

mantle cell lymphoma

435 APOPTOSIS-RELATED GENES IDENTIFY POOR SURVIVAL GROUP AMONG MANTLE CELL LYMPHOMA PATIENTS

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Introduction/Background: We previously reported that loss of region 2q13 was detected in five out of 29 (17%) of Mantle cell lymphoma (MCL) patients and five out of seven MCL cell lines. We also found that pro-apoptotic gene BIM was the target of this region, indicating that genetic defects of apoptosis-related genes can be assumed to play an important role in lymphomagenesis or aggressiveness.

Materials/Method: To examine the relationship between BIM protein expression and genomic BIM loss, we performed Western blotting analysis using whole cell lysates of the seven MCL cell lines. This expression was compared to the results of array CGH, especially for the relationship with BCL2, the antagonist of BIM. In order to understand the relevance of apoptosis-related genes in MCL, published micro array data (Rosenwald et al., Cancer Cell, 2003) was used for unsupervised hierarchical clustering analysis mainly focusing on BCL2-family genes. We then checked the relationship among the clustered groups by using the Kaplan–Meier method combined with Logrank examination.

Results: There were only three cell lines which had a detectable BIM protein, one with heterozygous loss and two without BIM loss. We found that the two cell lines without loss possessed BCL2 amplification by our array CGH (ACC ver.4.0). Clustering with pro-apoptotic genes of the BCL2 family identified the poor survival group with a five-year survival rate of less than one year ($P=0.0002$). This group is characterized by high expression of NOXA. Clustering with pro- and anti-apoptotic genes of the BCL2 family identified another group with poor survival ($P=0.0002$). The patients in this group overlapped with those in the first group and were characterized by high expression of NOXA and BCL2.

Conclusion: The findings of our study suggest that the loss of BIM protein occurs frequently in MCL cell lines, indicating that the apoptotic pathway plays an important role in MCL. By examining the gene expression profile of apoptosis-related genes, we were able to identify the poor survival group. We are currently investigating the protein expression of NOXA and BCL2 in cell lines as well as in patient samples.

436 CYTOGENETIC AND FISH ANALYSIS OF COMPOSITE MALIGNANCIES INVOLVING MANTLE CELL LYMPHOMA

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Mantle cell lymphoma (MCL) coexisting with another malignancy within the same organ or tissue is a rare event. Most cases previously described usually represent composite lymphoma characterized by a simultaneous occurrence of 2 distinct lymphomas. So far, 10 cases of composite lymphoma involving MCL and follicular lymphoma (3), small lymphocytic lymphoma (1), splenic marginal zone lymphoma (1), plasmacytoma (1) and Hodgkin lymphoma (4) have been published. Most of them are unrelated, as shown by molecular investigations. We report here 3 more cases of composite MCL in which cytogenetic analysis revealed presence of 2 unrelated aberrant clones. Case 1 (56-yr M) showed t(11;14)-*IGH/CCND1* rearrangement in 60% of analysed lymph node cells and the second clone harbouring *IGK*-associated t(1;2)(q21;p11) in 9% of interphase cells. Subtyping of this latter clone composed of small and large immunoblasts present in the internodular area and positive for CD20, however, was difficult. In case 2 (78-yr M) only bone marrow cells were available. Cytogenetics and FISH identified t(11;14)-*IGH/CCND1* in 13.5% of interphase cells, and t(7;14)(q35;q11) showing involvement of *TCRB* and *TCRA/D* in 18% of cells. We presume that the second clone represents a malignant T-cell proliferation in which this peculiar inter-*TCR* translocation occurred as a mistake of VDJ recombination prior to a submicroscopic oncogenic hit. Case 3 (65-yr M) with a blastic MCL showed t(11;14)-*IGH/CCND1* in 31% of interphase spleen cells. The second identified clone harboured t(4;12)(q12;p13), as a sole aberration. The breakpoints of this latter translocation were mapped by FISH in the 4q12 region of GSH2 and the 12p13 region of ETV6. Using immunohistochemistry, we demonstrated that this clone represented AML M0 diagnosed two months later in the bone marrow of this patient. In summary, we identified 3 cases of MCL showing concurrent with B-NHL NOS, T-cell malignancy and AML M0, respectively, as a consequence of independent malignant transformation events.

437 MANTLE CELL LYMPHOMA – A POPULATION BASED STUDY

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Introduction: Mantle cell lymphoma (MCL) is an uncommon lymphoma accounting for 3–4% of non-Hodgkin lymphoma (NHL) cases in the West of Scotland. MCL is largely incurable with current therapies although autologous transplant may improve survival in selected patients. A number of prognostic indices are available; the International prognostic index (IPI), Follicular Lymphoma International Prognostic Index (FLIPI) and the recently described Mantle Cell Prognostic Index (MIPI).

Material and Methods: We performed a population based study of patients diagnosed with MCL in the West of Scotland between 1998 and 2007. Ninety seven patients were identified through the regional pathology database. The outcome was evaluable in 69 (19 females, 50 males) patients on follow up in relation to clinical and laboratory data and the 3 prognostic indices (IPI, FLIPI and simplified MIPI).

Results: The median age was 67 years (range 39–91). The primary site at presentation was extranodal in 25 patients (15 peripheral blood / bone marrow (BM)). On staging, 49 patients (73%) had BM involvement. Initial therapy was varied and included >6 different chemotherapy regimens confirming the uncertainty in optimal treatment. Response to initial therapy was evaluable in 60 patients. Twenty three patients (38%) achieved a CR/CRu, 30 patients (50%) a PR, 2 stable disease and 5 progressive disease. Median overall survival was 51 months. Survival was improved if CR/CRu achieved ($p=0.0036$). Twelve patients received a stem cell transplant and all but one are alive at a median follow up of 19 months. There was a trend towards longer survival in patients with a MIB1 below 40% (69 vs 39 months). A high IPI was associated with extremely short survival (median 5 months, $p=0.001$) but the FLIPI and MIPI showed a non significant trend towards improved survival in the low risk groups only.

Conclusion: In this population based survey, we have confirmed the poor prognosis associated with mantle cell lymphoma. Achievement of (CR/CRu) in response to initial therapy confers an improved survival with additional benefit from an autologous stem cell transplant. The IPI was the only prognostic index to identify a statistically significant subgroup.

438 MANTLE CELL LYMPHOMA WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT: FREQUENCY AND CLINICAL FEATURES

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Background: The rate of reported central nervous system (CNS) involvement in mantle cell lymphoma (MCL) is highly variable (4–26%). CNS prophylaxis is not standard therapy and it is still unclear which patients are at highest risk for this complication.

Patients and methods: The baseline features and clinical course of 62 patients (18 female, 44 male) treated at a single institution were retrospectively examined for rate and risk factors of CNS involvement.

Results: The median age was 64 years (range 33–85). At diagnosis, stage III/IV disease was present in 81% and blastoid morphology in 11%. CSF cytology was not routinely sampled during staging. Initial therapy was alkylator-based in 18%, fludarabine-based in 6%, CHOP-like in 43%, and hyper-CVAD in 16%, and contained rituximab in 39%. With the exception of patients receiving high-dose methotrexate and cytarabine as part of initial therapy, only one patient received CNS prophylaxis with intrathecal therapy. Four patients developed CNS disease, at a median of 6 months (range, 0–84) from diagnosis, with a crude incidence of 6.5% and an actuarial incidence of $5\pm 3\%$ at 5 years. All patients with CNS disease were symptomatic. One patient had CNS disease at diagnosis, one developed symptoms as the first indication of relapse after achieving CR and two developed CNS disease in the context of relapsed refractory MCL. CNS disease occurred in 20% of patients with blastoid MCL vs 5% without blastoid MCL ($P=NS$). Treatment consisted of intrathecal chemotherapy (one case), systemic chemotherapy (one case) and radiotherapy (two cases). Median survival after development of CNS disease was 4 months with all patients dead from disease by 9 months. When analysed from baseline, patients who developed CNS disease had a significantly shorter survival than those who did not ($P=0.0024$).

Conclusions: As expected, the development of CNS involvement in MCL portends a poor prognosis. CNS relapse is usually seen in the context of blastoid morphology or relapsed/ refractory disease and has an incidence of 5%. This risk does not justify routine CNS prophylaxis as part of initial treatment for all patients but should be considered in those with blastoid morphology.

439 VALIDATION OF THE NEW PROGNOSTIC INDEX (MIPI) IN MANTLE CELL LYMPHOMA: A SINGLE INSTITUTION EXPERIENCE

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Background: a new prognostic index for mantle cell lymphoma (MIPI) has recently been proposed based on the German Low Grade Lymphoma Study Group experience.

Aim: to apply this new index to our own series of 42 patients consecutively diagnosed of mantle cell lymphoma from 1995 to 2006.

Patients and methods: we included 42 patients diagnosed of mantle cell lymphoma. Median age was 68 y. (from 45 to 81), male sex 31 (74%), blastic histology 8 (19%), stages III-IV 95%, increased LDH 17 (41%), extranodal involvement 39 (93%), 37 patients (88%) received antineoplastic-containing regimens. Median follow-up of the whole series was 26.5 months (8.84 to 124). 34 patients have died, median survival 32 months CI (21.11, 43.83). We calculated MIPI by the regression model as well as the simplified one.

Results: 16 patients were classified into the high risk group (38%), 18 in the intermediate risk group (43%) and 8 patients in the low risk (19%). Median survival for the high, and intermediate risk groups were 13.4 and 32.47 months, with the median not reached for the low risk group (p=0.0009). The International prognostic Index was not able to identify different prognostic groups.

Conclusions: the new prognostic index MIPI seems to identify three groups of patients with different prognosis in our experience. This could help to select patients to new or more intensive treatments.

440 MANTLE CELL LYMPHOMA VS. B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA: DIFFERENTIAL DIAGNOSIS BASED ON CD200 EXPRESSION

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B-cell Chronic Lymphocytic Leukemia (B-CLL) and Mantle Cell Lymphoma (MCL) are CD5+ lymphoproliferative disorders that share many morphologic and immunophenotypic features and whose differential diagnosis may be challenging, especially when a leukemic picture alone is present. In these cases flow cytometry with a relatively wide panel of monoclonal antibodies is useful, with CD23 being the most reliable. However, diagnosis of MCL has to be confirmed by immunohistochemical detection of cyclin D1 on tissue biopsy and sometimes this technique gives equivocal or even negative results; PCR and Western blot are other reliable methods, but time-consuming and not available in all centers. A recently characterized antigen named CD200, a membrane glycoprotein belonging to the immunoglobulin superfamily, has been reported to be expressed on B-CLL cells surface. We evaluated the expression of CD200 on fresh neoplastic cells of 91 patients with a CD5+ lymphoproliferative disease (79 B-CLL and 12 MCL in leukemic phase) by flow cytometry. CD200 was positive in all B-CLL patients, while in MCL patients CD200 was positive in less than 20% of CD5+ cells in 3 subjects (4, 7 and 16%) and totally absent in the remaining 9. To confirm these results, we examined CD200 by immunohistochemistry on paraffin-embedded lymphoid tissues and bone marrow trephine biopsies from 23 B-CLL and 44 MCL patients. Again, all B-CLL neoplastic cells were positive for CD200 both in lymph nodes and in BM while all MCL cells were negative. Notably, in all MCL CD200-negative lymphoid tissue biopsies, it was possible to observe CD200+ residual dendritic cells. B-CLL and MCL are characterized by very different prognosis and response to therapies. Therefore, differential diagnosis is essential and we would propose to add CD200 in flow cytometry and immunohistochemistry routine panels, as it can be an easy and reliable tool to distinguish between these two entities, in particular in patients with a prevalent leukemic expression.

441 METHOTREXATE/CYTARABINE ONLY AS INITIAL MANAGEMENT OF UNTREATED MANTLE CELL LYMPHOMA: RESULTS OF A PHASE II CCOP TRIAL

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Introduction: Untreated Mantle cell lymphoma (MCL) is resistant to conventional doses of agents used in CHOP-like chemotherapy regimens. Methotrexate and cytarabine (M/A) in high doses might play an important role in its management.

Materials/Methods: Between April 1999 and August 2002, the Community Clinical Oncology Program (CCOP) of the National Cancer Institute (NCI) conducted a phase II trial to examine this question. Eligibility criteria included age above 16 years, performance status of 2 or less (ECOG criteria), adequate organ function, no active infection, no positivity for the human immunodeficiency virus, and ineligibility for stem cell transplantation. Patients received a median of 4 cycles of M/A only (range 1-6) 14/18 responded (78%, with 2 complete responders). Sixteen patients were crossed over to HyperCVAD because of either a stable partial response (14 patients) or as consolidation to a complete response after 6 cycles of M/A (2 patients) up to a possible combined number of 8 cycles/patient. Nine of these sixteen patients (56%) converted from a partial response/stable disease to a complete remission (CR)/complete remission unconfirmed (CRu), for a total of 11 CR/CRu's. The overall response rate after M/A and HyperCVAD was 94% with a 61% CR. The principal toxicity for M/A was hematologic, with 65% and 71% grade 4 neutropenia and thrombocytopenia, respectively. Grade 3-4 neutropenic fever after M/A was 12%. The most common non-hematologic side effect was fatigue, with 3% and 4% grade 4 after M/A and HyperCVAD, respectively. There were no treatment-related toxicities and no patient developed myelodysplasia. After a median follow up of four years, the median failure-free survival was 33 months and the median survival was 75 months.

Conclusions: The methotrexate/cytarabine combination has important activity in MCL.

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442 SURVIVAL BENEFIT OF POST INDUCTION CONSOLIDATION THERAPY IN MCL (MANTLE CELL LYMPHOMA) – A POLISH LYMPHOMA RESEARCH GROUP (PLRG) RETROSPECTIVE MULTICENTER ANALYSIS

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Background: MCL is characterized by bad prognosis due to early occurrence of resistance, therefore the first line therapy must be efficient and relatively intensive.

Methods: 140 MCL cases in advanced clinical stage (III-IV), treated in the last 5 years in 8 PLRG centers were retrospectively analyzed. Patients median age was 60 years (31–86), IPI – 2.9 (1-5), LDH 497 IU/l (128–2800 IU/l). The first line treatment included consolidation in 72 of 140 patients: 32 were subjected to ASCT and 40 to Ibritumomab (Zevalin) Radioimmunotherapy. Rituximab was used in 36/72 patients subjected to consolidation and 25/65 treated without consolidation.

Results: There was a clear impact of consolidation on Overall and Progression Free Survival (OS, PFS): at 5 years OS 65 vs 22% (p=0.0003 in Gehan Wilcoxon test); and PFS 41 vs 0% (p=0.0003 in Gehan Wilcoxon test). Rituximab used in the first line therapy further increased its efficiency in terms of PFS, prolonging median time to progression from 15 to 26 months, however the OS benefit was seen only in consolidated patients (at 5 years 75% OS in those with Rituximab including induction followed by consolidation).

Conclusion: With all limitations of retrospective analysis, it strongly supports the necessity of post induction therapy in MCL patients. The role of ASCT is established in younger patients, radioimmunotherapy may prove to be a feasible approach for the elderly and unfit ones.

443 BORTEZOMIB (BOR) WITH RITUXIMAB (R), CYCLOPHOSPHAMIDE (C) AND PREDNISONE (P): TWO DOSING SCHEDULES OF A NOVEL PHASE I REGIMEN IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT AND MANTLE CELL LYMPHOMAS

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Aim: To determine the safety and efficacy of Bor with modified R-CVP (omitting vincristine). Rationale: V has marginal activity in indolent lymphomas, and preclinical data suggests that Bor dosed after chemotherapy may be synergistic and overcome drug resistance.

Methods: In this phase I trial, Bor and C (750 mg/m² or 1000 mg/m²) were alternately escalated. R (375 mg/m²) and C were dosed on day one, and P (100 mg daily) on days 2-6. In schedule 1, Bor was given on days 2 and 8, with doses escalated from 1.3 to 1.8 mg/m². In schedule 2, Bor was given on days 2, 5, 9 and 12 with doses escalated from 1.1 to 1.5 mg/m². Patients with PR or SD (modified Cheson criteria (1999)) after 4 cycles received 4 further cycles, those with CR got 2 further cycles. Toxicity was

assessed using NCI-CTC, v. 3.0. DLT was defined as: (1) grade ≥ 3 nonhematologic toxicity (NHT); (2) grade 4 neutropenia (NTP) ≥ 7 days and/or neutropenic fever (NTPF); (3) platelets $\leq 25k/mm^3$ for 7 days or requiring transfusion, or $<10k/mm^3$ for 1 day. Two patients are excluded for withdrawal prior to Bor. 16 patients were accrued to schedule 1. The only cohort expansion was triggered by a grade 3 diarrhea in cohort 2. No DLT was seen at maximum doses of Bor and C. Schedule 2 has accrued 25 of 27 planned patients at the time of submission. Due to 2 neutropenic fevers, G-CSF was added, allowing accrual to the highest planned dosing level. Both schedules were well tolerated, with similar toxicity profiles. Most hematologic toxicities (HTs) and NHTs across all dose levels and cycles were grade 1-2. Significant grade 3-4 NHTs included grade 3 diarrhea (n=1), dehydration (1), and neuropathy (n=2). Of 13 patients assessable for response on schedule 1, 2CR, 5 PR, 5 SD and 1 POD were seen. Of 17 patients thus far assessable on schedule 2, 3 CR, 9 PR, 4 SD and 1 POD were seen. R-CBorP is well-tolerated in patients with NHL when Bor is dosed on a weekly schedule up to 1.8 mg/m² and twice-weekly up to 1.5 mg/m². Updated response and duration data will be presented at the meeting. A randomized phase II study is planned to compare the two dosing schedules above at the MTD.

444 PHASE I TRIAL OF BORTEZOMIB IN COMBINATION WITH RITUXIMAB-HYPERCVAD / METHOTREXATE AND CYTARABINE FOR UNTREATED MANTLE CELL LYMPHOMA

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Background: Intense therapy improves outcome of MCL, but patients still relapse. Bortezomib produces 33% responses in relapsed MCL and has been safely combined with intensified doxorubicin-containing regimens, but not with high doses of the methotrexate plus cytarabine combination, where there is concern about lung toxicity.

Materials and methods: Patients with adequate organ function without HIV-1 infection or any significant medical condition were accrued and treated with bortezomib added to R-HyperCVAD as a fixed dose of 1.3 mg/m² IV given after the first infusion of cyclophosphamide and after doxorubicin bolus. Bortezomib added to R-M/A after rituximab and day 6, in increasing doses of 0.7, 1, and 1.3 mg/m² in cohorts of 3 patients. Dose limiting toxicity was defined initially as a drop of 10% in diffusing lung capacity and later increased to 25%.

Results: Since April 2007, seven patients have been enrolled. There has been no DLT. After 32 cycles, toxicities according to NCI criteria are:

Parameter	Grade 3%	Grade 4%
Diffusion capacity lung	0	0
Neutropenia	42	44
Thrombocytopenia	50	63
Neutropenic fever	6	-
Neuropathy	0	1

Two patients developed grade 1 sensory neuropathy. No patient developed Herpes Zoster infection. All patients responded and 6 achieved a complete remission.

Conclusion: Bortezomib can be safely combined with R-M/A at 0.7 mg/m², toxicity similar to prior experience with R-HyperCVAD. Accrual is ongoing. More patients and dose levels will be reported at the meeting.

445 BORTEZOMIB, RITUXIMAB, AND DEXAMETHASON (BORID) IS AN ACTIVE SALVAGE REGIMEN FOR PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

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Background: Bortezomib (B) is a proteasome inhibitor with documented activity in multiple myeloma and mantle cell lymphoma (MCL). Preclinical studies suggest synergistic activity of B with rituximab (R), which provides a rationale for the exploration of treatment combinations. We therefore performed a phase II trial of B plus R and dexamethasone (BORID) in patients (pts) with relapsed/refractory MCL.

Methods: B (1.3 mg/m²) was administered on days 1, 4, 8, and 11, R (375 mg/m²) on day 1, and dex (40 mg) on days 1 to 4. Cycles were repeated every 3 weeks (up to 6). Responding pts received 4 additional doses of R as maintenance (every 8 weeks). Pts with progressive MCL after at least one prior line of therapy (including CHOP or a CHOP-like regimen) were eligible.

Results: 16 pts (median age, 66 years; range, 48 to 75 years) were enrolled. Median number of prior therapies was 3 (range, 1 to 7; prior rituximab in 88%; thalidomide in

50%; high-dose therapy in 31%; FCM in 31%). 10 pts (63%) had a high IPI score. Median time between start of frontline therapy and study inclusion was 42 months (range, 11 to 98 months). Severe adverse events (\geq grade II) included infections (herpes zoster in 2 pts, bacterial pneumonia, mucosal candidiasis), peripheral neuropathy (7 pts), fatigue (6 pts), diarrhea (3 pts), and vasculitic skin infiltrates in 3 pts. Thrombopenia (<50 G/L) occurred in 3 pts. All adverse events were manageable by standard means of supportive care and prolongation of the treatment interval between cycles. Overall response rate was 81% (13 of 16 pts), with 7 pts achieving a CR (44%; negative FDG-PET in 6 pts) and 6 pts reaching a PR. Skin infiltrates (histologically proven T-cell infiltrates) preceded achievement of CR in 2 pts. Median progression-free survival (PFS) was 12.1 months, and pts in CR experienced longer PFS (median not reached at 16 months) than pts in PR (median PFS 7.5 months). Median OS was 25.7 months.

Conclusion: BORID has promising activity and manageable toxicity in pts with heavily pretreated MCL. Achievement of CR emerged as an important factor for sustained disease control.

446 BORTEZOMIB IN ASSOCIATION WITH FCM-R AS SALVAGE TREATMENT FOR PATIENTS WITH NON HODGKIN LYMPHOMA

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Introduction: Previous reports highlighted the therapeutic activity of Bortezomib as salvage treatment for patients with low grade (LG) and mantle cell lymphoma (MCL), with overall response (OR) rate ranging between 20 and 50% and with a complete response (CR) rate $<10\%$. In these studies thrombocytopenia was the principal grade III-IV side effect (30-50%). Preclinical studies indicated a potential synergistic activity between Bortezomib and various cytotoxic agents, in particular Fludarabine and Rituximab. On these grounds we performed a pilot clinical study combining Bortezomib to FCM-R (Fludarabine, Cyclophosphamide, Mitoxantrone, Rituximab) (FCM-BR) in patients with relapse/refractory LG lymphoma and MCL.

Methods: Four male patients, median age 60 years (42-63), including 1 lymphoplasmocytic lymphoma (LPC) and 3 MCL, all with active, advanced stage and progressive disease, were treated with FCM-BR between May and June 2007. FCM-BR was planned to be administered every 4 weeks for 4 courses according to this schedule: Bortezomib 1.3 mg/m² on day 1, 4, 8, 11, Rituximab 375 mg/m² on day 1, Fludarabine 25 mg/m² on day 1-2-3, Cyclophosphamide 200 mg/m² on day 1-2-3, Mitoxantrone 8 mg/m² on day 1 (\pm G-CSF support).

Results: Two patients with MCL completed the therapeutic programme with 4 courses of FCM-BR achieving 1 CR and 1 PR still maintained after 9 and 10 months. One patient with MCL interrupted therapy after the first course because of stable disease and underwent an allogeneic stem-cell transplantation. The patient with LPL after 4 FCM-BR achieved PR still maintained after 12 months. Grade IV neutropenia was observed in 3 patients requiring G-CSF support (1 patient had grade II neutropenia), 2 patients had a grade IV and 1 patient had a grade III thrombocytopenia, one patient had grade II anemia. No infectious or other extra-hematological toxicity was observed during and after the study period.

Conclusions: The results of this pilot study indicate that FCM-BR can be administered without major toxicity and with good activity in the majority of cases. Studies on larger scale are warranted.

447 R-CHOP + THALIDOMIDE FOR PREVIOUSLY UNTREATED MANTLE CELL LYMPHOMA

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Despite favorable response rates of R-CHOP in mantle cell lymphoma (MCL), R-CHOP has only a moderate effect on progression-free survival (PFS), which highlights the need for additional therapeutic strategies in MCL. We have previously shown that rituximab (R) plus thalidomide (Thal) has marked activity in patients (pts) with relapsed/refractory MCL (Blood 2004; 104: 2269). To further explore the role of Thal in MCL, we have performed a phase II trial of R plus Thal combined with standard CHOP in previously untreated MCL. Treatment consists of standard R-CHOP being administered every 3 weeks for a total of 6 cycles with added Thal (concomitantly with R-CHOP at a daily dose of 100mg during cycle 1, 200mg at cycle 2 and beyond including maintenance until progression/relapse). Dalteparin (5000 I.E. sc daily) is included as prophylaxis for venous thromboembolism (VTE). Pts with CD20+, newly diagnosed MCL up to the age of 75 years are eligible. Primary endpoint is the activity of R-CHOP-Thal on PFS, secondary endpoints are tolerability, overall response, CR-rate and survival. To date, we have enrolled 32 pts (median age, 65 years; range, 51 to 75 years). A planned safety interim analysis after the first 10 pts revealed grade III

peripheral neuropathy in 1 pat (concomitant diabetes mellitus) and pulmonary embolism in 1 pat, who received full oral anticoagulation due to atrial fibrillation. The low rate of VTE is further documented by only one event among 30 pts receiving R-CHOP-Thal and dalteparin prophylaxis. No unexpected adverse events of R-CHOP were noted by the addition of Thal. All 10 pts experienced a response to R-CHOP-Thal (with 8 patients in CR; 4 pts were also negative by FDG-PET). Results are currently updated and evaluated in comparison with a reference population of MCL patients treated with CHOP/R-CHOP without Thal, and data will be presented at the meeting.

448 DURABLE RESPONSES WITH THE ANTI-ANGIOGENIC METRONOMIC REGIMEN RT-PEPC IN RECURRENT MANTLE CELL LYMPHOMA (MCL)

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Background: Targeting tumor microenvironment and angiogenesis is a novel therapeutic strategy in lymphoma. Two putative anti-angiogenic regimens, RT (rituximab with thalidomide) and PEPC (prednisone, etoposide, procarbazine and cyclophosphamide) have shown clinical efficacy. We report phase II safety and activity of the novel combination RT-PEPC, and present angiogenic profiling of MCL patients to date.

Methods: Pts with recurrent MCL were enrolled. RT-PEPC includes an induction phase (months 1-3) of daily thal (50 mg) and PEPC with weekly rituximab × 4. A maintenance phase continues with daily thal (100 mg), PEPC dosing titrated to ANC >1K, and rituximab every 4 months. Endpoints included safety, efficacy, and FACT-G quality of life (QoL). Translational studies assessed the angiogenic phenotypes of tumor cells, and dynamic levels of circulating endothelial and hematopoietic progenitors after treatment.

Results: Twenty pts (15 males) were enrolled, with 15 evaluable (3 never received rx, 2 early). Median age was 73 yrs (range 52-81), 17 (85%) had stage IV, and 70% IPI 3-5. Fourteen pts (70%) had 2+ prior rx, and 12 (60%) progressed on bortezomib. At a median followup of 27.5 months, overall response rate is 73% (40% CR, 33% PR, n=15). Nonresponders experienced stable disease (range 6-11 mos). Median TTP was 15 months, with est 2-yr PFS of 27% (95% CI: 0.11-0.67) and 2-yr OS of 67% (95% CI: 0.45-0.99). Three CRs of 16, 34 and 36 months are ongoing. In 91% pts achieving a response, PFS after RT-PEPC was longer than PFS after preceding therapy. Main toxicities included fatigue, rash and neuropathy as well as gr 1-2 thrombocytopenia (45%) and gr 3 neutropenia (73%). QoL was maintained or improved on rx. Correlative studies demonstrate pre-therapy increased angiogenesis in MCL (VEGFR1 expression by IHC and qPCR analysis). Circulating levels of hematopoietic and endothelial progenitor cells decreased over time in responders.

Conclusions: RT-PEPC has significant and durable clinical activity in MCL by targeting both tumor cells and tumor angiogenesis. Novel low-intensity anti-angiogenic approaches warrant further evaluation in MCL and other NHL subtypes.

449 ARSENIC TRIOXIDE (ATO) AND ALL TRANS RETINOIC ACID (ATRA) INDUCE CELL DEATH IN MANTLE CELL LYMPHOMA (MCL) THROUGH DISTINCT PATHWAYS

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Introduction: Manipulation of reactive oxygen species (ROS) signaling pathways in MCL may induce cell death, and recently the retinoic acid receptor-alpha (RAR-a) has been implicated in survival of MCL cell lines. We interrogated cell death pathways in MCL by characterizing the effects of ATO and ATRA on cell death.

Methods: ATRA in these studies was packaged into nanoscale, disk shaped phospholipid bilayers (nano-disks, ND) stabilized by apolipoproteins. Granta MCL cells were incubated with ATO (2-5µM) or ATRA (50nM) and apoptosis was determined by Annexin-V/propidium iodide staining with flow cytometric analysis. ROS were measured by oxidation of 2',7'-dichlorofluorescein diacetate to dichlorofluorescein and detected by flow cytometry. Autophagy (Auto) was monitored by conversion of LC3BI to LC3BII protein by immunoblot. Caspase 3, 9 and PARP, Akt, mTOR, p21, p53, Bax, cytochrome c, histone 4 and RAR-a were all measured by Western blot.

Results: ATRA-ND and ATO induced apoptosis at 24 hours (hrs), while ATRA-ND caused 4-fold more apoptosis than ATRA alone or empty nanodisks. At 6 hrs, ATRA-ND, but not free ATRA, empty nanodisks or ATO, induced ROS production. ATO increased Bax, cytochrome c, and cleavage of caspases-9 and -3, and PARP, but resulted in decreased expression of RAR-a, p53, p21, Akt, and mTOR. ATRA-ND increased p21, p27, p53, cytochrome c, and acetylation of histone 4, and down regulated its receptor RAR-a. Since Auto may be an important cell survival or cell death pathway in cancer, we determined if Auto pathways were extant. LC3B-II protein was *upregulated* in cells treated with ATO and ATRA-ND, but not free ATRA.

Conclusions: ATO stimulates apoptosis in MCL cells through caspase pathways and is ROS independent, whereas ATRA-ND stimulates apoptosis through the activation of p53, CDK inhibitor proteins p21 and p27, cytochrome c, and acetylation of histone 4. Continued investigation of cell death pathways is warranted in order to expand the treatment targets/options available for MCL.