mantle cell lymphoma

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

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Background: aBCLL 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+ MZL and HCLv were excluded as already classified. The BCLL scoring system was used and scores 0-4 prevailed in MCL, aBCLL with 17p-,11q-,+12 and in t(14q32). The proposed DF ratio was calculated as follows: DF=(CD43%+FMC7%+CD79b%+CD38)/ (CD23%+CD11c%), with the percentages referring to the CD19+ B cell gate. The following CGN anomalies were sought in all patients: t(11;14),17p-,11q-,+12,t(14q32),13q-. Whenever any coexisted, diagnostic criteria were set as the following: t(11;14)>t(14q32)>17p->11q->+12>13q-.

Results: After FISH analysis we classified all cases as follows: MCL n=29,BCLL n=145 and IgH rearrangement (t14q32) n=12 [no co-existence of t(14;18) or t(11;14)]. The range of DF was 0.90 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 correctly characterised as either MCL or t(14q32) 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 CD38% in aBCLL 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(14q32) group. DF ratio does not appear to differentiate the newly recognized CD5+ LPD with t(14q32) from MCL and FISH analysis provides the accurate diagnosis.

297 B-CELL LYMPHOPROLIFERATIVE 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

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51 B-cell lymphoproliferative disorders with t(11;14) and 26 with t(14;18) were studied by chromosome banding, FISH, immunophenotyping and gene expression analyses. Based on immunophenotyping 13 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 +12 and -13q. In B-NHL cases additional aberrations were +1q, -4q, -6q, +7, +12, -15q, +der(18)t(14;18), +21, +22, and +X. 28 genes were significantly differentially expressed. In cases with t(11;14)+ 39 of 51 cases were classified as NHL and 12 were classified as CLL. The mean number of aberrations observed in addition to t(11;14) was 2.1 in CLL cases and 5.8 in NHL cases (p=0.011). While 67% NHL cases revealed a complex karyotype, only 25% CLL cases did (p=0.011). In CLL the only recurring additional aberrations were +3q, +12p, -13q, +15q, -17p. In NHL cases the following aberrations were observed in at least 5 cases: -1p, +3q, -6q, -8p, +8q, -9p, -9q, +11q, -11q, -13q, +13q, +15q, and -17p. 17p/TP53 deletion was significantly associated with a complex aberrant karyotype (41% vs. 9% p=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 low 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 CD10 and CD38 compared to t(14;18)+ NHL. In addition differences in the gene expression profile were observed. Also 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.

298 TARGETING CDK4/6 IN RATIONAL COMBINATION THERAPY RENDERS CHEMORESISTANT MCL CELLS SUSCEPTIBLE TO KILLING BY PROTEASOME INHIBITOR BORTEZOMIB

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Background: Mantle Cell Lymphoma (MCL) remains incurable, suggesting that effective control of aggressive tumor growth during relapse is essential. Loss of cell cycle control is a hallmark in all cancers, in particular in MCL where cell cycle progression through G1 is accelerated due to elevation of Cdk4 and constitutive cyclin D1 expression. Thus, one rational approach to improve MCL therapy is to target Cdk4/6 in combination with cytotoxic killing. Although targeting the cell cycle with broad-spectrum inhibitors has not been effective, it is now possible using PD 0332991, an orally bioactive, small molecule which inhibits Cdk4/6 with superior selectivity and potency. In addition, we have evidence that targeting Cdk4/6 with PD 0332991 in combination therapy overcomes chemoresistance in other haematopoietic tumor cells including myeloma cells and suppress tumor growth in animal models. An ongoing proof-of-mechanism study further demonstrate that PD 0332991 effectively inhibits Cdk4/6 and tumor growth with low toxicity in MCL patients (La Casce et al, ASCO 2008 abstract).

Methods: Primary MCL tumor cells and representative MCL cell lines are used to develop a strategy for targeting Cdk4/6 with PD 0332991 in combination with proteasome inhibitors including bortezomib. We determine the Cdk4/6 activity and cell cycle protein expression by immunostaining and western blotting; cell cycle progression by BrdU-uptake and DNA content; and cell death by analyzing mitochondrial depolarization and DNA fragmentation.

Results: PD 0332991 inhibits Cdk4/6 in MCL cells and induces exclusive G1 arrest despite extensive mutations. Because PD 0332991 acts reversibly, release of the G1 block leads to synchronous S phase entry. This sensitizes chemoresistant MCL cells to killing by suboptimal doses of cytotoxic agents including bortezomib at a cell cycle-specific apoptotic checkpoint, by inducing mitochondrial depolarization and caspase activation.

Conclusion: Targeting Cdk4/6 by PD 0332991 in combination with bortezomib overcomes drug resistance and represents a promising new class of cell cycle-based therapy for MCL.

299 SOX11, A NON-B CELL LINEAGE TRANSCRIPTION FACTOR, IS OVEREXPRESSED IN MANTLE CELL LYMPHOMA

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Background: Diagnosis of mantle cell lymphoma (MCL) is based on morphology, immunophenotype (CD20+, CD5+) and detection of t(11;14) by FISH or immunohistochemistry (IHC) for Cyclin D1 (CCND1). However, some cases may fail to express CCND1.

Material and methods: Gene expression profiling (Affymetrix U133 Plus 2.0) and immunohistochemistry using a polyclonal antibody targeting a Sox11 protein sequence, raised as part of the HPR project, was performed on tissue from MCL and other B-cell lymphomas, MCL cell lines and samples of normal adult tissue.

Results: The transcriptional level of Sox11 was 10 to 100 times higher for the MCL samples compared with other lymphomas. Primary MCL as well as leukemic MCL (L-MCL) and MCL cell lines all showed high transcript levels of Sox11. A few samples of DLBCL also showed elevated levels of Sox11 mRNA, reflected in an increased mean average value and a variable cytoplasmic IHC signal. Whole MCL tissue sections (17/18) and TMA of MCL (9/10) showed nuclear staining for Sox11, while other lymphomas generally were negative or showed cytoplasmic staining only. One case of MCL was positive for t(11;14), CCND1-negative, but overexpressed Sox11. When IHC for Sox11 was performed on various adult human tissues, nuclear staining was found in Schwann cells, keratinocytes, and other squamous cells, while all other tissue, including bone marrow and brain, failed to express nuclear Sox11. Sox11 does not have any known function in lymphocyte ontogeny, and is normally expressed in the developing central nervous system in the embryo. It shows sequence homology with Sox4, a transcription factor crucial for B lymphopoiesis. Sox11 mRNA is increased in gliomas compared to normal brain tissue, suggesting a role in malignant transformation.

Conclusions: Our novel finding of specific overexpression of Sox11 mRNA and nuclear protein in both CCND1-positive and negative MCL, may be useful for the diagnosis of

MCL as a complement to cyclin D1, and also suggests a functional role for Sox11 in MCL.

300 EUROPEAN MANTLE CELL LYMPHOMA NETWORK: AN UPDATE ON CURRENT FIRST LINE TRIALS

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Background: Conventional chemotherapy achieves only short term remission despite high initial response rates of 70%-80%. In the current study generation, the *European MCL Network* investigates the impact of various combined immuno-chemotherapy regimens. Additionally, in elderly patients the role of rituximab maintenance is being evaluated, whereas in younger patients dose-intensified regimens with implementation of high dose cytarabine are investigated based on the excellent results of the HyperCVAD regimen.

Methods: In *MCL elderly*, patients are initially randomized between 8 cycles of R-CHOP or 6 cycles of R-FC (experimental arm). Patients who achieve either a PR or CR, receive subsequently either interferon maintenance (standard arm) or a single rituximab dose every 2 months. In *MCL younger,* the standard arm (R-CHOP induction followed by myeloablative consolidation: 12 Gray TBI, 2x 60mg/kg cyclophosphamide) is compared to the implementation of high dose cytarabine into induction (R-CHOP/R-DHAP) and consolidation (10 Gray TBI, 4x1,5 g/m2 Ara-C, 140 mg/m^2 melphalan).

Results: In *MCL elderly*, 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/high risk IPI. Induction was well tolerated with mainly hematological toxicity (grade III/IV in R-CHOP/R-FC): Leukocytopenia 62/72%, thrombocytopenia 13%/40%, but only rare febrile neutropenia (23%/7%) or infections (19%/23%). Despite the poor risk profile, combined immuno-chemotherapy (total group) achieved a remarkable 84% response rate (52% CR/CR$_u$). Although the impact of maintenance is not yet evaluable, both progression-free and overall survival were encouraging with 79% and 86% at 12 months, respectively. Interestingly, especially the CR patients showed a favorable clinical course with only 2 relapses in 28 patients (7%) observed so far. In *MCL younger*, 286 of 314 patients were evaluable. Again, toxicity (grade III/IV in R-CHOP/alternating R-DHAP) was mainly hematological: leukocytopenia 58/77%, thrombocytopenia 14%/74%, but only rare febrile neutropenia (11%/22%) or infections (5%/7%). Combined immuno-chemotherapy achieved a 91% response rate (56% CR/CR$_u$) before subsequent high dose consolidation. Again, both progression-free and overall survival are remarkable with 82% and 88% at 12 months, respectively.

Discussion: Combined immuno-chemotherapy results in high response rates in two prospective international trials. Further recruitment and follow-up will determine the role of rituximab maintenance and high dose cytarabine in this distinct subtype of malignant lymphoma.

301 HYPERCVAD + RITUXIMAB FOLLOWED BY HIGH-DOSE BUSULFAN, MELPHALAN AND AUTOLOGOUS STEM CELL TRANSPLANTATION IN FIRST RESPONSE IS WELL-TOLERATED AND PRODUCES EXCELLENT EVENT FREE SURVIVAL IN PATIENTS WITH MANTLE CELL LYMPHOMA

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Introduction. Since 2000 we have offered Hyper-CVAD+Rituximab (R) alternating with high dose methotrexate + cytarabine (HDMTX/ARA-C +R) as initial therapy for patients <65 years old with mantle cell lymphoma (MCL). All patients have been initiated on therapy with the intention of undertaking consolidative BuMel PBPC autograft (AuSCT) if complete remission (CR) or near CR was achieved. Previous studies have shown improved remission rates (>85%) in MCL induced by the Hyper-CVAD regimen compared to CHOP alone (30%) or in combination with R (50%). Significant improvements in progression free survival (PFS) have also been reported using Hyper-CVAD+R (>50 months (m)) compared to CHOP+R (16m). The role of consolidating the excellent initial Hyper-CVAD+R responses with AuSCT remains controversial. In a published cohort of patients comparable to ours treated with Hyper-CVAD+R, but without AuSCT, the 24m PFS rate was 82% with a pattern of continuous relapsed so that by 60m PFS was < 50%.

Patient characteristics: n=19, female =8, median age= 53 (range 29-61), Stage IV n=17, ↑b2microglobulin n= 7, ↑LDH n= 8. Median calculated MIPI score = 5.5 (range 4.4 – 6.1). Seventeen patients have completed therapy, one patient declining AuSCT after achieving a CR. Two additional patients are yet to complete planned autografts.

Treatment outcome: Median follow up for all patients =48m (range 3-78m). Hyper-CVAD+R induced CR in 16 of 17 evaluable patients (94%). The median time to AuSCT was 9m (range 4-12m). One patient (age = 58) died of sepsis during Bu/Mel PBSC autograft at day 21 and two have relapsed at 35m post AuSCT. At 60m the EFS and OS for all 19 patients are 79±11% and 94±6% respectively. Of the 17 patients completing therapy, 14 (82%) remain in continuous CR. Both patients with relapse are alive, one in ongoing CR two years post sibling allogeneic transplant and one following a further brief CR to temsirolimus.

Conclusions: These data confirm the tolerability and efficacy of Hyper-CVAD+R in inducing remission in MCL. Further, they show that consolidation with BuMel AuSCT may reduce the rate of disease progression compared to Hyper-CVAD+R alone and improve the OS of 60% at 5 years predicted by the MIPI score.

302 BENDAMUSTINE PLUS RITUXIMAB VERSUS CHOP PLUS RITUXIMAB IN THE FIRST-LINE TREATMENT OF PATIENTS WITH INDOLENT AND MANTLE CELL LYMPHOMAS –INTERIM RESULTS OF A RANDOMIZED PHASE III STUDY OF THE STIL (STUDY GROUP INDOLENT LYMPHOMAS, GERMANY)

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In Oct 2003 we initiated a multicenter randomized phase-III study to compare efficacy and safety of the combination Bendamustine plus Rituximab (B-R) versus CHOP plus Rituximab (CHOP-R) as first-line therapy for follicular, indolent and mantle cell lymphomas. Patients (pts) were randomized to receive Rituximab 375 mg/qm (day 1) plus either Bendamustine 90 mg/qm (days 1+2) every 28 days or the standard CHOP regimen every 21 days for a max. of 6 cycles. The primary endpoint was event-free survival (EFS). A sample size of 474 pts were calculated to power the study sufficiently to demonstrate a non-inferior EFS associated with B-R treatment, as defined by a difference in EFS between the two regimes of less than 10% after 3 years. An event was defined by a response less than a PR, disease progression, relapse, or death from any cause. So far 483 pts have been randomized. 331 pts are evaluable for response for this interim analysis (B-R: n=173; CHOP-R: n=158). Median patient age is 64 years. Histologies are equally distributed: follicular 52%, mantle cell 20%, and other indolent lymphomas 28% in both treatment groups, each. The overall response rate for pts treated with B-R was similar to that associated with CHOP-R (94% vs 94%, respectively). CR-rate was also similar at 45% for B-R compared to 40% for CHOP-R. The median observation time for both groups is 19 months. Thus far, 26 deaths have been observed (B-R: 13; CHOP-R: 13). Progressive or relapsed disease has been documented during the follow-up period: 36 in pts treated with B-R and 41 in the CHOP-R group. The B-R regimen appears to have a better toxicity profile, as evidenced by a lower rate of total alopecia (40% CHOP-R vs. 0% with B-R) and a lower number of infectious complications (41 in CHOP-R pts vs. 19 in the B-R group). Correlating, the CHOP-R regimen was more hematotoxic: WHO grade 3/4 leukocytopenia was reported in 41% CHOP-R treated pts compared with 12% in pts treated with B-R. In this interim analysis the combination of Bendamustine plus Rituximab appears to be non-inferior to CHOP-R while showing a better tolerability profile. Updated results will be presented.

303 RADIOIMMUNOTHERAPY (RIT) AS AN ALTERNATIVE CONSOLIDATION OF MCL PATIENTS NOT ILLEGIBLE FOR TRANSPLANT PROTOCOLS – FINAL ANALYSIS OF MULTICENTER POLISH LYMPHOMA RESEARCH GROUP (PLRG) TRIAL WITH 90Y-ZEVALIN (90Y-IBRITUMOMAB TIUXETAN)

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Background: Post induction consolidation with ASCT is a standard in MCL. To investigate the possible alternative, feasible for the elderly or unfit pts, PLRG conducted a multicenter II phase study with radioimmunotherapy. It was postulated, that RIT could substitute TBI, used in a transplant conditioning regimens.

Methods: In our analysis we included 45 MCL cases subjected to RIT. After initial cytoreduction with FCM-R, FC-R or CHOP-R, responding patients (<25% BM infiltration, <30 mm lymph node and <12 cm spleen diameter) proceeded to RIT consolidation (2 doses of 250 mg/m2 Rituximab on day 1 and 8, followed by Zevalin 0.3 - 0.4 mCi/Kg). The medium follow-up is now over 3 years.

Results: 45 patients responding to initial chemotherapy (7 CR, 38 PR) were subjected to RIT. A further regression was achieved in 37 patients, with over 50% PR to CR conversion (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 medium time to progression was 10 months. Hematological toxicity 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) cytopaenia was very prolonged (23, 24 and 40 weeks). One procedure related mortality was reported (hemorrhagic stroke at day +80). RBC and Platelet transfusions were required 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: Z radioimmunotherapy consolidation is a feasible, outpatient approach for MCL patients not illegible for ASCT; it might have curative potential for patients treated at diagnosis or at first PR and may afford palliation for relapsed cases.

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

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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<65 yrs (Geisler et al, ASH 2007 LB1). 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 (C)) with R maintenance.

Methods: Eligible were pts with histologically confirmed MCL (WHO classification, CD5+, CD19/20+, cyclinD1+), age>65 yrs, with adequate organ functions. Induction: R-CHOP (C1,C3,C5), R-AraC (1g/m^2 4 doses, C2,C4), R-AraC with F (2 doses 25 mg/m^2, C6-8), CHOP (C9-10). Maintenance for pts with CR/PR: R 375 mg/m^2 bimonthly x 12.

Results: Thirty three pts were recruited, 28 are evaluable (5 too early). Age median 75 yrs (66-79 yrs). St IIA n=1, IVA n=19, IVB n=8. PS 0 n=11, 1 n=12, 2 n=2, 3 n=3. IPI 2 n=8, 3 n=12, 4 n=6, 5 n=2. Follow-up time median 19 mo (2-36 mo). Response to induction: CR 19, CRu 4, PR 4 (2 still on induction), PD 1. 19/20 pts with bone marrow involvement and CR/CRu were negative in flow cytometry (sensitivity 10^{-3}-10^{-4}). 2 responding pts have progressed and died, 1 pt died suddenly in CR after cycle 7, 1 pt developed myelodysplastic syndrome at 22 mo. At 2 yrs EFS is 82% and OS 89%.

Conclusions: Elderly patients with MCL and with good performance status can be treated relatively intensively with moderate toxicity. R, AraC and possibly F seem to increase response rate and prolong EFS and OS compared to CHOP. Flow cytometry is a powerful tool to study bone marrow involvement at diagnosis and minimal residual disease. A longer follow-up is needed to evaluate the maintenance treatment with R.

305 AUTOLOGOUS STEM CELL TRANSPLANTATION AND RITUXIMAB FOR MANTLE CELL LYMPHOMA

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Introduction: Mantle cell lymphoma (MCL) is a mature B-cell lymphoma comprising up 5% of non-Hodgkins 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 alternated with methotraxate 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 four courses of HyperCVAD-M/A followed by four once-weekly doses of rituximab 375mg/m^2 as purging prior to stem cell mobilization and harvesting, high-dose chemotherapy (ICT-CY or BEAM), stem cell reinfusion and four further doses of rituximab immunotherapy post-transplant.

Results: Forty-four MCL 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) (RC/RC nc/RP) was 33 (97.0%) patients following induction chemotherapy. Twenty-six (59.1%), 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 trasplant were 42.7% and 70.34% respectively.

Conclusions: this sequence of chemotherapy, in vivo purging with 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.

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

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Introduction/Background: Relapsed/refractory mantle cell lymphoma (MCL) is difficult to treat. 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 I/II study.

Materials and methods: None of 18 eligible patients (pts) with MCL had prior thalidomide and all received R. Len was given orally daily (days 1–21 of a 28-day cycle) and R 375 mg/m^2 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 mg, 15 mg, 20 mg, and 25 mg. Dose-limiting toxicity (DLT) was defined as grade (G) 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 DVT/PE. G3 hematologic toxic events included neutropenia (13), febrile neutropenia (1), and thrombocytopenia (2). The only G4-5 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, 7 pts achieved responses including 3 CRs (30%), 4 PRs (40%), 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

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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 IWLRC 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

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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.