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Breakthrough Treatment for Mantle Cell Lymphoma

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Abstract

MCL has a dismal prognosis ("the worst lymphoma to have"), with a median OS rate of 3 years only. Prognosis of limited stage disease is almost similar to that of stage lll MCL No curative therapy has been established so far. The US FDA granted breakthrough therapy designations to a bruton tyrosine kinase inhibitor, acalabrutinib in MCL patients who have previously received at least one line of therapy. Furthermore, the combination of bortezomib and a retinoid compound, fenretinide is synergistically cytotoxic against MCL lines and warrants further evaluation *in vivo* and in clinical trials. In addition, the combination of anti-Mcl-1 lipidoid nanoparticles with other forms of targeted therapy offers hope for reducing or replacing cytotoxic chemotherapy as standard treatment for MCL that over express Mcl-1.

Abbreviations : SOX11: Sry-related high-mobility-group box; MCL: Mantle Cell Lymphoma; NHL: Non-Hodgkin Lymphoma; OS: Overall Survival; CLL: Chronic Lymphocytic Leukemia; SLL: Small Lymphocytic Lymphoma; FL: Follicular Lymphoma; PLL: Prolymphocytic Leukemia; MIPI: MCL International Prognostic Index; FISH: Fluorescence *In Situ* Hybridization; MRD: Minimal Residual Disease; ASO-qPCR: Allele-Specific Oligonucleotide Quantitative Polymerase Chain Reaction; ISMCN: *In situ* mantle cell neoplasia; BM: Bone Marrow; siRNA: Short interfering RNA; ASCT: Autologous Stem Cell Transplantation; PR: Partial Response; R-HyperCVAD: rituximab + cyclophosphamide, doxorubicin, vincristine, dexamethasone alternating with methotrexate and cytarabine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, Vincristine, and prednisone; R-CVP: rituximab, cyclophosphamide, vincristine, and prednisone; R-FC: rituximab, fludarabine, and cyclophosphamide; BR: bendamustine with rituximab, R-DHAP: rituximab, dexamethasone, cytarabine, and cisplatin; VcR-CVAD: bortezomib, rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Introduction

MCL is an aggressive small B-cell lymphoma [1] that is derived from naïve, pre-germinal center cells of primary follicles or mantle regions of secondary follicles [2]. It constitutes nearly 6-8% of all NHL in Europe and North America. The median age at diagnosis is 65 years with a male preponderance of 3 to 1 [3]. These patients are typically Caucasian (about 2:1) [4]. A family history of hematopoietic malignancies has been linked with a 2-fold increased risk of MCL. The risk of MCL is linked with European strains of the Borrelia burgdorferi infection particularly when manifesting as acrodermatitis atrophicans. But, there is still a lack of solid evidence for such association. Body mass index, cigarette smoking, alcohol intake and severe immune suppression have not been implicated as risk factors for MCL [4].

MCL subtypes

Two subtypes with different clinicopathological manifestations and molecular pathogenetic pathways are recognized: Classical one largely with unmutated/minimally mutated IGHV and mostly SOX11+ and typically involves lymph nodes and other extranodal sites. The other is an indolent form, largely with mutated IGHV and mostly SOX11⁻ [1]. It is characterized by non-nodal leukemic presentation with mild to moderate lymphocytosis. Furthermore, these cases are associated with low Ki67 (≤10%) and kappa light chain expression [2].

ISMCN is a new name for *in situ* MCL characterized by the presence of CCND1+ cells, most typically in the inner mantle zones of follicles, and is often found incidentally, sometimes in association with other lymphomas. They appear to have a low rate of progression and may be disseminated [1].

Proposed model of molecular pathogenesis in the development and progression of MCL subtypes

Precursor B cells usually with but sometimes without a CCND1 rearrangement mature to abnormal naïve B cells which may initially colonize, the inner portion of the mantle zones, representing ISMCN. They may progress to classical MCL which is most frequently SOX11⁺. Being genetically unstable, acquisition of additional molecular/cytogenetic abnormalities can lead to progression to blastoid or pleomorphic MCL. A smaller proportion of neoplastic mantle cells may undergo somatic hypermutation, presumably in germinal centers, leading to SOX11⁻ MCL that preferentially involve PB, BM, and sometimes the spleen and are more genetically stable for long periods of time. Additional molecular/cytogenetic abnormalities, particularly TP53 abnormalities, may lead to clinical and sometime morphological progression [1].

The pathogenesis of MCL is complex and involves targeted genes and regulatory elements of the cell cycle machinery and senescence (ARF/BMI1/CDK4/INK4/RB1), DNA damage response pathways

(ATM/CHK2/p53), cell survival signals and genes representing other signalling pathways (BTK, AKT, mTOR, WNT, NF-κB, TNF, and NOTCH) [2]. Additionally, there is over expression of Mcl-1, an anti-apoptotic protein that is part of the Bcl-2 family [5].

Clinical Presentation

MCL patients typically present with generalized lymphadenopathy, often at clinical stage III or IV. Systemic symptoms such as loss of appetite, weight loss, fever, night sweats, nausea and/or vomiting, indigestion, and abdominal pain or bloating are commonly reported [2]. Eighty percent of patients with the mantle zone variant have splenomegaly which may be massive. Gastrointestinal involvement either in the stomach or colon is detected in 90% of cases [2] Lymphomatous polyposis, sometimes leads to the diagnosis of MCL [6]. Fifty percent of patients present with blood and marrow involvement [2]. MCL patients can present with pancytopenia or leukemic presentation with extensive leucocytosis [6]. Other extranodal sites include liver, Waldeyer's ring, skin, lacrimal glands and central nervous system [6].

Diagnosis

Complete blood count yields lymphocytosis along with anemia and cytopenia. The morphological spectrum of leukemic MCL ranges from 'small cells' resembling CLL or FL to 'large cells' mimicking PLL or acute leukemia. Large cell morphology is associated with more frequent additional cytogenetic abnormalities and poorer outcome [2]. BM aspiration and biopsy usually demonstrate nodular, interstitial, paratrabecular, or diffuse involvement or, in some cases, combination of these patterns [2].

The classic immunophenotype is strongly positive for pan-B cell antigens CD5, CD19, CD43, weakly positive for FMC7, and negative for CD10, CD23, and Bcl-6 with CCND1+ profile [2]. Variants of the classic immunophenotype include BCL-1+/CD5− lymphoma with morphologic features consistent with MCL [2]. The reciprocal translocation t(11;14)(q13;q32) involving CCND1 genes (CCND1, PRAD1, bcl- 1) on chromosome 11 and the Ig heavy chain locus on chromosome 14 is detected in almost 65% of cases by conventional karyotyping and in up to 99% of cases by FISH [2]. Gene CCND1 can deregulate cell cycle control by overcoming the suppressor effect of retinoblastoma 1 and the cell cycle inhibitor p27 [4]. CCND1-negative MCL cases were positive for overexpression of CCND2 or D3 [2].

SOX11 is a neural transcription factor that is expressed in nearly 90% of the cases. It has been identified as diagnostic and prognostic biomarker of MCL [2]. Its absence is characteristic of indolent MCL [6]. SOX11 regulates MCL homing and invasion via direct regulation of CXCR4 and FAK expression and PI3K/AKT and ERk1/2 signalling activation [7]. Biopsy of a lymph node: MCL most commonly presents with a diffuse effacement of the lymph nodes. In situ, mantle-zone, nodular and diffuse patterns are commonly seen [2]. Four cytologic variants of MCL are recognized in biopsy, small cell variant, mantle zone variant; diffuse variant, and the blastic variant [6].

Biopsy of a lymph node, tissue, or bone marrow shows the typical morphology of monomorphic small to medium sized lymphoid cells with irregular nuclear contours, [6] condensed chromatin, small nucleoli and scant cytoplasm [2]. Pathologically, MCL is classified into two main subtypes: classic and blastoid [2]. Cerebral spinal fluid evaluation is done if there are neurologic symptoms or if the patient has the blastoid variant or a high Ki-67 [6]. Serum chemistry is significant for elevated LDH and elevated Beta-2-microglobulin [2]. **Differential diagnosis** includes CLL or SLL, FL, and marginal zone lymphoma. CLL and SLL express sIgM, sIgD, CD19, and CD20, and have differential expression of T cell antigen CD5. However, MCL cells are positive for FMC7 and "typically" do not express CD23. They also exhibit greater staining intensity for B cell antigens and Igs. Like FL, MCL is positive for CD20 and Bcl-2, but in contrast to FL, MCL is negative for CD10, BCL-6, as well as CD23 [2].

Prognosis

No curative therapy has been established so far. It has a dismal prognosis ("the worst lymphoma to have"), with a median OS rate of 3 years only [3]. Prognosis of limited stage disease is almost similar to that of stage lll MCL [8] The overall 5-year survival rate is about 50% (for advanced-stage MCL) to 70% (for limited-stage MCL) [4]. Some predictors of clinical and biological outcome have been established. These are either assessable at baseline (mainly MIPI, Ki-67 proliferative index and genomic aberrations) or during treatment (functional imaging and MRD) [9].

Clinical predictors

Nodal presentation was predictive for poor overall survival [4]. Stage III and IV MCL are aggressive/ advanced MCL as they usually carry a high tumor burden and have poor prognostic features. Treatment should be initiated after the diagnosis even in asymptomatic patients [2]. Pathologically, the blastoid form is associated with a more aggressive clinical course [2]. Survival of most blastoid variants is shorter, although a subset may survive for up to 5 years [4]. **The MIPI** is the prognostic model most often used and incorporates ECOG performance status, age, leukocyte count, and lactic dehydrogenase. For each prognostic factor, 0–3 points are given and the points are summed up to a maximum of 11. The median OS of MIPI low-risk (0–3 points) is not reached (5-year OS 60%). The median OS was 51 months and 29 months for the intermediate (4–5 points) and high risk (6–11 points) group respectively [10]. MIPI does not reliably identify patients with indolent disease [11] but is an important tool in risk-adapted treatment decisions in advanced-stage patients [10]. A modification of the MIPI adds the Ki-67 proliferative index if available [6].

MRD assessment provides early feedback on the efficacy of the lymphoma clearance with different induction regimens and can provide an early prediction of disease recurrence. MRD has been used by some to guide pre-emptive therapy; e.g., rituximab after standard treatment, including ASCT consolidation. The most sensitive and the most commonly used and best standardized approach in MCL is ASO- qPCR method [9].

Other predictors

A. Highly mutated immunoglobulin heavy chain variable gene is associated with indolent MCL [4].

B. Some studies have suggested that CCND1-negative patients had poor clinical outcomes, while others reported no difference in survival rates between CCND1-positive and CCND1-negative patients [4].

C. SOX11 expression was predictive for poor overall survival [4]. Its expression increases cell adhesion mediated-drug resistance and contributing to a more aggressive MCL phenotype [7]. The lack of SOX11 protein expression correlated with a better prognosis [10].

D. Ki-67 index is a measure of tumor proliferative activity [10]. The median survival time was about 1 year for 61–90% Ki-67 and nearly 4 years for a 5–20% Ki-67 index [4]. High Ki-67 proliferation index or p53 mutations and p16 deletions are closely related to the more aggressive MCL subtypes such as the blastoid variants [6]. Ki-67 index along with MIPI score have not yet been validated as indicators for initiation of therapy [10].

E. Beta-2 microglobulin is a potential risk factor used primarily for MCL transplant patients. Values less than 3 yielded 95% overall survival up to 6 years, whereas over 3 yielded a median overall survival of 44 months [4].

F. Absolute natural killer count in peripheral blood has an important value for judging the prognosis of MCL patients and can be used as an important index to judge the disease status [12].

G. The poor prognosis group was characterized by high expressions of miR-18a, miR-18b, miR-20b and miR-363. The good prognosis group was characterized by higher expressions of miR-125-3p, miR-126, miR-10b, miR-143, and miR-145. MiR-127-3p and miR-615-3p were also found to be significantly associated with MCL overall survival. MiR-127-3p was combined with Ki-67 to create a new prognostic model. A similar model was created with miR-615-3p and MIPI. Seven microRNAs with prognostic significance independent of IGHV status and SOX11 expression were found [4].

H. Five frequently methylated genes (SOX9, HOXA9, AHR, NR2F2 and ROBO1) in MCL tumors were associated with a higher proliferation rate, an increased number of chromosomal abnormalities and poorer prognosis [4].

Treatment

MCL has diverse presentations ranging from very indolent cases to highly aggressive and refractory ones [3]. Currently, there is no standard therapy for MCL [10]. There is an urgent need to adapt therapy to accommodate these diverse presentations [3]. Risk-Adapted Therapy is usually tailored individually based on patient's age, symptoms and risk factors [2]. Asymptomatic elderly (based on low-MIPI patients and Ki-67 staining less than30%) [13] can be observed without any therapy "watch and wait". When they become symptomatic, first line therapy choices include R-Bendamustine, RCHOP (+/- rituximab maintenance), or a clinical trial [6]. Rituximab maintenance is a viable effective alternative to ASCT in older ASCT-ineligible patients [10]. For younger patients [6] (≤ 65 yr, no major comorbidities) [2] with intermediate or high risk MIPI: aggressive cytotoxic regimen followed by consolidation with ASCT in CR1 along with post-transplant maintenance rituximab [6] to achieve better PFS and OS [2]. Common combination regimens include R-HyperCVAD with high-dose cytarabine /methotrexate or a modified regimen such as the Nordic regimen. Possible alternatives for patients, not candidates for standard R-HyperCVAD with high dose cytarabine/methotrexate, include R-CHOP, R-CHOP alternating with R-DHAP, or R-Bendamustine [6].

ASCT consolidation is considered in patients achieving at least PR with induction [10]. It is reserved for patients younger than 65–70 years old, though no strict chronologic age limit exists [9]. Transplantation provides high responses and long survival rates, but hampered by acute and long-term toxicity [3]. It carries approximately 1%–5% risk of treatment-related mortality, as well as long-term increased risk for secondary malignancies [9].

At the time of relapse, agents directed at activated pathways in MCL cells such as ibrutinib (Bruton's Tyrosine Kinase inhibitor) have demonstrated excellent clinical activity [6]. Ibrutinib show durable single-agent activity in relapsed and refractory MCL. The favourable toxicity profile suggests that ibrutinib provides the opportunity for treatment with less intensive and more effective regimens than those currently available [14]. Bendamustine/rituximab is an option for a relapsed MCL patient who has not previously received Bendamustine. Other options include rituximab alone, bortezomib containing regimen (NF κ B inhibitor), lenalidamide (anti-angiogenesis) and or a clinical trial. If the patient is a candidate for stem cell transplantation, consider an autologous transplant if there was a long first remission or a reduced intensity allogeneic stem cell transplant should be given [6].

Practical Points

A. MCLs with both CCND1 and MYC translocations are known as "double hit" lymphomas and can be aggressive and show a high proliferation rate [6]. They can be distinguished from DLBCLs that have CCND1 and MYC translocations using SOX11 [4].

B. In addition to MCL, SOX11 is expressed in lymphoblastic lymphoma, some Burkitt lymphomas, and T-cell PLL, but is not expressed in other lymphoid neoplasms. SOX11 is also an important MRD marker used to monitor the clinical response to therapy and to predict relapse of MCL [2].

C. Limitations for common use of MRD measurement to guide treatment selection outside clinical protocols include: 10-15% of patients still lack a reliable molecular marker for MRD; and patients with low or absent BM invasion do not often carry a marker. In addition, hyper mutated IGH genes may hamper an optimal primer design. Moreover, no MRD data are available in

the context of the new targeted treatments, such as ibrutinib [9].

Future Direction

A.   The droplet digital PCR, a 3rd generation, end point, quantitative PCR has been shown to provide comparable results to ASO-qPCR for MRD monitoring in MCL [15].

B.   MRD targeting on plasmatic, circulating tumor DNA is extremely promising to track lymphoma clones residing outside the peripheral blood or bone marrow compartments [15].

C.   MCL remains an incurable disease [16]. Novel, improved treatments that maximize therapeutic benefits and minimize toxicities are needed [16]. The US FDA granted breakthrough therapy designation to acalabrutinib (a bruton tyrosine kinase inhibitor) in MCL patients who have previously received at least one line of therapy [17].

D.   The combination of bortezomib and a retinoid compound, fenretinide is synergistically cytotoxic against MCL lines. This appears to be mediated by modulation of IκK and IκBα, cell cycle dysregulation and apoptotic cell death. These combinations have moderate toxicity profile and warrants further evaluation *in vivo* and in clinical trials [16].

E.   Lipidoid nanoparticles siRNA therapy targeting Mcl-1 has potential as a new treatment modality for MCL that over express Mcl-1. The combination of anti-Mcl-1 lipidoid nanoparticles with other forms of targeted therapy offers hope for reducing or replacing cytotoxic chemotherapy as standard treatment for MCL [5].

Conclusion

Breakthrough in MRD assessment and treatment of MCL is emerging in the near future.

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