Mantle cell lymphoma

230 HIGH SOX11 EXPRESSION IS ADVERSELY PROGNOSTIC IN MCL

S. Smith[1], W. Zeng[2], E. Hsi[2]
[1]Hematologic Oncology and Blood Disorders, Cleveland Clinic Foundation, Cleveland, United States, [2]Anatomic Pathology, Cleveland Clinic Foundation, Cleveland, United States

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. We constructed a TMA with 29 cases of MCL. Sections were stained for Ki67 (Ventana Medical Systems) and SOX11 (Sigma, rabbit polyclonal 1:50) using an automated system (Ventana Discovery). Ki67 was scored via image analysis as % positive (Image Pro 5.0) and SOX 11 was scored semiquantitatively including % and intensity. % estimates were 0 (<10%), 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 (MCL-S) and analyses of MIPI-B score, Ki67>40% (vs less) and high SOX11 score (vs low) performed.

Results: Pts median age was 54 (range 37-85). MIPI-B score (using Ki67, as per Hoster et al 2008): low (3), int (9), high (9), unknown (8). Median follow-up of pts is 6.7 years. Treatment included autologous (n=6) or allogeneic (n=7) transplant. Most pts (21 of 29) received rituximab. Median FFS and MCL-specific survival for the 29 pts were 2.5 years and 5.3 years, respectively. The median SOX11 score was 3 (range 0-8), and high SOX 11 was defined as SOX11 score above the median (SOX11 score >3, n= 12). Median FFS for high SOX11 was 1.2 yrs (vs 2.7 years for low SOX11, p=.65). Median MCL-specific survival for high SOX11 was 3.5 years vs. not reached for low SOX11 (p=.02). Four pts survived longer than 10 years; 3 had low SOX11 nuclear expression and 1 had a score of 8 but underwent allogeneic HPCT. MIPI-B score was prognostic for MCL-specific survival, which was only 1.2 years in the high-risk group (p=.02 for 3-group comparison). Ki67 >40% showed a trend for inferior MCL-specific survival (p=.06).

Conclusions: SOX11 nuclear expression predicted MCL-S but not FFS among 29 pts. Heterogeneity in this sample precludes conclusions regarding different therapies. We conclude that that while disease progression remains inexorable, low SOX11 nuclear staining identifies pts with a relatively favorable MCL-S. SOX11 appears to be a prognostic marker in MCL that should be assessed further, including studies to elucidate its biologic function.

231 MARKED IMPROVEMENT OF OVERALL SURVIVAL IN MANTLE CELL LYMPHOMA; A POPULATION BASED STUDY FROM THE SWEDISH LYMPHOMA REGISTRY

A. Abrahamsson[1], N. Dahle[1], M. Jerkeman[1]
[1]Oncology, Skane University Hospital, Lund, Sweden

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% C.I. 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 2regimen, 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

M. Bernard[1], R. W. Tsang[2], L. W. Le[3], D. C. Hodgson[2], A. Sun[2], W. Wells[2], M. Crump[4], M. K. Gospodarowicz[2]
[1]Radio-Oncologie, Hôpital Maisonneuve-Rosemont, Montréal, Canada, [2]Radiation Oncology, Princess Margaret Hospital, Toronto, Canada, [3]Biostatistics, Princess Margaret Hospital, Toronto, Canada, [4]Medical Oncology, Princess Margaret Hospital, Toronto, Canada

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 ≥2. 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 ≥6 cycles (79%). The RT median dose was 35Gy (range 33.25-40.2Gy) 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

C. Pott[1], M. Delfau-Larue[2], K. Beldjord[3], E. Macintyre[3], S. Boettcher[1], V. Asnafi[3], R. Siebert[4], A. Plonquet[2], E. Callet-Bauchut[5], W. Klapper[6], F. Berger[7], M. Unterhalt[8], M. Dreyling[8], J. C. Kluin-Nelemans[9], E. Hoster[8]
[1]2nd Department of Medicine, University of Schleswig-Holstein, Campus Kiel, Kiel, Germany, [2]Service d'Immunologie Biologique, Hôpital Henri Mondor, Créteil, France, [3]Laboratoire d'Hématologie, Hôpital Necker-Enfants-Malades, Paris, France, [4]Institute of Human Genetics, University of Schleswig-Holstein, Campus Kiel, Kiel, Germany, [5]Service d'Hématologie Biologique, Centre Hospitalier Lyon Sud, Lyon, France, [6]Department of Haematopathology and Lymph Node Registry Kiel, University of Schleswig-Holstein, Campus Kiel, Kiel, Germany, [7]Department of Pathology, Centre Hospitalier Lyon Sud, Lyon, France, [8]Department of Internal Medicine III, University of Munich, Munich, Germany, [9]Dept. Hematology, University Medical Center Groningen, Groningen, Netherlands

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

efficacy of R-CHOP and a fludarabine based induction as well as the role of maintenance by clinical and molecular response monitoring.

Methods: [Patients >65 yrs with stage II-IV MCL not eligible for high dose therapy were randomized between 8 cycles of R-CHOP-21 or 6 cycles of 4-weekly R-FC. Responding patients underwent a second randomization between maintenance with rituximab (R) or interferon-alfa (IFN), given until progression. Minimal residual disease (MRD) was monitored by real time quantitative (RQ-) PCR at diagnosis, midterm (after 3 or 4 induction cycles), after complete induction and at 2-3-monthly intervals thereafter.

Results: 1535 samples (1189 PB, 346 BM) from 208 patients were investigated (103 receiving R-CHOP and 105 R-FC). Median age was 70 yrs and clinical parameters such as stage, LDH elevation, BM involvement and MIPI were distributed equally in both arms. Overall clinical response after induction was 87% after R-CHOP and 78% after R-FC (p=0.0581) with a CR in 34% and 38%, respectively. However, MRD clearance at midterm was rapid in the R-FC arm with 26/39 (67%) MRD- patients compared to 15/48 (31%) after R-CHOP (p=0.0013). MR in clinical responders after induction was significantly more prevalent (50/56, 89%) after R-FC compared to R-CHOP (38/73, 52%) (p<0.0001) and was a strong independent prognostic factor for remission duration (RD) (adjusted HR 2.6, 95%CI 1.6-4.3, p=0.0003). Sustained MR during the first year after end of induction was more frequent in patients after R-FC (80%) compared to R-CHOP (41%) and was predictive for outcome in both treatment arms (pooled cohort n = 99, 84% vs. 35 % in clinical remission at 24 m, p<0.0001, R-CHOP: 86% vs. 35%, p=0.0009 and R-FC: 83% vs. 38%, p=0.017). R-maintenance resulted in a significantly longer RD than IFN (51 vs 24 m; p=0.012) in the whole study cohort. This effect was clearly seen in MRD- patients (RD at 2-years 80% vs. 53%, p=0.0088). Remarkably, in MRD+ patients, R-maintenance was not able to prevent early relapses resulting in only 53% relapse free patients at 24 months.

Conclusion: MRD monitoring shows rapid and effective MRD clearance and sustained MR after R-FC in responding patients and suggests that the effect of rituximab maintenance is dependent on the residual tumour burden.

234 HIGH DOSE ARACYTINE IN INDUCTION MIGHT COUNTERACT THE ADVERSE PROGNOSTIC VALUE OF GENE COPY NUMBER ALTERATION IN AUTOGRAFTED MCL PATIENTS. A EUMCL NETWORK STUDY

M. Delfau-Larue[1], E. Hoster[2], F. Berger[3], F. Jardin[4], J. Briere[5], P. Feugier[6], C. Haioun[7], V. Ribrag[8], G. Salles[9], C. Thieblemont[10], O. Casasnovas[11], M. Unterhalt[2], M. Dreyling[2], C. Pott[12], E. Macintyre[13], O. Hermine[14]
[1]Immunobiology, Hôp H. Mondor, Creteil, France, [2]Int Med, Munich Univ., Grosshadern, Germany, [3]Pathology, CHU Lyon-Sud, Pierre-Benite, France, [4]U918, Centre H. Becquerel, Rouen, France, [5]Pathology, Hôp St Louis, Paris, France, [6]Hematology, CHU Brabois, Nancy, France, [7]Hematology, Hôp Henri-Mondor, Creteil, France, [8]Hematology, IGR, Villejuif, France, [9]Hematology, CHU Lyon-Sud, Pierre-Benite, France, [10]Hematology, Hôp St Louis, Paris, France, [11]Hematology, CHU, Dijon, France, [12]Med Dept II, Campus Kiel, Kiel, Germany, [13]Hematobiology, Hôp Necker, Paris, France, [14]Hematology, Hôp Necker, Paris, France

Introduction: Mantle cell lymphoma is of poor prognosis. Several secondary genetic abnormalities have been shown to correlate with prognosis in heterogeneously treated cohorts. In 2004, we initiated a randomized trial comparing two induction regimen 6 R-CHOP (Arm A) versus 3 alternating R-CHOP/ R-DHAP (ArmB) followed by ASCTin previously untreated MCL stage II-IV (<65 years). The arm B increases significantly complete response rate and TTF (49 months vs NR) (Hermine ASH 2010). Our purpose was to revisit the prognostic value of some gene imbalances in this trial.

Methods: Samples from 158 out of 163 patients randomized in France within GELA have been collected at diagnosis. Lymph nodes and samples with more than 60% tumor load were eligible for detection of genetic imbalances in tumor cells. MYC, CDK2, ATM, RB1, P53, CDKN2AP16), CDKN1B (P27) and MDM2 gene dosage were analysed using quantitative multiplex PCR of short fluorescent fragment (QMPSF) as previously described (Jardin, BJH 2009).

Results: Seventy two patients (Low/Intermediate/High MIPI (50%/26%/24%), ArmA/B(46%/54%)) fulfilled the inclusion criteria. Myc and CDK2 amplification (Amp) were detected in 21% and, 6% respectively. Rb1, ATM, P53, P16 Deletion (Del) were found in in (31%), (28%), (26%), (21%), respectively. P27Amp/Del in (14%), and MDM2Amp/Del in 4 (7%). Only P53 and P16 Del were associated with worse MIPI at presentation (p=0.05). In univariate analysis, only P53 Del was associated with shorter TTF (p=0.04), ATM Del with longer TTF (p=0.02). When looking in the 2 treatment arms, we found exclusively in the R-CHOP arm the previously described association of P16 Del with shorter TTF (median 13 vs 44 months, p=0.005), independently of MIPI score (p=0.01).

Conclusions: Our results suggest that HD-AraC, a cell cycle dependent chemotherapy, might counteract the bad prognostic value of P16 deletion in MCL. To confirm our findings we are currently collecting and analysing up to 120 tumoral tissues.

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 GISL

F. Merli[1], S. Luminari[2], F. Ilariucci[1], C. Visco[3], A. Ambrosetti[4], C. Stelitano[5], M. Petrini[6], N. Di Renzo[7], F. Angrilli[8], A. M. Carella[9], E. Barbolini[1], M. Federico[2]
[1]Dept. of Hematology-Oncology, S.C. Ematologia, Reggio Emilia, Italy, [2]Dept. of Oncology-Hematology, University of Modena and Reggio Emilia, Modena, Italy, [3]Hematology, S. Bortolo Hospital, Vicenza, Italy, [4]Hematology, University of Verona, Verona, Italy, [5]M. Morelli Hospital, Hematology, Reggio Calabria, Italy, [6]Hematology, University of Pisa, Pisa, Italy, [7]Hematology, V. Fazzi Hospital, Lecce, Italy, [8]Hematology, Spirito Santo Hospital, Pescara, Italy, [9]Hematology, San Martino Hospital, Genova, Italy

Background: R-HCVAD has been tested in patients with newly diagnosed MCL with promising results (Romaguera et al. JCO 2005). In 2005 the Gruppo Italiano Studio Linfomi (GISL) 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 3 cycles. Treatment was discontinued due to AEs (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) analisys was 83%, including 43 patients achieving a CR and 7 patients showing a PR. ORR rose to 98%, according to "per protocol analisys" (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% to 84%), 63% (95%CI 43-78%) and 49% (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 were 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

C. Visco[1], L. Lissandrini[1], R. Zambello[2], R. Paolini[3], R. Zanotti[4], F. Pomponi[1], G. Nadali[4], L. Trentin[2], F. Elice[1], E. Rodella[3], G. Semenzato[2], G. Pizzolo[4], F. Rodeghiero[1]
[1]Hematology, San Bortolo Hospital, Vicenza, Italy, [2]Clinical and Experimental Medicine, Padova University, Padova, Italy, [3]Oncohematology, S. Maria della Misericordia Hospital, Rovigo, Italy, [4]Hematology, Azienda Ospedaliera Integrata of Verona, Verona, Italy

Background: Bendamustine (B) and rituximab (R) in combination have relevant clinical activity in mantle cell lymphoma (MCL), and a favorable toxicity profile. We combined cytarabine, a key drug in the treatment of younger patients with MCL, with B and R (R-BAC) in previously untreated patients with MCL aged ≥65, and in patients relapsed or refractory to previous immunochemotherapy.

Materials and Methods: This safety/efficacy phase II study started with a dose-finding stage based on three stepwise dose-escalations of cytarabine. 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, cytarabine 800 mg/m2 (fixed as maximum tolerated dose) on Day 2, 3, and 4. Cycles were administered every 4 weeks as outpatient. 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 89%, 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 very 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/or 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 had alopecia. According to the recently revised response criteria (Cheson 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 response. 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 (85%±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.

237 PHASE I-II STUDY OF BORTEZOMIB IN COMBINATION WITH R-HCVAD AND R-METHOTREXATE/ CYTARABINE (R-MA) IN UNTREATED MANTLE CELL LYMPHOMA (MCL)

J. E. Romaguera[1], M. Wang[1], F. Hagemeister[1], P. Weaver[1], K. Hartig[1], M. Fanale[1], L. E. Fayad[1], T. Feldman[2], N. Fowler[1], R. Orlowski[1], J. Smith[2], P. Ford[2], M. Ekaney[2], L. W. Kwak[1], A. Goy[2]
[1]Lymphoma, University of Texas M D Anderson Cancer Center, Houston, United States, [2]Lymphoma, Hackensack University Medical Center, Hackensack, United States

Although 87% of patients with advanced MCL achieve a CR with R-HCVAD/R-MA, patients still relapse over time, especially in those > 65 yrs of age, who have a median time to failure free survival of 3 years. Bortezomib (B) has 31% single agent response rate in relapsed/refractory MCL and synergizes *in vitro* with many of the drugs in the above regimen. A phase I study of BR-HCVAD/BR-MA did not show increased toxicity (Br. J. Haem. August 2010) and resulted in an elected dose of 1.3 mg/m2 bortezomib. We present preliminary data on the phase II study. Sixteen patients have been entered, and their clinical presentation is shown in Table 1.

Table 1.

Patient characteristics	
Number patients	16
Median age (range)	60 (49-75)
Male	11 (69%)
Blastoid variant	1 (6%)
Ann Arbor stage IV	16 (100%)
Median ß$_2$ microglobulin (range)	3 (1.9-9.7)
MIPI score low, int, high	37%, 44%, 19%
Ki-67 (8 pts) < 20, 21-40, > 40	25%, 37%, 38%

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 3) 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 has progressed with a median follow up of 10 months for the combined group. Grade 3-4 toxicity was mainly hematologic, as expected, and one patient died from 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

W. Y. Au[1], C. R. Kuamana[1], Y. L. Kwong[1]
[1]Medicine, Queen Mary Hospital, Hong Kong, Hong Kong

Background: Oral arsenic trioxide (As_2O_3, Arsenol ™) is an active agent in acute promyelocytic leukaemia. It is licensed for the treatment of hematological malignancies in Hong Kong. As_2O_3 shows *in vitro* cytotoxicity against mantle cell lymphoma (MCL) lines. We present our 7-year experience of using oral-As_2O_3 in refractory MCL patients.

Material and Methods: A total of 38 patients with relapsed / refractory MCL were recruited. Daily oral-As_2O_3 (10 mg/day), ascorbic acid (AA, 1 g/day) and chlorambucil (Clb, 2-4mg/day) were given in the outpatient department until maximum response or disease progression. In responding patients, maintenance with oral-As_2O_3 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-As_2O_3+AA+Clb 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 As_2O_3 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 As_2O_3 treatment was 2 (0–31) months. Responses were observed in 26 patients (68%), including 10 complete remissions (CR) / CR unconfirmed (CRu), and 16 partial remissions (PR). In 15 responding cases, chlorambucil was stopped after a median of 4 (2–15) months, and oral-As_2O_3 maintenance was continued for a median 16 (4–37) months. Disease progression occurred in 11 responding patients at a median of 17 (2–60) months. At a median follow up of 13 (1–87) months, 19 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-As_2O_3 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 As_2O_3, AA and Alkylators is a feasible out-patient based option for relapsed and refractory MCL, which may result in durable disease control.

239 ELDERLY PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) – FEASIBILITY AND EFFICACY OF PROLONGED IMMUNOCHEMOTHERAPY WITH RITUXIMAB (R), ARAC AND FLUDARABINE ADDED TO CHOP AND FOLLOWED BY RITUXIMAB MAINTENACE. A PROSPECTIVE STUDY BY THE FINNISH LYMPHOMA GROUP

R. Räty[1], T. Honkanen[2], E. Jantunen[3], S. Jyrkkiö[4], M. Karjalainen-Lindsberg[5], O. Kuittinen[6], M. Lehto[2], M. Mikkola[7], E. Poikonen[1], A. Rauhala[8], J. Rimpiläinen[9], A. Räsänen[10], S. Siitonen[5], M. Suominen[11], M. Vapaatalo[1], E. Elonen[1]
[1]Dept of Hematology, Helsinki University Central Hospital, Helsinki, Finland, [2]Dept of Medicine, Päijänne Tavastia Central Hospital, Lahti, Finland, [3]Dept of Medicine, Kuopio University Hospital, Kuopio, Finland, [4]Dept of Oncology, Turku University Hospital, Turku, Finland, [5]Huslab, Dept of Laboratory, Helsinki University Central Hospital, Helsinki, Finland, [6]Dept of Medicine, Oulu University Hospital, Oulu, Finland, [7]Dept of Medicine, Mikkeli Central Hospital, Mikkeli, Finland, [8]Dept of Medicine, Vaasa Central Hospital, Vaasa, Finland, [9]Dept of Medicine, North Karelia Central Hospital, Joensuu, Finland, [10]Dept of Medicine, Kymenlaakso Central Hospital, Kotka, Finland, [11]Dept of Medicine, Kanta-Häme Central Hospital, Hämeenlinna, Finland

Background: There are no consensus of treatment strategies for elderly patients (pts) with MCL ineligible for high-dose therapy. The outlook with conventional CHOP/CHOP-like chemotherapy even in combination with R is dismal.

Patients and Methods: In this prospective multicenter phase II study we investigated whether the poor outcome could be improved with reasonable toxicity by prolonging the immunochemotherapy. Ten cycles of chemotherapy (alternating CHOP/AraC) with 8 doses of R were given. The potential synergism of intermediate-dose AraC and fludarabine was tested in cycles 6-8. Induction was followed by bimonthly R maintenance (375mg/m^2) for two years.

Results: Median age of the 50 previously untreated consecutive pts was 74 yrs (65-83), and 62% were males. 48/50 patients had a stage IV disease. MIPI index was high/intermediate/low in 25/24/1 pts. The ORR was 96%, CR or CRu 86%. The response of 9 pts (18%) improved with cycles 6–8 (R-fludarabine-AraC). With the median follow-up time of 36 months 8 pts have relapsed/progressed and 7 pts have died: 5 of progressive MCL, 1 of MDS/AML and 1 of sudden cardiac attack. PFS at 3-years is 75%, EFS 70%, and OS 86%, respectively. G-CSF was given in 82% of the cycles. Severe infections were rare with only 1 grade 4 infection. More dose reductions were needed during fludarabine-containing courses as compared to R-AraC. In 19 pts a transient grade 4 neutropenia without severe infections was recorded during maintenance.

Conclusions: Elderly MCL pts can be treated relatively intensively with moderate toxicity. Long term efficacy of R maintenance is too early to assess, but transient neutropenia demands laboratory monitoring over maintenance period.