Mantle cell lymphoma

230 HIGH SOX11 EXPRESSION IS ADVERSELY PROGNOSTIC IN MCL
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Introduction: Mantle cell lymphoma (MCL) is generally aggressive but exhibits great variability. The novel biomarker SOX11 may provide key insights into MCL, though its prognostic significance is debated. The purpose of this study is to examine SOX11 and Ki67 expression in newly diagnosed MCL patients at Cleveland Clinic, and assess patient (pt) outcome.

Methods: An IRB-approved database of MCL was developed, including pathology tissue and clinical data. Sections were stained for Ki67 (Ventana Medical Systems) and SOX11 (Sigma, rabbit polyclonal 1:50) using an automated system (Ventana Discover). Ki67 was scored via image analysis as % positive (Image Pro 5.0) and SOX 11 was scored semiquantitatively in % and intensity, % estimates were 0 (0%), 1 (10-25%), 2 (26-50%), 3 (51-75%) and 4 (>75%) and intensity scored as 0 (negative), 1 (weak), and 2 (strong). SOX11 score was defined as the product of % (0-4) and intensity (0-2), yielding a score from 0 to 8. Kaplan-Meier projections of failure-free (FFS) and MCL-specific survival were performed. A 3-group comparison. Ki67 >40% showed a trend for inferior MCL-specific survival, which was only 1.2 years in the high-risk group (p=.02 for high SOX11 vs. not reached for low SOX11). Median FFS for high SOX11 was 3.5 years vs. not reached for low SOX11 (p=.65). Median age was 63 years. Presenting sites were H&N in 19 (73%), mediastinum -2 (8%) and pelvis –5 (19%). None presented in Gl tract. Five had a blastoid variant of MCL. Eleven pts had a stage modified IPI 22. Five pts were managed with palliative intent. Twenty-one pts (81%) were treated with radical intent: 17 chemotherapy (CT) + radiotherapy (RT), 2 RT alone, 2 CT followed by autologous stem cell transplant (ASCT), although 1 did not receive ASCT because of lack of response to CT. 13 pts received CHOP, 5 - RCHOP, 1 CVP; and of these, most received 26 cycles (97%). Ten pts were treated with palliative intent and median follow up was 60.2 months (range 15-232 months). The overall response rate was 95% (CR: 18 pts, CRu: 1 pt, PR: 1 pt, SD: 1 pt). Local control was 95%. Among the 19 CR/CRu pts, 9 relapsed for a 5-year relapse rate of 46% (95%CI: 21%-71%). Relapses were observed at distant sites (8 pts), 3 were in GI tract. One pt had both local and distant relapse. Following initial treatment failure (relapse/persistent disease, n=11), the subsequent treatment intent was radical in 2 (ASCT for 1 pt and gastric RT for the other) and palliative in 9. In univariate analysis, blastoid variant and clinical stages II were prognostic factors for PFS, HR 5.9 (95%CI: 1.6-21.5, p=0.007) and 5.1 (95%CI: 1.1-24.2, p=0.04), respectively. Median PFS and OS were 3.2 yrs and 6.4 yrs, respectively. 5-year OS was 62% (95% CI: 43%-89%).

Conclusions: With an aggressive treatment approach for stage II-II MCL using combined CT+RT, local control was achieved in 94%. Systemic relapse remained a significant problem, especially for stage II and blastoid variant. Stage I-II MCL is associated with better outcomes than reports indicate for stage III-IV pts not managed with ASCT. Radiotherapy should remain part of curative treatment plan in stage I-II MCL.

231 MARKED IMPROVEMENT OF OVERALL SURVIVAL IN MANTLE CELL LYMPHOMA; A POPULATION BASED STUDY FROM THE SWEDISH LYMPHOMA REGISTRY
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Background: Mantle cell lymphoma (MCL) accounts for approximately 5% of all cases of lymphomas in western countries. In recent years, more intensive chemotherapy regimens have been associated with prolongation of progression-free and overall survival. In this study, our aim was to investigate prognostic factors for overall survival in a population based dataset, and to evaluate if any improvement in survival in MCL may be detected on a population level.

Methods: Our patient cohort included all patients diagnosed with MCL from January 1 2000 to March 31, 2010 in the Swedish Lymphoma Registry. This registry includes data on >95% of patients with malignant lymphomas nationwide. Survival data were obtained from the Swedish Population Registry. Detailed data on primary treatment were available for patients registered from January 1, 2007.

Results: 785 patients with MCL were identified during this time period. Age, WHO Performance status (PS) and the presence of B-symptoms were significant prognostic factors for overall survival (OS) in MCL in multivariate analysis in this population-based dataset.

OS was markedly improved (HR=0.8, 95% CI 0.7-0.9) for patients diagnosed during the last time period, 2006-2010, also when corrected for prognostic factors as above. Estimated OS at 3 years was 62%, compared to 47% for patients diagnosed earlier (p<0.01).

Detailed data on treatment was available for 133 patients. Patients treated according to the Nordic Lymphoma Group MCL2 protocol or receiving R-Bendamustine had an excellent outcome. For patients treated with the NLG-MCL Zegrem, 33 of 34 patients are alive after a median of 23 months of follow-up. For patients receiving RB, 9 of 10 patients are alive after a median of 18 months of follow-up.

Conclusion: Overall survival has improved considerably for patients with MCL during the last decade. The reasons are not yet clear, but may be due to the introduction of specific and more potent therapeutic regimens.

232 STAGE I & II MANTLE-CELL LYMPHOMA: CLINICAL OUTCOMES WITH COMBINED MODALITY THERAPY
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Introduction/background: Mantle-cell lymphoma (MCL) is an uncommon non Hodgkin’s lymphoma, with the majority of patients having stage III-IV disease, and poor clinical outcomes (median survival 36-48 months). To determine the curability of localized MCL, we examine treatment outcomes of stage I-II disease at our institution.

Material and Methods: Through the lymphoma database, we identified 26 patients (pts) with stage I (38%) and stage II (62%) MCL between 1990 and 2007. Median age was 63 years. Presenting sites were H&N in 19 (73%), mediastinum -2 (8%) and pelvis –5 (19%). None presented in GI tract. Five had a blastoid variant of MCL. Eleven pts had a stage modified IPI 22. Five pts were managed with palliative intent. Twenty-one pts (81%) were treated with radical intent: 17 chemotherapy (CT) + radiotherapy (RT), 2 RT alone, 2 CT followed by autologous stem cell transplant (ASCT), although 1 did not receive ASCT because of lack of response to CT. 13 pts received CHOP, 5 - RCHOP, 1 CVP; and of these, most received 26 cycles (97%). The RT median dose was 35Gy (range 33.25-40.25Gy) and the majority received IFRT (15/17). Analysis was focused on pts treated with a curative intent (n=21).

Results: Among 21 pts treated with curative intent, median follow up was 60.2 months (range 15-232 months). The overall response rate was 95% (CR: 18 pts, CRu: 1 pt, PR: 1 pt, SD: 1 pt). Local control was 95%. Among the 19 CR/CRu pts, 9 relapsed for a 5-year relapse rate of 46% (95%CI: 21%-71%). Relapses were observed at distant sites (8 pts), 3 were in GI tract. One pt had both local and distant relapse. Following initial treatment failure (relapse/persistent disease, n=11), the subsequent treatment intent was radical in 2 (ASCT for 1 pt and gastric RT for the other) and palliative in 9. In univariate analysis, blastoid variant and clinical stages II were prognostic factors for PFS, HR 5.9 (95%CI: 1.6-21.5, p=0.007) and 5.1 (95%CI: 1.1-24.2, p=0.04), respectively. Median PFS and OS were 3.2 yrs and 6.4 yrs, respectively. 5-year OS was 62% (95% CI: 43%-89%).

Conclusion: With an aggressive treatment approach for stage I-II MCL using combined CT+RT, local control was achieved in 94%. Systemic relapse remained a significant problem, especially for stage II and blastoid variant. Stage I-II MCL is associated with better outcomes than reports indicate for stage III-IV pts not managed with ASCT. Radiotherapy should remain part of curative treatment plan in stage I-II MCL.

233 R-CHOP VS R-FC FOLLOWED BY MAINTENANCE WITH RITUXIMAB OR IFN: FIRST RESULTS OF MRD ASSESSMENT WITHIN THE RANDOMIZED TRIAL FOR ELDERLY PATIENTS WITH MCL
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Introduction: Induction with R-CHOP achieves only low rates of complete (CR) and molecular remission (MR) as recently demonstrated in younger MCL patients. In the European MCL elderly trial of the European MCL Network we studied treatment
235 RITUXIMAB PLUS HYPERCVAD ALTERNATING WITH HIGH DOSE METHOTREXATE AND CYTARABINE (R-HCVAD) FOR PATIENTS WITH NEWLY DIAGNOSED MANTLE CELL LYMPHOMA (MCL): A MULTICENTER TRIAL FROM GISS

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Background: R-HCVAD has been tested in patients with newly diagnosed MCL with promising results (Romaguera et al. EJC 2005). In 2005 the Gruppo Italiano Studio Linfomi (GISSL) started a phase II multicenter study investigating clinical activity and toxicity of R-HCVAD in a similar group of patients.

Patients and methods: Histologically confirmed MCL, age ≤ 70 years and adequate organ function were main inclusion criteria. Chemotherapy consisted of 2 different alternating blocks (A and B), for a total of 4 cycles as originally reported by Romaguera et al. Only patients achieving partial response (PR) were to be addressed to HDC followed by ASCT.

Results: Sixty-three patients were enrolled and 60 were eligible. Median age was 57 yrs (22 to 66), 75% were males and 93% were in stage III-IV. Sixty %, 33% and 7% were classified at low-, intermediate- or high-risk according to MIPI, respectively. All 4 cycles were completed in 35% of patients; 75% completed at least 4 cycles. Treatment was discontinued due to AE (19), unsatisfactory response (4), physician’s decision (16). Overall 3 patients died due to treatment toxicity. Overall response rate (ORR) according to intention to treat (ITT) analysis was 83%, including 43 patients achieving a CR and 7 patients showing a PR. ORR rose to 98%, according to “per protocol analysis” (PPA) on 51 patients with assessable response. Grade 3-4 neutropenia occurred in 87% of patients, anemia in 61%, thrombocytopenia in 56%, infections in 14%. After a median follow-up of 31 months (range 1–65), 28 patients had a failure, 11 had progressive disease, and 13 died. Considering ITT, the estimated 5-year OS, PFS and FFS rates were 71% (95% CI: 52-84%), 63% (95% CI: 43-78%) and 50% (95% CI 34 to 62%), respectively. MIPI score maintained the prognostic value when applied at the 60 patients enrolled in our trial; the estimated OS at 5 yr was 80%, 75% and 30% for low, intermediate and high risk score respectively (log-rank P=0.001).

Conclusions: This multicentric trial confirms that R-HCVAD is an active regimen for the initial treatment of patients with MCL, but is affected by significant toxicity that may limit its use outside well trained centres.

236 RITUXIMAB, BENDAMUSTINE AND CYTARABINE (R-BAC) IS A VERY ACTIVE REGIMEN IN PATIENTS WITH MANTLE CELL LYMPHOMA NOT ELIGIBLE FOR INTENSIVE CHEMOTHERAPY OR AUTOLOGOUS TRANSPLANT

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Background: Bendamustine (B) and rituximab (R) in combination have relevant clinical activity in mantle cell lymphoma (MCL), and a favorable toxicity profile. We combined cytaraibne, a key drug in the treatment of younger patients with MCL, with B and R (R-BAC) in previously untreated patients with MCL aged 66, and in patients relapsed or refractory to previous immunomochemotherapy.

Materials and Methods: This safety/efficacy phase II study started with a dose-finding stage based on three stepwise dose-escalations of cytaraibne. Subsequently, in the treatment stage, patients received 4 to 6 cycles of R 375 mg/m2 on day 1, B 70 mg/m2 on day 2 and 3, cytaraibne 800 mg/m2 (fixed as maximum tolerated dose) on Day 2, 3, and 5. Rituximab was administered on Days 1 and 8 of each treatment cycle. The primary objectives were the safety of R-BAC, and assessment of overall and complete response rates (ORR and CRR).

Results: From June 2009, 28 patients were prospectively enrolled, of whom 15 were previously untreated. Median age was 71 years (range 55–88). Ann Arbor stage was III-IV in 49%, 39% had bulky disease, and MIPI was high in 54%. Cytologic subtype was blastoid in 18%, and mean ki-67 was 20% (range 5–40). Overall, R-BAC was well tolerated. After 118 administered cycles the dose limiting toxicity was haematological, with 72% and 90% of patients experiencing transient grade 3-4 neutropenia and 25% to 40% thrombocytopenia, respectively (duration 2 to 5 days). Four patients (14%) had febrile neutropenia with pneumonitis in one. Eight patients (29%) had grade 1-3 elevation of gamma-GT. No other significant toxicity was observed. None of the patients hadMahon growth. According to the recently proposed response criteria (Chez BD et al, JCO 2007), ORR was 96% and CRR 92% (24 of the 26 patients evaluable for response). One patient had stable disease, and one had partial residual. Residual masses were routinely
analyzed with PET. With a median follow-up from the start of therapy of 12 months two patients have relapsed, and one died of a stroke while in CR. All other treated patients (65%±9%) are alive and in CR.

Conclusions: This interim analysis reveals that R-BAC is a well tolerated and very active regimen in the treatment of older patients with MCL.

### Table 1.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number patients</td>
<td>16</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>60 (49-75)</td>
</tr>
<tr>
<td>Male</td>
<td>11 (66%)</td>
</tr>
<tr>
<td>Blastoid variant</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Ann Arbor stage IV</td>
<td>16 (100%)</td>
</tr>
<tr>
<td>Median FII microglobulin (range)</td>
<td>3 (1-9-87)</td>
</tr>
<tr>
<td>MIPI score low, int, high</td>
<td>37%, 44%, 19%</td>
</tr>
<tr>
<td>Ki-67 (8 pts) &lt; 20, 21-40, &gt; 40</td>
<td>25%, 37%, 38%</td>
</tr>
</tbody>
</table>

All 14 evaluable pts for response have responded: 10 have finished treatment (3-8 cycles, median of 4), of whom 7 have achieved a CR and 3 patients achieved a partial response. These 3 patients were responding but had delays in recovery of platelet counts and either were removed from study as per protocol guidelines (2 pts, ages 52 and 54 years, both with MIPI score of 5) or progressed while awaiting recovery (1 pt, 65 yrs old, MIPI score 5). At a median follow up of 8 months only this last patient has relapsed/progressed while on the study. When combining Phase I and II patients who received a similar dose of bortezomib of 1.3 mg/m2 and completed therapy (18 patients), 100% of the patients have responded, 83 % have achieved a CR, and only one patient died of neutropenic infection with methicillin-resistant staphylococcus aureus bacteremia. She did not have prolonged neutropenia. Seven patients went off study due to delayed recovery of counts, usually after cycles 3-5, five of them after achieved a CR (currently all five remaining in CR). There was no grade 2-4 neuropathy.

In conclusion, this phase II portion of the study demonstrates continued high rates of complete remission. The study is currently accruing and updated information will be presented at the time of the symposium.

### 238 SEVEN YEAR UPDATE OF ORAL ARSENIC TRIOXIDE BASED THERAPY IN THE TREATMENT OF REFRACTORY MANTLE CELL LYMPHOMA

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Background: Oral arsenic trioxide (As2O3, Arsenol®) is an active agent in acute promyelocytic leukaemia. It is licensed for the treatment of hematological malignancies in Hong Kong. As2O3 shows in vitro cytotoxicity against mantle cell lymphoma (MCL) lines. We present our 7-year experience of using oral-As2O3 in refractory MCL patients.

Material and Methods: A total of 38 patients with relapsed / refractory MCL were recruited. Daily oral-As2O3 (10 mg/day), ascorbic acid (AA, 1 g/day) and chlorambucil (CB, 2-4 mg/day) were given in the outpatient department until maximum response or disease progression. In responding patients, maintenance with oral-As2O3 and AA for 2 weeks was given every month for a planned two years, followed by gradual dosage tapering until cessation. When disease progression occurred, oral-As2O3+AA+CB therapy was resumed.

Results: There were 31 men and 7 women, at a median age 65 (range 43-90) years. The median time from initial diagnosis to oral As2O3 treatment was 33 (6-174) months. The median number of previous treatment was 2 (1–7), and the median time from last lymphoma therapy to As2O3 treatment was 2 (8-31) months. Responses were observed in 26 patients (68%), including complete remissions (CR) in 25, 2 CR unconfirmed (Cru) and 16 partial remissions (PR). In 15 responding patients, chlorambucil was stopped after a median of 4 (2-15) months, and oral-As2O3 maintenance was continued for a median 16 (4-37) months. Disease progression occurred in 11 responding patients at a median of 11 (1-47) months. A median of 12 (1–60) treatments with As2O3 were given. Two patients had died from progressive lymphoma, and 2 patients had died of pneumonia. Hence, 17 patients were still alive, at a median of 24 (1–87) months from commencement of oral-As2O3 treatment. Reversible elevation of transaminases (n=10), herpes zoster reactivation (n=9) and gastrointestinal discomfort (n=12) were observed. No prolongation of QT interval or arrhythmia was recorded.

Conclusion: Our results compares favorably with other novel salvage therapy for refractory MCL. An oral combination of oral As2O3, AA and Alkylators is a feasible outpatient based option for relapsed and refractory MCL, which may result in durable disease control.