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Journal of Clinical Haematology Commentary

Mantle Cell Lymphoma and Hematopoietic Cell Transplantation in the Era of Cellular Therapy

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Introduction

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin Lymphoma (NHL) characterized by cyclin D1 translocations [1-3]. Outcomes are heterogenous, but the disease is generally incurable. High-risk patients been shown to have a median overall survival (OS) of only 37 months and 20% five-year OS [4-6]. In some patients, the disease is more indolent; such cases are associated with leukemic phase of the disease, SOX11-negativity, and mutated IGHV [7,8]. Additionally, even across SOX11 positive cases outcomes vary, with worse overall survival in MCL with cytoplasmic staining as compared to nuclear staining [9]. For patients with indolent clinical behavior, observation is frequently employed, and large case series suggest the possibility of prolonged periods before treatment becomes necessary, as long as 128 months, and favorable outcomes even once treatment has been initiated [7,10].

A variety of induction strategies have been published, but there remains no standard of care for upfront management of MCL. Outcomes after treatment with R-CHOP (rituximab, cyclophosphamide, vincristine, and prednisone) were shown to be suboptimal, with only 34% of patients achieving complete remission and 4-year OS of only 62% [11]. Thus more aggressive approaches are typically used for young patients, specifically regiments that integrate cytarabine such as alternating R-DHAP (rituximab, dexamethasone, high dose cytarabine, and cisplatin) with R-CHOP [12], R-DHAP alone [13], the "Nordic regimen" (dose-intensified rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone alternating with rituximab and high dose cytarabine) [14], and HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose methotrexate and cytarabine) [15,16]. More recently, an induction strategy of RBAC (rituximab, bendamustine, and cytarabine) has shown high rates of PFS, OS, and minimal residual disease (MRD) negativity [17]. For eligible patients who respond to induction, consolidative autologous hematopoietic cell transplantation (AHCT) in first remission is frequently offered. The majority of the data for such a strategy is retrospective [10,15,18-22], with only a single randomized trial conducted in the pre-rituximab era. In this randomized trial, most patients also received interferon maintenance after AHCT. Although a PFS benefit could be demonstrated, at 3 years, there was no OS benefit [23]. The lack of strategies that are widely used today, namely rituximab, intensive induction regimens, cytarabine based induction, and rituximab maintenance after induction raises questions as to the generalizability to a modern patient population. The role of consolidative AHCT remains uncertain, especially with the availability of targeted agents such as the BTK inhibitors ibrutinib, acalabrutinib, and zanubrutinib, as well as venetoclax, lenalidomide, and bortezomib, and the recent approval of chimeric antigen receptor T-cell (CART) therapy for relapsed mantle cell lymphoma.

Recent Data on the Role of AHCT

More recent analysis on the role of AHCT as consolidation has revealed mixed results. Multiple retrospective analyses have suggested that this therapy improves PFS and perhaps OS [10,15,18-21]. Several recent retrospective analyses have confirmed these observations. A study of the Spanish lymphoma group (GELTAMO) considered 268 patients with MCL who underwent AHCT as consolidation, and reported PFS of 38 months and OS of 74 months, with improved outcomes for patients in CR at the time of transplant [24]. An analysis of the National Cancer

Database utilized records from over 10,000 patients diagnosed between 2004 and 2012. 17% of these patients underwent AHCT. After propensity matched scoring, consolidative AHCT was associated with improved OS (hazard ratio of 0.46, 95% confidence interval 0.41-0.52, p<0.001); of note this data was presented in abstract form but not yet published [25]. In a large retrospective patient-level analysis of over 1000 patients aged 65 and younger with MCL [22], the investigators utilized a propensity score weighted (PSW) analysis to control for inherent bias in the selection of patients for AHCT. After a median of 6.3 years, the median PFS for the entire cohort was 5.2 years and median OS 11.5 years. Consolidative AHCT improved PFS after even after PSW; however, the OS benefit observed before PSW did not persist after PSW. Subgroup analysis suggested preferential OS benefit for certain patient populations, such as patients with a high risk MIPI score or the more aggressive blastoid variant of MCL.

Furthermore, the optimal induction regimen and conditioning regimen for AHCT remains unknown. For example, the prospective S1106 trial randomized patients with newly diagnosed MCL to R-HyperCVAD or bendamustine with rituximab, both of which were followed by consolidative AHCT. Though outcomes were favorable, with 5-year PFS of 62-66% and 5-year OS of 74-80%, the trial was closed early due to stem cell mobilization failures and thus was underpowered [26]. Similarly, the LYSA group reported an interesting novel strategy of switching from the most commonly used carmustine, etoposide, cytarabine, and melphalan (BEAM) based conditioning regimen prior to AHCT in MCL to bendamustine based, substituting bendamustine for the carmustine. This retrospective analysis suggested improved PFS but not OS when using this conditioning regimen [27].

In contrast, recent data demonstrating long-lasting disease control with regimens in which transplant in first remission has been omitted raises questions as to the role of autologous HCT in the modern era. For example, induction with R-HyperCVAD without HCT consolidation was shown to provide long term remissions, with a reported 3-year freedom from survival of 64% and OS 82% [28,29]. Several recent trials have utilized novel agents as part of induction, or in lieu of chemotherapy as first therapy, especially in the transplant ineligible population. First, the LYM-3002 trial was a randomized controlled trial of 487 patients with MCL ineligible for transplant. Patients were randomized to R-CHOP or VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicine, and prednisone). PFS was initially reported as 24.7 months for VR-CAP vs 14.4 months for R-CHOP [30], and the results were updated in 2018, when a benefit in OS benefit was shown with VR-CAP, with median OS 90.7 months for VR-CAP vs 55.7 for R-CHOP [31]. Second, Lenalidomide with rituximab was used as first line therapy in a small non-randomized study of 38 patients with median age 65; the overall response rate was 92%, with 85% 2-year PFS and 97% 2-year OS [32]. In 2018 an update on this trial was published and demonstrated 3-year PFS 80% and 3-year OS of 90%. Additionally, the authors reported minimal residual disease (MRD) status in 10 patients who had completed at least 3 years of follow up, 8 of whom were negative [33]. Finally, three recent early phase trials have demonstrated encouraging results for the up-front treatment of MCL with ibrutinib based regimens. An abstract presented at the 15th International Conference on Malignant Lymphoma in Lugano, Switzerland reported outcomes of 42 newly diagnosed patients treated with ibrutinib plus rituximab. The overall response rate (ORR) was 95%, with 69% CR, and MRD negative CR in 65% [34]. Similar results were presented by the Spanish Lymphoma Group at the 2019 American Society of Hematology Annual Meeting – 40 patient with newly diagnosed MCL and indolent disease were treated with ibrutinib and rituximab, with a reported ORR of 82% and CR rate of 75% [35]. And at the 2020 European Hematology Association annual congress, the OAsis trial reported on the combination of ibrutinib, obinutuzumab, and venetoclax as first-line therapy for 15 patients with MCL. The 1-year PFS was 93%, 1-year OS 100%, and the MRD negativity rate was reported at 100% [36]. Though encouraging, use of novel agents in the up-front setting remains investigational and should be limited to a clinical trial setting, especially given two occurrences of blastoid transformation in the first of these trials.

Maintenance Rituximab

In contrast to follicular lymphoma, where maintenance rituximab has shown only PFS but not OS benefit [37], maintenance rituximab in MCL has shown an OS benefit in multiple trials. In the non-transplant setting, rituximab maintenance for 2 years was first shown to be of benefit as compared to maintenance interferon alpha following induction with R-CHOP or rituximab, fludarabine, and cyclophosphamide [11]. This dataset was recently updated in 2019 and demonstrated ongoing PFS and OS benefit [38] Rituximab maintenance for 3 years following AHCT consolidation was similarly shown to improve both PFS and OS. Transplant eligible patients were induced with 4 cycles of D-HAP followed by consolidative HCT, followed by randomization to three years of maintenance rituximab versus observation. This trial reported 4-year PFS at 83% for maintenance versus 64% without, as well as improved OS (89 versus 80%, respectively) [13]. Of note, there is conflicting data as to the benefit of maintenance rituximab after bendamustine based induction in MCL, with data presented in abstract form but yet unpublished suggesting against a benefit [39], contrasting to a more recent abstract (also yet unpublished) that reported a PFS and OS benefit, potentially only for patients with a partial response to induction, for the same strategy [40].

Cellular Therapy

With the advent of CD19-directed CART-cell therapy in the treatment of relapse/refractory pediatric B-cell acute lymphoblastic leukemia/lymphoma and diffuse large B-cell lymphoma [41,42], there has been significant interest in expanding use to other subtypes of lymphoma. The ZUMA-2 trial treated patients with relapsed or refractory MCL with KTE-X19, an autologous CD19 CART-cell construct. Results were first reported at the 2019 American Society of Hematology annual meeting. Seventy-four patients were treated, of whom 43% had relapsed after prior AHCT and 100% had relapsed after treatment with ibrutinib, acalabrutinib, or both. Of evaluable patients, the ORR was 93% with 67% achieving CR. These data were subsequently published in the New England Journal of Medicine [43]. On February 10, 2020, the FDA granted priority review, and on July 24th, 2020 the agent, now named brexucabtagene autoleucel (Tecartus) was FDA approved for the treatment of relapsed or refractory MCL.

Commentary

MCL remains an incurable lymphoma that has an aggressive clinical course for the majority of patients. In the modern era, most patients, if young and eligible, are treated with intensive induction followed by consolidation with AHCT. This leads to mostly good outcome, with OS ranging 6-10 years with this strategy. However, a subgroup of patients are refractory to induction, or suffer early relapse. Furthermore, older patients may tolerate even less intensive induction poorly. Though multiple novel agents are currently available at relapse, the duration of response with these agents is suboptimal. Thus, new strategies are needed.

The approval of brexucabtagene autoleucel signifies that cellular therapy will now be an option for patients with relapsed and refractory disease. However, questions as to the optimal use of this agent remain, especially due to its significant risk for toxicities and cost. Should this therapy be reserved for patients with certain high-risk disease features, and if yes, how do we best define these patients? For example, the mantle cell lymphoma international prognostic index (MIPI) may allow identification of patients with high risk for poor outcome. This score combines age, performance status, lactase dehydrogenase level, and white blood cell count. Subsequently, Ki-67, an immunohistochemical marker of cell proliferation, was integrated into the MIPI score and further refined prognostication (biological MIPI or MIPI$_B$) [44]. Another feature may be certain genetic abnormalities such as TP53 alterations, which is an independent predictor of poor outcome. TP53 mutations, but not deletions, were shown to portend a dismal prognosis in 183 younger MCL patients. Intensive induction and AHCT may have limited utility in patients with such an alteration [45]. Additionally, TP53 mutations may predict resistance to ibrutinib as well, as suggested in a cohort 11 of 15 MCL patients with TP53 mutations who progressed on ibrutinib therapy [46], Finally, blastoid and pleomorphic variants of MCL may benefit from new approaches. These variants, which comprise up to 20% of cases [47,48] and may develop at relapse, are associated with poor outcome [49-51].

One strategy for such high risk patients has been allogenic HCT in first remission, which is sometimes employed for patients with high MIPI score, a TP53 mutation, or blastoid and pleomorphic variants [49], based solely on small series and retrospective data. Data supports a graft-versus-tumor effect of allogenic HCT [52] as well as prolonged remissions for some patients; however treatment related mortality remains an issue. The largest dataset characterizing outcomes with allogenic HCT comes from the EBMT Lymphoma Working Party, which pooled data from over 600 transplant centers and included 324 patients who underwent reduced intensity allogenic HCT between 2000 and 2008. The cumulative relapse rate was 25% at 1 year and 40% at 5 years [53]. One recent report of 42 patients with TP53 alterations who underwent allogenic HCT demonstrated 2 year PFS of 61% and 2-year OS of 78% [54], which suggests allogenic HCT as a viable strategy for such patients. Though the optimal management of patients with blastoid and pleomorphic variant is unknown, some experts recommend similarly consideration of allogenic HCT for these patients [49].

Another high-risk group may be patients who are MRD positive after induction or consolidative AHCT, or at first relapse. MRD negativity is associated with improved prognosis independent of clinical response and MIPI score [55]. MRD negativity is achieved at higher rates after consolidation with AHCT as compared to after RCHOP-like induction [56]. Rituximab maintenance appears to improve outcome irrespective of MRD status [57,58]. Additionally, re-treatment with rituximab may achieve MRD negativity in patients who were previously MRD negative but turned positive, allowing preemptive therapy for patients without clinically apparent disease [59]. However, whether the toxicities of more aggressive therapy are warranted for patients who are MRD positive after induction or AHCT, or for those who convert from negative to positive, remains to be seen. To this point, the ongoing E4151 clinical trial (NCT03267433) may shed light on this issue. This trial tests MRD after investigator's choice of induction, and for patients who are MRD negative, randomizes them to AHCT or no AHCT. Both groups are also treated with maintenance rituximab. The results are eagerly awaited.

While the data on and approval of brexucabtagene autoleucel is encouraging and exciting, it is unclear as yet to

define how this approval changes the current management of MCL, especially in the upfront setting. Even at relapse, many patients can achieve meaningful remission duration and quality of life with modern biological agents, although outcomes, particularly if poor risk features are present, remain suboptimal. Though a small number of patients on ZUMA-2 harbored TP53 mutations (17%) or had blastoid or pleomorphic morphology (31%) [43], the outcomes for patients were not stratified based on presence of these features. Follow up on the study was short at only 2 years, which is quite disparate to the 10 year follow up reported for some retrospective analysis of AHCT. No new toxicities were observed; however rates of adverse events, specifically immune effector cell-associated neurologic syndrome (ICANS), were high, with grade 3+ ICANS occurring in 31% of patients. Finally, the optimal therapy immediately prior to brexucabtagene autoleucel, as well as the optimal bridging therapy remains unknown.

Thus, for young, fit patients, intensive induction followed by consolidation with AHCT likely remains at this point in time the appropriate up-front management for most patients with MCL, as this strategy is associated with prolonged remission for many patients. Non-cytotoxic therapies may offer a benefit particularly in the face of risk factors that have been associated with chemo-refractoriness or brief treatment responses. As brexucabtagene autoleucel is used commercially in the relapsed and refractory setting, longer follow up as well as data on this agents in certain high risk patients with high MIPI score, TP53 mutations, blastoid and pleomorphic morphology, short remission duration, MRD positivity after induction, and those previously treated with a variety of second line therapies, will inform future decisions for the management of this challenging disease and help optimize outcomes particularly in the presence of adverse features.

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