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REVIEW

Update on the molecular pathogenesis and clinical treatment of mantle cell lymphoma: report of the 11th annual conference of the European Mantle Cell Lymphoma Network

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Abstract

Mantle cell lymphoma (MCL) is a distinct subtype of malignant lymphoma characterized by the chromosomal translocation t(11;14)(q13;q32), resulting in constitutional overexpression of cyclin D1 and cell cycle dysregulation in virtually all cases. Clinically, MCL displays an aggressive course, with a continuous relapse pattern and a median survival of only 3–7 years. However, a subset of up to 15% long-term survivors has recently been identified with a rather indolent clinical course. In general, conventional chemotherapy is only palliative and the median duration of remissions is only 1–2 years. In 2000, the European MCL Network (http://www.european-mcl.net) was founded, which consists of 15 national lymphoma study groups supplemented by experts in hematopathology, cytogenetics and molecular genetics. During the last decade, the European consortium has successfully initiated the largest phase III trials in MCL worldwide. In the current study generation, the addition of high dose cytosine arabinoside (Ara-C) to an R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)-like regimen followed by myeloablative consolidation achieved a significant improvement of progression-free survival. Similarly, in elderly patients, rituximab maintenance until progression led to a marked prolongation of remission duration. Emerging strategies include proteasome inhibitors, immune modulatory drugs (IMiDs), mammalian target of rapamycin (mTOR) inhibitors and others, all based on the dysregulated cell cycle machinery and impairment of several signaling transduction and apoptotic pathways. Future strategies will apply individualized approaches according to the molecular risk profile of the patient. At the annual conference in Lisbon, recent results of molecular pathogenesis, analyses of current clinical trials and new study concepts were discussed.

Keywords: Mantle cell lymphoma, chemotherapy, transplantation, rituximab maintenance, molecular pathogenesis

New molecular insights in mantle cell lymphoma

Cyclin D gene translocations in MCL

Almost all mantle cell lymphomas (MCLs) carry the t(11;14)(q13;q32) translocation, which results in the constitutive overexpression of cyclin D1 protein. This translocation is detected in about 65% of cases by conventional karyotyping, but can be identified in up to 99% by fluorescence

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in situ hybridization (FISH). Interestingly, pathologists have recognized a small subset of lymphomas with morphologic and phenotypic features resembling conventional MCL but characterized by the absence of t(11;14)(q13:q32) and the lack of cyclin D1 messenger RNA or protein overexpression. A gene expression study from the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) Consortium reported a study of six cases of cyclin D1-negative lymphoma with morphologic, pathologic, clinical and molecular features similar to typical MCL [1]. Noteworthy, these cases had high levels of cyclin D2 or D3, but without evidence of chromosomal translocations or genomic amplifications that could explain their overexpression. In subsequent studies using conventional comparative genomic hybridization (CGH) [2] and single nucleotide polymorphism (SNP) arrays [3] we showed that cyclin D1-negative MCL had a similar profile of secondary genomic alterations to conventional MCL, supporting the idea that cyclin D1 negativity may be a real biological variant of MCL.

Subsequent studies in other cyclin D1-negative MCL detected high levels of cyclin D2 due to chromosomal translocations involving CCND2 and immunoglobuin (Ig), such as t(2;12)(p11;p13), t(12;22)(p13;q21) and cryptic t(12;14)(p13;q32), and two other translocations with unidentified partners, both cases expressing high levels of cyclin D2, whereas only one case of MCL with translocation of CCND3 has been reported so far [4]. The use of immunohistochemistry for cyclin D2 and cyclin D3 in diagnosis may not be useful to identify cyclin D1-negative MCL, as these cyclins are also expressed in other B-cell lymphomas [5,6].

SOX11 is a transcription factor that is expressed in 90% of cases of MCL but which is negative in mature B and T cell lymphomas, with the exception of 30% of Burkitt lymphomas and some T-prolymphocytic leukemias. SOX11 has also been detected in 12 cyclin D1-negative MCLs [5], demonstrating that it is a highly specific biomarker for MCL.

Ki67, proliferation and cell cycle deregulation in MCL

The use of the proliferation index as measured by the percentage of Ki67 positive lymphoma cells has been established by the European MCL Network as a very powerful prognostic biomarker in MCL [7], and the recently published guidelines will allow a standardized assessment in future trials [8]. However, several questions regarding the biology of proliferation in MCL remain unsolved. It is assumed that the dysregulation of cyclin D1 in MCL induced a cell cycle deregulation [9]. Interestingly, the level of cyclin D1 mRNA correlates with the proliferation index [10]. Since cyclin D1 acts at the G1 to S phase transition, one might assume that a high cyclin D1 level in highly proliferative MCL is associated with a shorter G1 phase. The duration of the single cell cycle phases in MCL can be analyzed by immunofluorescence multi-staining with antibodies against proteins restricted to certain cell cycle phases. Combined analysis of Ki67 (not expressed in G0) and survivin (not expressed in G0 and G1) indicates that the duration of G1 phase is similar in MCL with high or low overall proliferation rate. Thus the "cell cycle dysregulation" in MCL primarily refers to disrupted checkpoints such as Tp53 and ATM but does not result in a shortened G1 phase.

Prognostic value of aneuploidies detected by QMPSF in MCL

The R-CHOP/R-DHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone/rituximab, dexamethasone, cytarabine, cisplatin) arm of the MCL Younger trial has showed significantly improved CR rate and time to treatment failure [11]. The objective of this analysis was to revisit the prognostic value of gene imbalances and determine whether high dose cytarabine could counteract some of those risk factors.

The principle of QMPSF (quantitative multiplex polymerase chain reaction [PCR] of short fluorescent fragments) is based on the simultaneous PCR amplification of small fragments, each fragment representing a target (gene/locus). PCR was performed under semi-quantitative conditions (20–21 cycles) using fluorescent primers, and analyzed by Genescan software. The patient profiles were compared to that of a healthy control. The analysis focused on the major alterations of cell cycle and DNA repair. *MYC*, *CDK2*, *ATM*, *RB1*, *TP53*, *CDKN2A* (*P16*), *CDKN1B* (*P27*) and *MDM2* gene dosage were analyzed by QMPSF as previously described [12].

A total of 114 eligible samples (58 lymph nodes and 56 peripheral blood or bone marrow) were analyzed, including 89 French samples (72 previously reported [13]) and 25 German samples. Deletions of *Tp53* and *p16* were associated with higher MCL International Prognostic Index (MIPI) score at presentation, with a tendency for P27 and MDM2 anomalies. In univariate analysis, *Tp53* deletions were associated with a shorter time to treatment failure (TTF), with significant effect in each treatment arm. In contrast, *p16* deletions were associated with shorter TTF, mainly in the R-CHOP arm, but not in the R-DHAP arm, suggesting that more intensive induction therapy can overrule such a poor prognostic factor.

PI3K/mTOR pathway in MCL and DLBCL

Exploration of targeted therapy has currently focused mainly on the signal transduction pathways and the role of tumor microenvironment. Accordingly, a number of novel drugs are available for the treatment of B-cell non-Hodgkin lymphoma (B-NHL), including those targeting B-cell activation (PCI-32765, fostamatinib, enzastaurin, BAFF antibody, CAL101) and the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway (CAL101, MK2206, CCI-779), but also the cell cycle (PD0332991), DNA damage response pathways (RG7112, olaparib), regulatory proteins of cell death (ABT-737/ABT263, GX-15-070/AT-101), cellular stress response (17AAG, carfizomib), the ubiquitin–proteasome pathway (bortezomib, carfilzomib, NPI-0054) and epigenetic modifications (decitabine, BLL1, 3, vorinostat) [14–18].

We focused on three pathways described to be most important for the pathogenesis of B-cell lymphoma, namely the B-cell receptor, the PI3K/Akt and the mTOR pathways. Three inhibitors of the above-mentioned pathways (BTK: PCI-32765, PI3K: CAL101 and mTOR: temsirolimus) were analyzed alone and in combination in five MCL and six diffuse large B-cell lymphoma (DLBCL) cell lines (four germinal center B-cell [GCB] and two activated B-cell types [ABC]).

While the sensitivity to temsirolimus alone was similar in all cell lines, DLBCL cell lines were more susceptible to BTK and CAL101 inhibitors, with especially the ABC cell lines being most sensitive to BTK inhibition. MCL cell lines were also less susceptible to combined treatment. To determine potential molecular markers of susceptibility we compared the protein expression and phosphorylation status of central regulators of the inhibited pathways. Higher grade of phosphorylation of BTK and Akt, but lower phosphorylation of Syk and Raptor in DLBCL were observed. In contrast, CCND1, c-myc and MNK protein were more highly expressed accompanied by a higher grade of phosphorylation of eIF-4E in the MCL cell lines (Figure 1).

Clinical features of mantle cell lymphoma

CNS involvement in MCL

Central nervous system (CNS) relapse is often associated with systemic relapse. The true incidence is unknown, and the relevance of DLBCL risk factors to MCL remains unclear (Table I) [19–23].

CNS involvement is often a feature of relapsed/refractory MCL. In retrospective series an incidence of 4–25% has been observed in cases, with blastoid morphology and elevated lactate dehydrogenase (LDH) being risk factors in multivariate analysis.

According to current recommendations, pretreatment work-up in patients with MCL does not include routine assessment of the cerebrospinal fluid (CSF). In fact National Comprehensive Cancer Network (NCCN) guidelines recommend CNS staging only if CNS symptoms or blastoid morphology are present. Aims of the current project will be to explore the impact of the following factors on CNS relapse:

- Identify risk factors other than blastoid histology;
- Role of Ki67, LDH and MIPI;
- Impact of the addition of rituximab, intensive protocols with CNS penetrating drugs (e.g. hyperCVAD [hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethsone], R-MaxiCHOP), or upfront autologous stem cell transplant;
- Impact of CNS prophylaxis;
- Develop consensus guidelines for CNS prophylaxis.

Indolent mantle cell lymphoma

The definition of indolent MCL (iMCL) is a matter of debate. Clinically, Martin *et al.* identified a subgroup of patients without need for treatment in a retrospective analysis [24]. Navarro and Campo defined this new entity as a MCL with a low proliferation index, predominance of highly mutated immunoglobulin heavy chain variable (IgHV) gene, lack of secondary cytogenetic alterations and clinically non-nodal disease with splenomegaly and leukocytosis [25].

Several groups tested the expression of SOX11, a neuronal transcription factor highly expressed in MCL. Cytoplasmic expression of SOX11 correlated with a shorter survival compared to MCL with nuclear SOX11 expression [26]. Fernandez *et al.* evaluated SOX11 protein expression in an independent

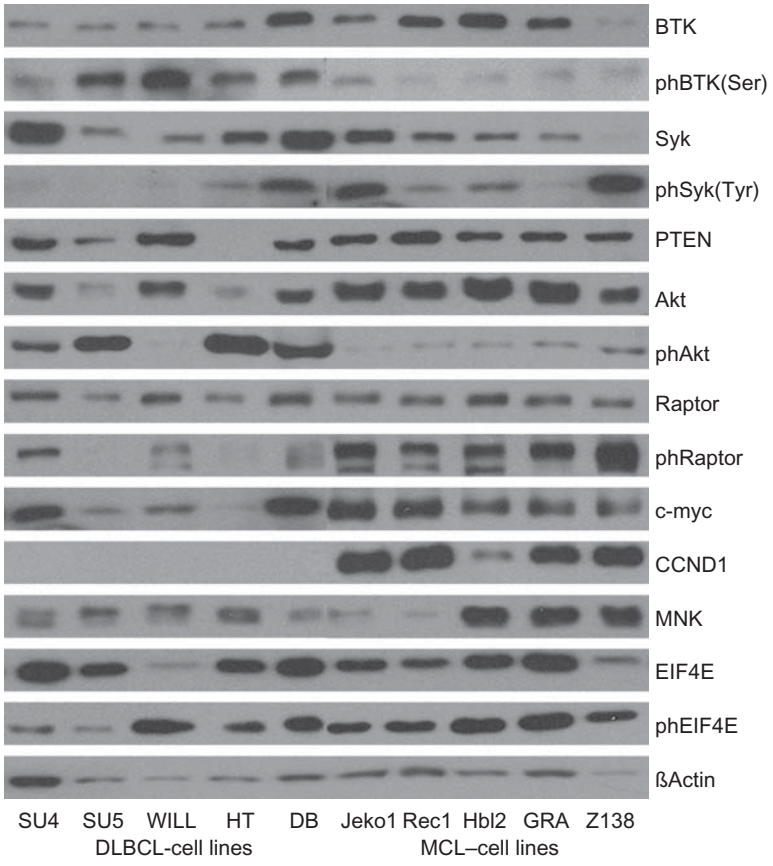

Figure 1. Western blot analysis of protein expression and phosphorylation status in untreated DLBCL and MCL cell lines.

Table I. Frequency of CNS involvement in MCL.

Study	Patients with CNS involvement/ total no.	Median time to CNS involvement	Patients with blastoid morphology	Patients with CNS involvement at diagnosis	First-line with CNS-penetrating agents	Prophylaxis with intrathecal therapy
Oinonen [21]	4/94 (5%)	51	1	0	Unknown	Unknown
Valdez [22]	25/108 (23%)	15.5	2	1	Unknown	0
Ferrer [20]	11/82 (13%)	25	5	1	20%	0
Gill [23]	4/62 (6.5%)	12	2	1	16%	10%

CNS, central nervous sytem; MCL, mantle cell lymphoma.

series of 112 cases of MCL. Some 13% of patients had SOX11-negative tumors with a predominantly non-nodal presentation and a better survival compared with SOX11-positive patients ($p = 0.0019$) [27].

Due to the rarity of this disorder, biological characteristics and clinical course of indolent MCL are not well characterized. The European Mantle Cell Network proposes a registry of iMCL to characterize its clinical characteristics, biology pattern and survival (Figure 2). Secondary objectives are the establishment of a tumor bank with histological blocks and fresh blood/bone marrow samples for biological studies. The identified cases will be registered online and centrally reviewed by expert pathologists. Biological samples will be collected by a referral laboratory to perform immunohistochemistry and flow cytometry, quantitative real-time reverse transcription PCR (qRT-PCR), FISH [t(11;14)(q13;q32)], IgVH analysis, gene expression, DNA SNP array and methylation. Clinical data will be recorded in electronic documentation form.

Current trials (younger patients)

Role of total body irradiation in MCL

Treatment of MCL has recently improved by the combination of monoclonal anti-CD20 immunotherapy, cytarabine-containing regimens and autologous stem cell transplant (ASCT). However, the use of total body irradiation (TBI) as part of the conditioning regimen of ASCT has drastically decreased during the last decade, although a retrospective study suggested that TBI may improve the event-free survival (EFS) [28].

The European Group for Blood and Marrow Transplantation (EBMT) registry investigated the role of TBI in 418 patients with MCL who underwent an ASCT between 2000 and 2007. Median age was 50.8 years. At diagnosis, 81.1% of the patients presented with an extended stage IV disease, and most of the patients (85%) had received one line of chemotherapy prior to ASCT. Induction regimens included rituximab in 226 patients (58%), high dose cytarabine in 176 patients (45%) and both in 122 patients (31%). At transplant, 283 patients (68%) were in complete remission (CR) and 135 (32%) in first partial remission (PR). The conditioning regimen contained TBI in 152 patients (37%).

With a median follow-up of 29 months, median overall and disease-free survival (OS and DFS) of all patients were 99 and 57 months, respectively. TBI did not influence the outcome of patients transplanted in CR. In contrast, in patients with PR, TBI was associated with a significant reduction of relapse rate in both univariate ($p = 0.034$) and multivariate analysis ($p = 0.007$), and also a trend toward a prolonged DFS in patients with PR (median DFS 50 months vs. 30 months, $p = 0.123$). However, overall survival and non-relapse mortality (NRM) were similar in both patient cohorts.

Thus, TBI or other radiotherapy-based conditioning should still be considered in patients with only PR at transplant.

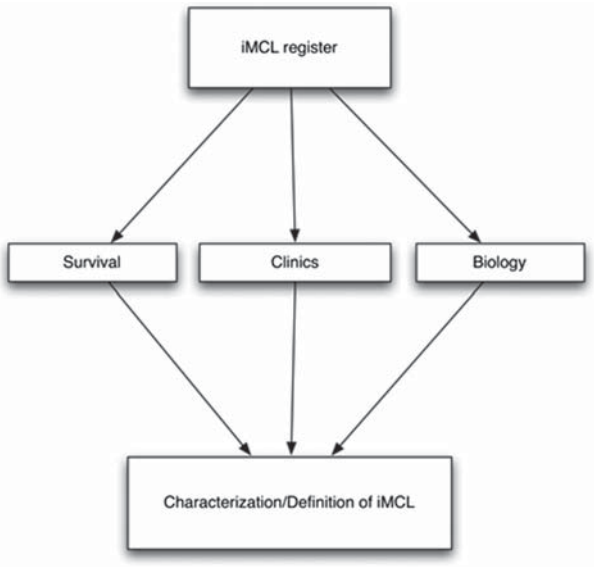

Figure 2. Indolent MCL register.

MCL 0208: role of lenalidomide maintenance after ASCT

MCL 0208 is a phase III, multicenter, randomized study by the Fondazione Italiana Linfomi (FIL) to determine the efficacy and safety of lenalidomide [29] maintenance after first-line intensified induction and ASCT consolidation [30]. The primary end-point is 2-year progression-free survival (PFS) from the start of randomization.

Enrolment of 250 patients is planned in 59 FIL sites and 11 additional centers of the Portuguese and Croatian Lymphoma cooperative groups. Patients receive three cycles of R-CHOP, followed by a consolidation phase (high-dose cyclophosphamide, two cycles of high-dose Ara-C [cytarabine arabinoside], BEAM [carmustine, etoposide, Ara-C, melphalan] and ASCT) (Figure 3). CD34+ cell harvest is performed after the first course of high-dose Ara-C. After ASCT, responding patients are randomized between lenalidomide maintenance (15 mg days 1–21 of a 28-day cycle) and observation.

From May 2010 to December 2011, 68 patients have been enrolled by 24 Italian centers. To date, 17 out of 40 histological blocks sent for centralized histological review have been confirmed and 23 are still being analyzed. Until now, four

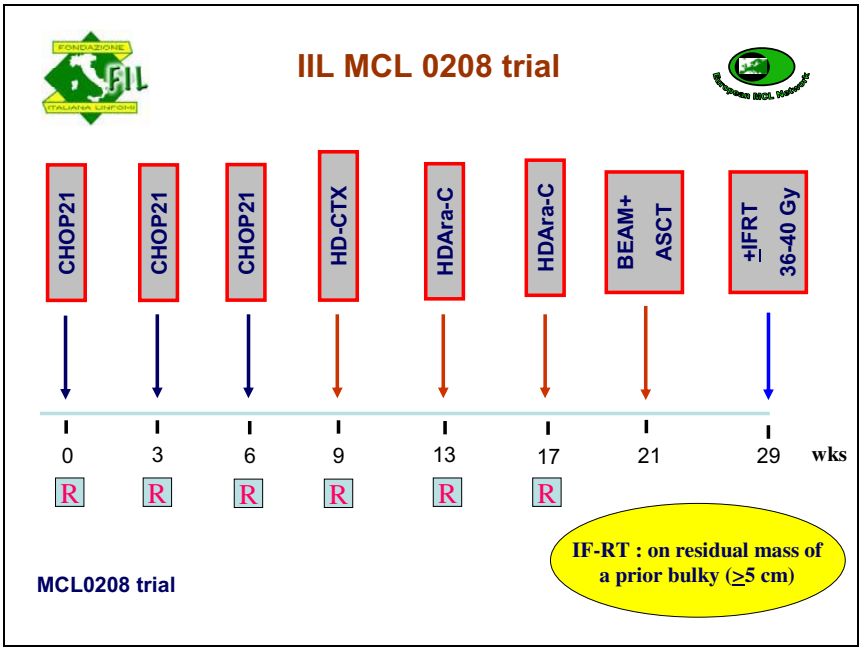

Figure 3. MCL 2008 study scheme.

patients have interrupted the treatment: one did not have a response after cytarabine, three did not achieve hematologic recovery after ASCT and one died from a road accident.

The MCL 0208 study also includes regular PCR monitoring of minimal residual disease (MRD) [31] during therapy and follow-up. So far, in only three out of 68 cases no molecular marker could be identified.

MCL Elderly finalized data and plans for the future

The prognosis of elderly patients with MCL used to be dismal. Patients achieved only low CR rates, and subsequently almost all patients relapsed [32]. Therefore, we performed a randomized intergroup trial within the European MCL Network to investigate both whether a fludarabine-containing induction regimen could improve the CR rate, and whether rituximab maintenance could prolong remission duration.

Patients aged >60 years with advanced stage MCL were randomized between eight cycles of R-CHOP or six cycles of R-FC (rituximab, fludarabine, cyclophosphamide). The median age of 560 patients was 70 years; 51% exhibited a high risk according to the MIPI. After a median follow-up of 3 years, the CR and overall response rates after R-FC were not different, and progressive disease was more frequent compared to R-CHOP, but this difference did not translate into a different TTF. However, overall survival was significantly inferior after R-FC, and hematologic grade 3–4 toxicities were also more frequent.

A total of 316 responding (CR, CR unconfirmed [CRu], PR) patients underwent a second randomization between rituximab maintenance and interferon-α. Second randomization was stratified for induction regimen, study group, age, IPI and response (CR/CRu vs. PR). Rituximab maintenance almost doubled the remission duration compared to interferon-α, but overall survival did not differ. However, the sub-cohort of patients treated with R-CHOP showed a significantly improved overall survival after rituximab maintenance. Hematologic grade 3–4 toxicity was higher in the interferon arm but non-hematologic toxicity was infrequent. We concluded that the new standard treatment for elderly patients should consist of R-CHOP induction followed by rituximab maintenance.

Both induction and maintenenance treatment should be further improved, as no survival plateau has been observed so far. Bendamustine combinations are currently being investigated. For the European MCL Network, cytarabine is obviously one of the most attractive drugs based on the superior results of the alternating R-CHOP/R-DHAP scheme in younger patients [11]. Accordingly, R-DHAP will be adapted for elderly patients by omitting cisplatin and decreasing the doses of cytarabine and dexamethasone.

Even during rituximab maintenance, a delayed relapse pattern has been observed. Potential candidates for further improvement are combinations with lenalidomide or one of the newer anti-CD20 monoclonal antibodies [25].

The European MCL Network will launch its next randomized phase III trial during 2012 (Figure 6).

MRD in the MCL Elderly trial

Recently our group has shown that MRD assessment after immunochemotherapy induction followed by ASCT is a highly reliable prognostic marker in MCL.

In the MCL Elderly trial, MRD was prospectively monitored to reveal response kinetics on the molecular level. MRD samples were collected at diagnosis, at mid-term (after four induction cycles), after completed induction (six cycles) and at 3-monthly intervals during maintenance.

MRD results obtained from real-time quantitative PCR (RQ-PCR) were evaluated according to European Study Group (ESG) criteria [33] and compared to clinical outcome. RQ-PCR was designed to reach a sensitivity of 10^{-5}, and MRD negativity was defined as a negative RQ-PCR result

with a sensitivity of at least 10^{-4}. Molecular response (MR) was defined as MRD-negative in peripheral blood and/or bone marrow at any sampling time point.

A total of 1931 samples from 241 patients were investigated (117 receiving R-CHOP, 124 R-FC). The MR rate was higher after R-FC at mid-term (66% vs. 31%; $p = 0.0002$) and after induction (86% vs. 51%; $p < 0.0001$), and was also an independent prognostic factor for remission duration. Furthermore, sustained MR during the first year after the end of induction was predictive for outcome in the pooled treatment arms (Figure 4). Thus, MRD monitoring revealed that R-FC has a high potential to clear lymphoma cells. However, due to the increased toxicity, R-FC treatment did not achieve a superior clinical outcome.

Rituximab maintenance resulted in a significantly longer remission duration (51 vs. 24 months; $p = 0.0109$) in the whole study cohort. This effect was also seen in MRD-negative patients, but R-maintenance could not prevent early relapses in MRD-positive patients. Thus, the effect of maintenance treatment seems to be dependent on the residual tumor burden, which underlines the importance of a highly effective induction regimen.

Phase II trials

BeRT: bendamustine and rituximab combined with temsirolimus

mTOR inhibition has been shown to be effective in various subtypes of malignant lymphomas. In relapsed MCL, a large phase III trial could prove superiority of temsirolimus in comparison to standard options, and subsequently this drug was approved in Europe [18]. In addition, in follicular and diffuse large B-cell lymphoma, promising response rates could be observed [34]. Whereas the combination of temsirolimus with rituximab seems to be feasible and to improve efficacy [35], there is limited information on its combination with chemotherapy. Bendamustine has been shown to be effective in various lymphoma entities and has a favorable side effect profile [36]. To evaluate the potential of the combination of temsirolimus with bendamustine and rituximab, a phase I/II trial was initiated.

Patients with either follicular or mantle cell lymphoma and 1–3 prior treatment lines were treated with bendamustine 90 mg/m^2 day 1–2, rituximab 375 mg/m^2 day 1 and temsirolimus days 2, 8, 15 of a 28-day cycle. In the ongoing phase I part (3 + 3 design) three dose levels were completed: A 25 mg, B 50 mg, C 75 mg.

To date, nine patients (eight with MCL, one with follicular lymphoma) are evaluable, with a median age of 64 and a median of two prior treatment lines. Generally the treatment was well tolerated. Toxicity was predominantly hematologic, with leukopenia and thrombocytopenia present in all patients. Five patients have completed the entire treatment; in one patient treatment was stopped after cycle 3 due to delayed recovery of platelets, and in three patients treatment is ongoing. So far all nine patients have achieved a partial remission after two cycles.

Based on the observed dose-limiting toxicities, the phase II part of the trial will be initiated in 2012, enrolling 30 patients with FL and MCL each.

Phase II study of age-adjusted R-BAC (rituximab, bendamustine, cytarabine) as induction therapy in older patients

Bendamustine is a purine analog alkylating agent, which has been evaluated in the treatment of various lymphoma types. The addition of rituximab reduced the dose of bendamustine required to induce apoptosis in lymphoma cell lines *in vitro*. The combination of bendamustine and rituximab has also shown considerable activity in relapsed or refractory MCL, with an overall response rate (ORR) of 75% with a 50% CR rate. The major toxicity was myelosuppression, with grade ¾ leukocytopenia in 16% of patients, although thrombocytopenia was rare [36]. A recent trial compared bendamustine plus rituximab (BR) versus R-CHOP in previously untreated patients with MCL. The two regimens gave similar results for ORR (BR: 86%, R-CHOP: 96%) and CR (42% vs. 41%), but the

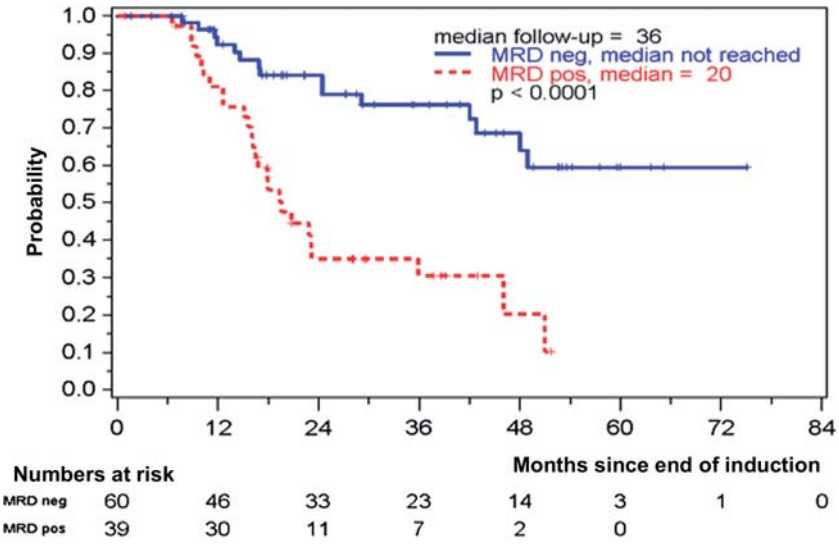

Figure 4. Remission duration according to sustained clinical and MRD response during first year after end of induction (pooled results from both treatment arms of MCL Elderly trial).

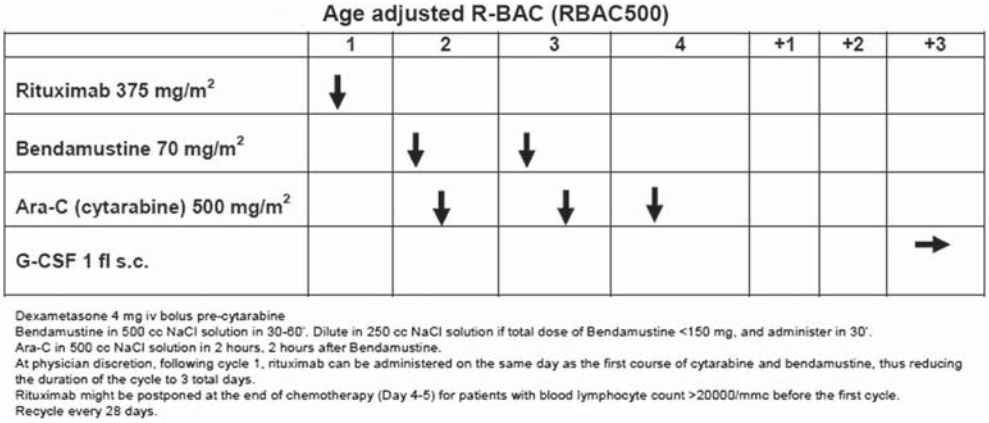

Figure 5. Treatment Schedule.

bendamustine combination was less toxic [37]. *In vitro* bendamustine modulated the cytarabine metabolism in leukemic blasts, enhancing the apoptotic effect of cytarabine [38].

This phase II study of standard R-BAC (rituximab 375 mg/m^2, bendamustine 70 mg/m^2, cytarabine 800 mg/m^2) completed enrollment at the Vicenza Hematology Department in November 2011. An interim analysis of 37 patients showed that the R-BAC combination had excellent clinical activity, but also relevant hematological toxicity, especially in previously treated and older patients [39].

In order to reduce the hematologic toxicity and to improve the safety, an age-adjusted scheme with dose-reduced cytarabine (R-BAC 500, Figure 5) was developed. The primary objective of this study is to determine the activity (CR according to Cheson 2007 criteria) and safety of age-adjusted R-BAC 500.

Observational study of high dose cytarabine

The Czech Lymphoma Study Group (CLSG) designed an observational study of newly diagnosed patients with MCL not eligible for ASCT. The patients will have three alternating cycles of R-CHOP and three cycles of R-cytarabine (2×1–2 g/m^2).

Primary endpoints of the study are the objective response rates by positron emission tomography–computed tomography (PET-CT), and assessment of MRD status by PCR. Secondary endpoints will be the exploration of selected molecular markers by immunohistochemistry and cytogenetics (e.g. Ki67, SOX11, p53, CDKN2A, ATM).

Thalidomide in mantle cell lymphoma

Thalidomide is the oldest member of the immunomodulatory drugs group. It was shown to be active in relapsed/refractory MCL already a decade ago, but has been largely overshadowed by newer targeted drugs, such as bortezomib, lenalidomide and temsirolimus.

In the initial study, 100–200 mg thalidomide was given continuously in combination with four weekly rituximab injections, and resulted in an 81% response rate with 31% CR [40]. Median PFS was 20 months and 3-year OS was 75%. Only one patient out of 16 had to discontinue treatment due to toxicity. At the last Lugano meeting a similar study was presented, using the combination of rituximab and lenalidomide [41]. Rituximab was given once weekly for four injections, and the MTD of lenalidomide was 20 mg daily for 3 weeks every 4 weeks. The response rate was 58% with a 33% CR rate, a median PFS of 13 months and a median OS of 25 months. Of course, the two patient groups differed substantially. Most patients in the thalidomide study failed CHOP only, whereas all patients in the newer study previously received rituximab and modern chemotherapies.

However, these data suggest that thalidomide has significant activity in MCL. In addition, thalidomide is not associated with myelotoxicity, which might be an important parameter in previously treated patients. At the University Hospital Center Zagreb the experience with thalidomide in MCL was retrospectively reviewed. We identified six patients, two with induction failure after R-CHOP/DHAP and four with thalidomide maintenance. Both refractory cases responded to the same treatment in combination with thalidomide, were able to undergo ASCT, and are still in remission after 4 and 13 months. Three of four patients receiving thalidomide maintenance in second remission (three of them relapsing after ASCT) are in continuous remission after 16, 13 and 19 months. Four patients tolerated 100 mg daily well, with few side effects, while two had to stop the drug due to neuropathy.

A retrospective survey is currently being performed in France as part of a national program of the French health authorities. Early results seem to confirm the findings of the Croatian group [42]. Thus, thalidomide 100 mg daily is well tolerated, and might offer a cost-effective alternative to more expensive targeted agents, especially in countries with limited health-care resources.

Conclusion

The 11th annual conference of the European MCL Network identified interesting aspects of the molecular pathogenesis as well as potential targets of new molecular approaches. However, to interpret recent phase II/III results, it is essential to consider the wide variation of clinical behavior. Thus, the incorporation of molecular markers (Ki67) and clinical risk

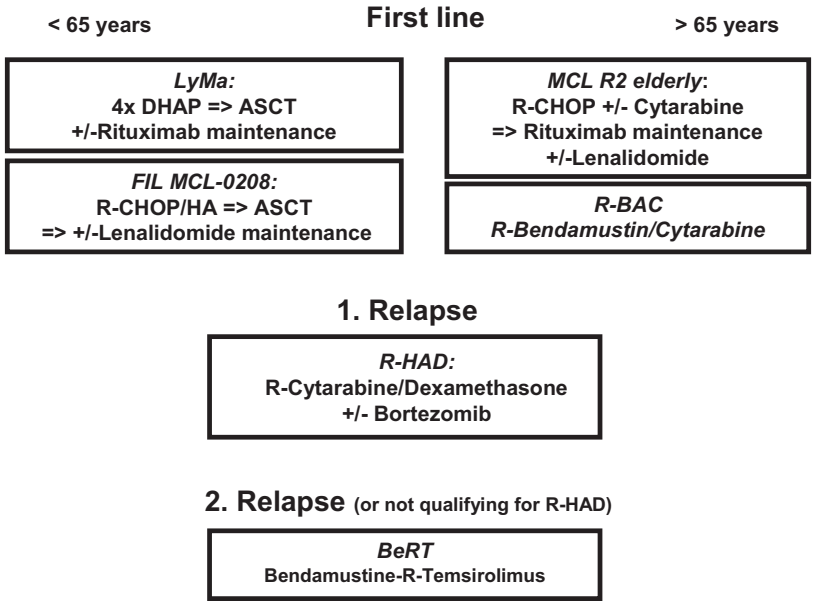

Figure 6. Current study generation 2012 of the European MCL Network.

scores (MIPI) as well as individual predictors of outcome (MRD) is crucial. The current study generation of the European MCL Network implements all of them to explore innovative targeted approaches in MCL (Figure 6).

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