296 DEVELOPMENT OF A SIMPLE DISCRIMINANT FUNCTION SCORE (DF) DIFFERENTIATING ATYPICAL B-CELL CHRONIC LEUKEMIA (ABCCL) FROM MANTLE CELL LYMPHOMA (MCL)

C.M. Vadikola1, S.J. Papadimitriou1, D. Skoumi1, N. Kertou1, N. Tsagaradis1, K. Papadimitriou1, M. Papacosta2, G. Paterakis1

1Immunology and Haematology, Gennimatas Hospital, Athens, Greece, 2Int. Medicine, Democritus Univ. Hospital, Alexopoulos, Greece

Background: ABCCL and MCL share common immunophenotypic features. The aim of this study was to compare immunophenotype with FISH analysis and apply a simple DF index to distinguish the two groups.

Methods: 186 CD5+ unclassified by flow cytometry cases were studied after FISH results were available. CD5+ MCL and HCLw were excluded as already classified. The BCLL scoring system was used and scores 0-4 prevailed in MCL, bAECM with t(17p;11q) >12 and in t(14q2). The proposed DF ratio was calculated as follows: DF = (CD43% + MC% + CD79b% + CD39) / (CD39% + CD11c%), with the percentages referring to the CD19+ B cell group. The following CGN anomalies were sought in all patients: t(11;14), t(14q2), t(13q21), 1q+21. Whenever any coexisted, diagnostic criteria were set as the following: t(11;14) = t(14q2) + t(13q21) + 1q+21. The number of CGN anomalies and their combination was compared with the area under the curve for the proposed DF was 0.9185 (Confidence Interval 95% 0.87, 0.97). Sensitivity and specificity of the test were 66.67% and 98.62% respectively with a positive likelihood ratio (LR) of 48.33% and a negative LR of 0.34.

Results: After FISH analysis we classified all cases as MCL: n=29, BCLL: n=145 and IgH rearrangement (t14q32) n=12 [no co-existence of t(14q18) or t(11;14)]. The range of DF was 0.9 to 139 and after ROC analysis we decided to use a value of 8 as the cutoff point with best performance. 91.44% of all patients were classified correctly in their disease group and 98.62% of patients with DF>8 were successfully characterized as either MCL or t(14q2) disorder. The area under the curve for the proposed DF was 0.9185 (Confidence Interval 95% 0.87, 0.97). Sensitivity and specificity of the test were 66.67% and 98.62% respectively with a positive likelihood ratio (LR) of 48.33% and a negative LR of 0.34.

Conclusions: DF ratio can be applied in atypical cases, as defined by the BCLL score, and could suggest a diagnosis before FISH results are available. Its discriminating value is attributed to the increased CD11c% and CD39% in bAECM and MCL respectively. By using a cut off value of 8 we could successfully predict for the atypically presenting patients that their disease will be classified in the MCL and the t(14q2) group. DF ratio does not appear to differentiate the newly recognized CD5+ LPD with t(14q2) from MCL and FISH analysis provides the accurate diagnosis.

297 B-CELL LYMPHOBLASTIC DISORDERS WITH T(11;14)(Q13;Q32) OR T(14;18)(Q32;Q21) SHOW VARIATIONS IN THE PATTERN OF ADDITIONAL CYTOGENETIC ABERRATIONS, GENE EXPRESSION PROFILE AND ANTIGEN EXPRESSION

C. Hafnerlach, L. Reinl, F. Dicker, S. Schritter, W. Kern, T. Hafnerlach

Munich Leukemia Laboratory, MLL, Munich, Germany

51 B-cell lymphoblastic disorders with t(11;14) and 26 with t(14;18) were studied by chromosome banding, FISH, immunophenotyping and gene expression analysis. Based on immunophenotyping t(14;18)+ cases were classified as NHL and 13 cases as CLL. The mean number of cytogenetic aberrations observed in addition to t(14;18) was 1.1 in CLL cases and 4.2 in NHL cases (p=0.016). While 69% B-NHL cases revealed a complex karyotype none of the CLL cases did (p=0.0002). In CLL the only recurring additional aberrations were +1q, -4q, -6q, +7q, +12q, +der(13)(14q18). In B-NHL cases additional aberrations were +1q, -4q, -6q, +7q, +12q, +der(13)(14q18), +21q, +22q, +X and 28 genes were significantly differentially expressed. In cases with t(14;18)+ 39 of 51 cases were classified as NHL and 12 were classified as CLL. The mean number of aberrations observed in addition to t(14;18) was 2.1 in CLL cases and 5.8 in NHL cases (p=0.011). While 87% NHL cases revealed a complex karyotype, only 25% CLL cases did (p=0.011). In CLL the only recurring additional aberrations were +3q,-12q, +15q, -17q. In NHL cases the recurring aberrations were observed in at least 5 cases: -1p, -7q, -8q, -9p, -q, +11q, -13q, +13q, +15q, and -17p. TP53 deletion was significantly associated with a complex aberrant karyotype (p-value vs. 0.01). An ATM deletion was detected in 9/29 with complex karyotype and in 0/17 without a complex karyotype (p=0.004). However, gene expression profiling did not identify statistically significantly differentially expressed genes. In conclusion t(14;18)+ CLL were characterized by a lower number of additional chromosome aberrations. In contrast, t(14;18)+ NHL frequently demonstrated a complex karyotype. t(14;18)+ CLL were further characterized by a higher expression of CD11c, CD23, and CD5 and a lower expression of CD3 and CD38 compared to t(14;18)+ NHL. In addition differences in the gene expression profile were observed. t(11;14)+ CLL are characterized by a lower number of additional chromosome aberrations as compared to t(11;14)+ NHL and show a higher expression of CD23 and a lower expression of CD22.

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INDUCTION (R-CHOP/R-DHAP) AND CONSOLIDATION (10 Gray TBI, 4x1.5 g/m² Ara-C, induction followed by myeloablative consolidation: 12 Gray TBI, 2x 60mg/kg rituximab dose every 2 months. In

WITH MANTLE CELL LYMPHOMA

TRANSPLANTATION IN FIRST RESPONSE IS WELL-TOLERATED

BUSULFAN, MELPHALAN AND AUTOLOGOUS STEM CELL

EVALUATION

EVALUATED, WHEREAS IN YOUNGER PATIENTS DOSE-INTENSIFIED REGIMENS WITH IMPLEMENTATION OF RITUXIMAB MAINTENANCE IS BEING CONSIDERED. ADDITIONALLY, IN ELDERLY PATIENTS THE ROLE OF RITUXIMAB MAINTENANCE AND HIGH DOSE CYTARABINE IN THIS DISTINCT SUBTYPE OF MCL IS NOT YET EVALUABLE, BOTH PROGRESSION-FREE AND OVERALL SURVIVAL WERE ENCOURAGING WITH 70% (R) AND 60% (R-DHAP) RESPECTIVELY.

RESULTS: IN MCL ELDERY, 269 OF 302 PATIENTS WERE EVALUABLE BASED ON THE ANNUAL INTERIM ANALYSIS. MEDIAN AGE WAS 70 YEARS WITH 66% OF PATIENTS DISPLAYING AN INTERMEDIATE HIGH-LOW RISK IP. INDUCTION WAS WELL TOLERATED WITH MAINLY HEMATOLOGICAL TOXICITY (GRADE III/IV IN R-CHOP/R-DHAP/FC). LEUKOPENIA 52/72%, THROMBOCYTOPENIA 13/40%, BUT ONLY RARE FEPTONEUBRA (2%/7%) OR INFECTIONS (19%/23%). DESPITE THE POOR RELAPSE-CR, HOSPITAL NEURO-ENTOMATOLOGICAL, MALADI, PARIS, FRANCE.

CONCLUSIONS: COMBINED IMMUNO-CHEMOTHERAPY RESULTS IN HIGHER RESPONSE RATES THAN INDUCTION CHEMOTHERAPY. THE ROLE OF RITUXIMAB MAINTENANCE AND HIGH Dose CYTARABINE IN ELDERLY PATIENTS WOULD BE OF GROWING INTEREST.

MCL AS A COMPLEMENT TO CYCLOID D1, AND ALSO SUGGESTS A FUNCTIONAL ROLE FOR SOX11 IN MCL.
304 IMMUNOCHEMOTHERAPY WITH RITUXIMAB (R), CYTARABINE (ARAC) AND FLUDARABINE (F) ADDED TO CHOP PROLONGS EVENT FREE SURVIVAL (EFS) OF ELDERLY PATIENTS WITH MANTLE CELL LYMPHOMA (MCL). A STUDY BY THE FINNISH LYMPHOMA GROUP

E. Ellen1, R. Rahty1, T. Honkakangas2, E. Jantunen2, S. Jyrkko2, O. Kuttinen2, M. Lehto1, E. Pokonen1, A. Raula2, J. Rimpläinen2, A. Räsänen2, S. Liljen2, M. Suominen1, M. Vapaataalo1

1Haematology, Helsinki University Hospital, Helsinki, Finland, 2Medicine, Päijät-Häme Central Hospital, Lahti, Finland, 3Haematology, Kuopio University Hospital, Kuopio, Finland, 4Oncology, Turku University Hospital, Turku, Finland, 5Oncology, Oulu University Hospital, Oulu, Finland, 6Medicine, Vaasa Central Hospital, Vaasa, Finland, 7Medicine, Porvoo–Konjärga Central Hospital, Joensuu, Finland, 8Medicine, Kymenlaakso Central Hospital, Kotka, Finland, 9HUSLAB, Helsinki University Hospital, Helsinki, Finland, 10Medicine, Kanta-Häme Central Hospital, Hämeenlinna, Finland

Background: Nordic Lymphoma Group has shown that adding AraC and R to high dose CHOP and autologous stem cell transplantation increases response rate, EFS, and overall survival (OS) of patients with MCL. Most elderly patients are not candidates for high dose chemotherapy or transplantations and no satisfactory standard treatment is known for them. In a pilot trial we explored the feasibility and efficacy of a prolonged standard dose induction therapy (10 cycles) with R in maintenance.

Methods: Eligible were pts with histologically confirmed MCL (WHO classification, stage II/III/IV, age>65 yrs, with adequate organ functions. Induction: R-CHOP (C1,C2,H,C,R), AraC (1g/m2 4 doses, C2,C5,C8), AraC (1g/m2 4 doses, C1-8). Maintenance: for pts with CR/PR: R 375 mg/m2 bimonthly x 12.

Results: Forty-four patients (33 male, 11 female; 40 previously untreated) enrolled on the protocol between 21/02/2000 and 01/06/2006. Among evaluable patients overall response rate (ORR) (CR/PR on RP) was 37 (97.0%) patients following induction chemotherapy. Twenty-nine (91.9%), received ASCT. On intent-to-treat analysis, ORR for patients who received consolidative ASCT was 100% (CR 55%). Therapy was well-tolerated with 4 (9.1%) treatment-related mortality (including ASCT). The 5-year event-free survival (EFS) and overall survival (OS) for all patients were 34.6% and 62.0% respectively. Furthermore, with a 36.9 months as median follow-up, the 5-year EFS and OS for patients underwent transplant were 42.7% and 70.34% respectively.

Conclusions: This result of chemotherapy, in vivo purging with R rituximab, autologous stem cell transplantation (ASCT) and Rituximab immunotherapy post-ASCT is safe and feasible, produces durable remissions and may offer new therapeutic opportunities for the treatment of patients with mantle cell lymphoma.

305 AUTOLOGOUS STEM CELL TRANSPLANTATION AND RITUXIMAB FOR MANTLE CELL LYMPHOMA

F. Capote1, E. González-Blanca1, J. Bergua1, J. Fernández Calvo1, A. Oríd1, P. García-Boyer1, M. Ramírez2, D. Caballero1, A. Romero1, E. Pérez1, J. Quiñónez1, M. Pascual1, A. Cantalapiedra3, P. Giraldi1, L. Palomera1, M. Guaita1, A. Léon1, J. Curbach1, A. Fernández-Sevilla1

1Haematology, GEL/TAMO, Spain, Spain

Introduction: Mantle cell lymphoma (MCL) is a mature B-cell lymphoma comprising up to 5% of non-Hodgkin’s lymphomas. Although the prognosis for MCL patients has improved in recent years, the outlook for those with advanced or recurrent disease remains poor and the role of hematopoietic stem cell transplantation is unclear. The HyperCVAD-M/A regimen (fractionated high-dose cyclophosphamide, vincristine, doxorubicin and prednisolone alternating with methotrexate and cytarabine) has yielded encouraging results when combined with autologous stem cell transplantation (ASCT). In an effort to improve these results, we have combined rituximab in vivo purging and post-transplant consolidation with HyperCVAD-M/A plus ASCT.

Methods: Patients aged <70 years with previously untreated or relapsed MCL were treated with 4 courses of HyperCVAD-M/A followed by four once-weekly doses of rituximab 375mg/m2 as purging prior to stem cell mobilization and harvesting, high dose chemotherapy (ICT-CY or BEAM), stem cell reinfusion and further doses of rituximab immunotherapy post-transplantation (25 CR and 12 PR). Patients enrolled at diagnosis or with PR after the first line therapy had a considerably better outcome (OS and PFS at 36 months is 80% and 50% respectively) than those after relapse, where median time to progression was 10 months. Hematotoxicity was important, with WBC < 2000/ul and Plt < 50 000/ ul for 6,2 and 6,5 weeks respectively. In 3 cases (alive; in CR) cytopenia was, however, profound and procedure related mortality was reported (hemorrhagic stroke at day +80). RBC and Platelet transfusions were reported in 42 and 37% of the patients; G-CSF support in 17%. No pts developed life-threatening infections, however hospital admission was necessary in 16 cases (35%).

Conclusions: 2 Cycle immunochemotherapy consolidation is a feasible, outpatient approach for MCL patients not eligible for ASCT; it might have curative potential for patients treated at diagnosis or at first PR and may palliate mortality for relapsed cases.

306 LENALIDOMIDE IN COMBINATION WITH RITUXIMAB IS EFFECTIVE WITH MANAGEABLE TOXICITY IN A PHASE II STUDY IN RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

M. Wang1, L. Fayad1, F. Hagenbeek1, S. Neelapu1, B. Sanders1, F. Samanolo1, B. Pro1, D. Yi1, N. Belt1, G. Byrne1, P. Weaver1, K. Hartig1, R. Knight1, J. Zeldis1, L. Kwak1, J. Romagnuolo1

1Lymphoma/Mycosis, University of Texas M.D. Anderson Cancer Center, Houston, United States, 2Celgene Corporation, Summit, United States

Introduction/Background: Relapsed/refractory mantle cell lymphoma (MCL) is difficult to treat. R rituximab targets CD20 antigen on the surface of MCL cells while lenalidomide (Len) may target the microenvironment of MCL cells and enhance the ADCC activity of R. We investigated Len/R in relapsed/refractory MCL in a single-center, phase Ill study.

Materials and methods: None of 18 eligible patients (pts) with MCL had prior lenalidomide and all received R. Len was given orally daily (days 1–21 of a 28-day cycle) and R 375 mg/m2 by IV infusion weekly for 4 weeks only during the first cycle with the first dose on day 1 in cycle 1. Standard 3+3 dose escalation was used to determine maximum tolerated dose (MTD) with Len doses at 10, 15, 20, 25, and 30 mg. Dose-limiting toxicity (DLT) was defined as grade 3 or 4 non-hematologic or G4 hematologic toxicity during cycle 1. Phase I has been completed with 15 pts. Phase II is ongoing with 3 pts enrolled at MTD. 80 cycles of therapy were given to 18 pts.

Results: In phase I, the median age was 73 years; median prior therapies were 2 (1–4). Two DLTs occurred at 25 mg. One G3 hypercalcemia and 1 G4 non-neutropenic fever during cycle 1. Common non-hematologic toxic events included fatigue (21 G1-2), pruritis (17 G1-2), rash (11 G1-2, 1 G3) and myalgias (6 G1-2, 1 G3). There was no DFI/PE. G3 hematologic toxic events included neutropenia (13), febrile neutropenia (1), and thrombocytopenia (2). The only G4 hematologic toxic events were neutropenia (9) and lymphopenia (1). The pts at MTD (20 mg) received a median of 5 treatment cycles. Of the 10 pts at MTD evaluable for response, 7 in phase I plus 3 in phase II had pts achieved responses including 3 CRs (33%), 4 PRs (48%), 1 SD and 1 PD. Median time to response was 2 months (range 2–4).

Conclusion: The MTD for Len/R in relapsed/refractory MCL was 20 mg (days 1–21 of a 28-day cycle). Early evidence of response is promising with a favorable toxicity profile at 20 mg. The Phase II trial is ongoing.

307 HIGH RESPONSE RATES WITH LENALIDOMIDE IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE-CELL LYMPHOMA


1Davis Cancer Center, University of California, Sacramento, United States, 2Sylvester Cancer Center, University of Miami, Miami, United States, 3Pacific Coast Hematology/Oncology Medical Group, Fountain Valley, United States, 4Nebraska Medical Center, University of Nebraska, Omaha, United States, 5Celgene Corporation, Summit, United States, 6Mayo Clinic, Rochester, United States

Introduction/Background: Mantle cell lymphoma (MCL) is a distinct type of non-Hodgkin’s lymphoma characterized by being incurable with a low response rate and short progression-free survival when treated with conventional chemotherapy agents. We investigated the activity and safety of the immunomodulatory drug lenalidomide (LEN) in relapsed/refractory MCL.

Materials and methods: Patients (pts) with relapsed/refractory MCL and measurable disease ≥2 cm after at least 1 prior treatment regimen were eligible. Pts received 25 mg LEN orally once daily (Days 1–21 every 28 days) and continued therapy for 52 weeks as tolerated or until disease progression. Response and progression were evaluated using the IWLCM methodology.

Results: Fifteen pts with MCL were enrolled. Median age was 66 (45–84) years (yrs) and 7 were female. Median time from diagnosis to LEN was 5.1 (0.7–12.6) yrs and median number of prior treatments was 4 (2–6). Eight pts (53%) exhibited a response,
including 1 complete response (CR) and 1 unconfirmed CR, and 2 pts had stable disease. Two of 5 patients (40%) with prior bortezomib responded as did 4 of 5 pts (80%) with a prior stem cell transplant. Median duration of response was not reached as of June 29, 2007. Seven pts (47%) required at least one dose reduction with a median time to first dose reduction of 2.3 (1.2–4.9) months. Grade 4 adverse events were neutropenia (13%) and thrombocytopenia (13%). Most common grade 3 adverse events were neutropenia (33%) and leukopenia (27%).

Conclusion: LEN oral monotherapy is very effective in the treatment of pts with relapsed/refractory MCL, leading to a 53% response rate with manageable side effects.

308 BSC2118, A NOVEL PROTEASOME INHIBITOR, CAUSES GROWTH INHIBITION, CELL CYCLE ARREST AND CYCLIN D1 DEGRADATION IN MANTLE CELL LYMPHOMA (MCL) CELL LINES

G. Jakob1, J. Sterz1, I. von Metzler1, U. Kuckelkorn2, H.A. Braun2, M. Kaiser1, U. Heider1, J. Rademacher1, L. Kleeberg1, P.M. Kloetzel2, O. Sezer2

1Centrum für Tumormedizin, Med. Klinik m. S. Hämatologie/Onkologie, Charité - Universitätsmedizin Berlin, Berlin, Germany; 2Institut für Biochemie, Charité - Universitätsmedizin Berlin, Berlin, Germany

Introduction: The ubiquitin-proteasome complex was recently identified as a novel therapeutic target in various types of cancer. An increased proteasome activity was also described in mantle cell lymphoma (MCL). The proteasome inhibitor bortezomib has shown markedly in vitro activity and clinical efficacy in MCL. We previously described the novel tripeptide compound BSc2118, which inhibits all three proteolytic activities of the 20S proteasome.

Materials and methods: We investigated the anti-tumor effects of BSc2118 in the MCL cell lines HBL-2, JeKo-1 and Granta-519 and studied its effects on cell cycle progression and the expression of the cell cycle regulatory proteins p21, p27 and cyclin D1. Furthermore the inhibition of intracellular proteasome and NF-kappa B activity was analyzed.

Results: In the MCL cell lines HBL-2, JeKo-1 and Granta-519, BSc2118 caused growth inhibition, induction of apoptosis and inhibition of intracellular proteasome activity. After TNF-alpha stimulation we found a low NF-kappa B activity in untreated MCL cells, which could be slightly inhibited by BSc2118. Incubation of MCL cells with 40–260 nM BSc2118 lead to a time- and dose-dependent cell cycle arrest in the G2/M phase in the MCL cell lines. Furthermore we could demonstrate a stabilization of p21 and a degradation of cyclin D1, while no significant changes in p27 expression were detected under proteasome inhibition with BSc2118.

Conclusions: In the present study we demonstrate the anti-tumor effects of the novel proteasome inhibitor BSc2118 on growth inhibition, induction of apoptosis and cell cycle arrest in MCL cells. We could show that inhibition of proteasome activity, cyclin D1 degradation and p21 stabilization are crucial mechanisms of action for this compound. Since recent clinical trials have shown efficacy of proteasome inhibition in refractory/relapsed MCL, our preclinical data suggest considering BSc2118 as a novel agent in drug development against MCL.