>2</sup> + cyclophosphamide 250 mg/m<sup>2</sup>, both iv day 1-3). Responding patients underwent a second randomization between maintenance with rituximab (R) or interferon-alfa (IFN), given until progression.

**Results:** Randomization was closed Oct 2010 with 395 of the 559 patients currently evaluable for response. Median age was 70 yrs, 69% male, 81% stage IV, 41% interm. and 50% high-risk MIPI. Whereas CR rates after R-CHOP and R-FC were similar (38 vs 34%), the overall response (CR/CRu/PR) was higher after R-CHOP (87%) compared to 78% after R-FC ( $p = 0.0581$ ). Progressive disease was more frequent in the R-FC arm (15% vs 5%). Of note, median overall survival was significantly inferior after R-FC (38 vs 64 mo;  $p = 0.0117$ ). More patients died from lymphoma during induction (12% vs 3%) or in first remission (9% vs 3%) in the R-FC arm. Hematologic grade 3-4 toxicities were more frequent during R-FC, especially thrombocytopenia (41% vs 16%). Non-hematologic grade 3-4 toxicity was rare, except neutropenic fever (10% R-FC; 17% R-CHOP) and infections (17% R-FC; 14% R-CHOP). R maintenance resulted in a significantly longer remission duration compared with IFN maintenance (51 vs 24 months;  $p = 0.012$ ). R-CHOP followed by R maintenance had an excellent outcome with 3-year OS of 83% vs 67% after R-FC ( $p = 0.0494$ ).

**Conclusions:** R-CHOP induction followed by rituximab maintenance should be considered the new standard for elderly MCL patients, to which new regimens should be compared.

## 017 PHASE II STUDY OF R-CHOP FOLLOWED BY <sup>90</sup>Y-IBRITUMOMAB TIUXETAN IN UNTREATED MANTLE CELL LYMPHOMA (MCL): 5 YEAR FOLLOW-UP OF EASTERN COOPERATIVE ONCOLOGY GROUP E1499

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**Background:** As MCL has a continuous relapse pattern with current therapy, we designed a study to determine safety and efficacy of the anti-CD20 radioimmunoconjugate <sup>90</sup>Y-ibritumomab tiuxetan (<sup>90</sup>Y-RIT), following 4 cycles of R-CHOP induction.

**Methods:** Patients (pt) with untreated stage II-IV MCL (CD20+, cyclin D1+)  $\geq 18$  yr with measurable disease and adequate organ function were eligible. At 4-8 wk after 4 cycles of R-CHOP, responding (CR/PR) and stable (SD) pt received 0.4 mCi/kg <sup>90</sup>Y-RIT. Primary endpoint was time to treatment failure (TTF). Study design required 52 eligible pt to demonstrate prolonging TTF by 50% compared with R-CHOP alone (median FFS 16 months (mo) Howard JCO 2002).

**Results:** 57 eligible pt with median age 60 (33-83) yr enrolled. Pt characteristics: 74% male, 91% stage III/IV, 67% >1 extranodal site, 81% + marrow, 25% B symptoms. Prognostic indices by IPI factors were 0-1 (18%), 2 (30%), 3 (40%), 4-5 (11%) and by MIPI low 51%, intermediate 26% and high 21%. Therapy was well tolerated and 52 (91%) pt received all therapy. Of 5 not receiving RIT, 3 had PD on R-CHOP, 1 died and 1 chose other therapy. For all 57 pt, response rate was 81%, 56% CR/CRu + 25% PR. Response improved in 23 pt after RIT (16 PR to CR/CRu, 4 SD to CR/CRu, 3 SD to PR). With median follow-up 64 mo, median TTF is 28 mo. For age  $\leq 65$  vs  $> 65$  yr TTF is 31 mo vs 25 mo ( $p = ns$ ). Median overall survival (OS) has not been reached, with estimated 3 yr OS 79% (86% for age  $\leq 65$  vs 67%  $> 65$ ) and 5 yr OS 71% (77% for age  $\leq 65$  vs 62%  $> 65$ ;  $p = 0.023$ ). TTF by MIPI is 12, 19 and 36 mo for high, intermediate and low risk respectively. For 8 pt with leukemic presentation (WBC  $> 15,000/uL$ ), median TTF was 13 mo. Of 46 pt with re-calculated MIPI prior to RIT, 4 had high risk and PFS of only 9 mo.

**Conclusions:** <sup>90</sup>Y RIT after R-CHOP x 4 in untreated MCL is safe and improves response number and quality. <sup>90</sup>Y-RIT consolidation is applicable to most pt with MCL and met the primary endpoint of 50% prolongation of TTF over that expected for R-CHOP x 6 alone. While there is no apparent plateau in TTF, median OS is not

yet reached at 5 yr. OS at 3 and 5 yr compares favorably with reports using more intensive therapy, calling into question need for intensive initial therapy.

**018 OUTCOME OF PATIENTS WITH MANTLE CELL LYMPHOMA UNDERGOING AUTOLOGOUS VERSUS REDUCED-INTENSITY ALLOGENEIC TRANSPLANTATION.**

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**Introduction/Background:** In recent years, progress has been made in the treatment of mantle cell lymphoma (MCL). One possible reason for improved outcomes in MCL may relate to a more effective use of hematopoietic stem cell transplantation (HSCT).

**Materials and Methods:** We studied the outcome of 640 patients with MCL who underwent a first autologous (Auto, n=433) or reduced-intensity allogeneic (Allo, n=207) HSCT between 1996 and 2007, reported to the CIBMTR.

**Results:** Overall, there were no significant differences between the Auto and Allo groups with regard to gender, performance status, disease stage at transplantation, or

bone marrow involvement at diagnosis. The Allo group overall was more heavily pretreated, with a lower proportion of patients with chemosensitive disease, and a slightly lower median age. We classified patients as "Early" MCL if they were in first complete or partial remission (with 1-2 prior chemotherapy regimens). The remaining patients were designated "Late" MCL. For Early MCL, there were 251 Auto and 50 Allo patients. One year treatment-related mortality (TRM) was significantly higher in the Allo group (25% versus 4%, p=0.001), while 5 year progression/relapse was lower in the Allo group (16% versus 32%, p=0.012). Five year overall survival (OS) was similar (62% Allo versus 61% Auto, p=0.941). Chronic GVHD was seen in 56% of the Allo patients. For Late MCL, restricting analysis to chemosensitive patients, there were 159 Auto and 99 Allo patients. One year TRM was again significantly higher in the Allo group (18% versus 9%, p=0.036). Unlike Early MCL, in Late MCL progression/relapse was similar at 5 years for Allo and Auto (38% versus 49%, p=0.148). Five year OS was also similar (32% in Allo versus 44% in Auto, p=0.193). Chronic GVHD was seen in 45% of Allo patients

**Conclusions:** When applied early in the disease course, both autologous and allogeneic HSCT result in favorable long-term survival, with RIC allogeneic HSCT associated with higher TRM but lower relapse rates. For more heavily pre-treated patients, long-term survival is less favorable for both allogeneic and autologous HSCT, although a subset of patients do appear to benefit from transplant even in this setting.