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Evolving treatment strategies in mantle cell lymphoma

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ABSTRACT

Mantle cell lymphoma is an incurable, moderately aggressive B cell lymphoma. While a small proportion of patients with indolent disease can be managed expectantly, most patients require treatment. The therapeutic approach is driven by physician recommendation, patient choice, age, fitness and comorbidities. Young, fit patients often receive combination chemoimmunotherapy, including high dose cytarabine, with autologous stem cell transplant. Recent data has indicated benefit from maintenance rituximab following autologous stem cell transplant. Ongoing trials are investigating combinations of chemotherapy and targeted agents as well as the role of minimal residual disease guided therapy. Older, less fit patients often receive bendamustine and rituximab or anthracycline based regimens. Maintenance rituximab is typically administered in older MCL patients after anthracycline based chemotherapy although its use after bendamustine based therapy is not supported by current data. Current trials focus on refining this regimen with the addition of targeted agents. In the relapsed and refractory setting, novel agents have demonstrated activity although durability of responses remains unsatisfactory.

1. Introduction

Mantle cell lymphoma (MCL) is an aggressive but incurable B cell lymphoma. It represents approximately 6% of all non Hodgkin's lymphoma [1,2]. The 2016 World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues describes two subtypes:

- Classical MCL, which typically comprises IgHV unmutated B cells, expressing SOX11. Clinically, this predominantly involves lymph nodes and extra nodal sites.
- Leukemic non-nodal MCL is generally composed of IgHV mutated, SOX11 negative B cells. This presents as involvement of the peripheral blood, bone marrow and spleen.

The pathognomonic hallmark and putative initial oncogenic driver of MCL is t(11;14)(q13;q32). This places the cell cycle regulator cyclin D1 (*CCND1*) (11q13) under control of the immunoglobulin heavy chain (*IGH*) locus (14q32) and leads to constitutive overexpression of cyclin D1 [3]. Secondary mutations resulting in disruption of DNA damage response (*CHK1* and *CHK2*), and cell survival pathways (*BCL2*), are frequently found in aggressive MCL [4,5].

In terms of clinical presentation, MCL usually manifests as generalized lymphadenopathy. The median age at presentation is 66 years. MCL exhibits 3:1 male predilection. Extra nodal disease is extremely common, usually noted in the peripheral blood, spleen,

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and GI tract [6,7]. Central nervous system involvement is seen in fewer than 5% of patients [8].

Much has been learned in recent years regarding clinical and biological features which help determine risk stratification of patients with MCL. Treatment strategies continue to evolve and outcomes appear to be improving over time. Novel agents are firmly established for the management of relapsed MCL and are now being tested in frontline settings.

2. Identification of clinical and biological risk factors

The clinical course of MCL is highly variable. In 2008, the MCL International Prognostic Index (MIPI) became the first risk stratification tool specifically developed for patients with MCL [9]. The MIPI is based on four independent prognostic factors: age, performance status, lactate dehydrogenase, and leukocyte count. The MIPI categorizes patients into three distinct risk groups: low risk (44% of patients, 5 year overall survival (OS) 83%), intermediate risk (35%, 5 year OS 63%), and high risk (21%, 5 year OS 34%) [10]. Cell proliferation (Ki-67) has also been identified as an important biologic marker. Ki-67 of greater than or equal to 30% was observed to have strong adverse prognostic significance independent of the MIPI. The combination of Ki-67 index and MIPI (MIPI-C) generates four risk groups with distinct 5-year OS: low risk (32% of patients, 5 year OS 85%) low intermediate risk (34%, 5 year OS 72%), high intermediate risk (23%, 5 year OS 43%), and high risk (11%, 5 year OS 17%) [11].

Genomic studies have helped identify mutations carrying prognostic significance independent of MIPI. *CDKN2A* mutations have been associated with poor outcomes in adults treated with intensive treatment regimens including autologous stem cell transplant [12]. *TP53* mutations identify a MCL subtype associated with high-risk characteristics, poor response to standard treatment with adverse overall outcomes [13]. Gene expression profiling of 17 select genes using the NanoString platform (MCL35) elegantly summates established high-risk disease morphologic features, including blastoid and pleomorphic morphology and genetic aberrations such as *TP53* overexpression, and truncation of the 3′ UTR of *CCND1* mRNA transcripts in a unified risk model. The MCL35 assay has been demonstrated to be a reproducible and valid biomarker and is a promising tool to define patients with varying outcomes as well as support risk adapted clinical trials [14].

3. Management of treatment naïve mantle cell lymphoma

Although MCL is often aggressive, not all patients require immediate treatment. Asymptomatic patients and/or individuals with low tumor burden may benefit from expectant management. In a retrospective analysis of 97 patients treated for MCL, 31 patients (32%) were observed for over 3 months prior to initiation of systemic therapy with median time to initiation of therapy of 12 months (range 4–128 months). The cohort of patients who were observed tended to have better performance status and lower MIPI scores compared to the treatment group. At a median follow up of 55 months, the observation cohort had superior survival (NR vs 64 months, $p = 0.004$) [15]. A British Columbia based retrospective registry reported similar results among 75 of 440 (17%) newly diagnosed patients with MCL who received expectant management [16]. The median time to treatment was 35 months (range 5–79 months) with significantly prolonged OS in the deferred treatment group when compared to the patients treated early (72 vs 52.5 months, p value = 0.041) While prospective validation is lacking, these retrospective studies have identified individuals with good performance status, no B symptoms, low LDH, non-bulky disease, non-blastoid morphology, and lower Ki67 values as those who might benefit from a “wait and watch” approach [16].

4. Choice of treatment strategy

For patients who require treatment, the initial management is determined by patient age, comorbidities and patient preference. In younger patients with few/no comorbidities (“fit” individuals) an intensive approach is typically utilized. Non-intensive strategies are preferred for frail or older patients. In general, older patients tend to receive fewer systemic therapies and fare less well than younger patients. In a population based dataset from the Swedish and Danish lymphoma registry, of 1389 patients with MCL treated between 2001 and 2011, 375/460 (82%) patients aged under 65 years were treated with systemic therapy and the estimated 3-year OS for this group was 76%. Of patients over the age of 65 years, 683/929 patients (73%) received systemic therapy and 3-year OS for this group was 46% ($p < 0.001$) [17].

5. Management of frail, older patients

Intensive therapies are beneficial for younger patients but yield poorer results in older patients.

A combination of R-HyperCVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with R-MA (rituximab, high dose methotrexate and cytarabine) for 6 to 8 cycles resulted in an overall response rate (ORR) of 97% [complete response (CR)/unconfirmed CR (CRu) rate 87%] The median failure free survival was significantly inferior in patients over 65 years (n = 32) when compared to younger patients (n = 65) (3 years vs 5.5 years $p < 0.05$) [18–20].

A retrospective study from the University of Pennsylvania compared outcomes between 19 patients who received R-CHOP with 19 patients receiving R-hyperCVAD with or without autologous stem cell transplant (ASCT) [21]. Progression free survival (PFS) was significantly longer after R-CHOP + ASCT (3.2 years) or R-HyperCVAD alone (4.0 years) compared with R-CHOP alone (1.6 years) ($p = 0.013$ and $P = 0.009$, respectively). Compared to R-CHOP alone a higher incidence of toxicity was seen with R-HyperCVAD. The incidence of adverse events was the same among patients who received R-hyperCVAD alone and those that had R-CHOP + ASCT. These results indicate that while R-CHOP was clearly an inferior strategy for fit older patients with MCL, the prolongation of PFS seen