Current Hematologic Malignancy Reports (2019) 14:239–246
https://doi.org/10.1007/s11899-019-00520-0

B-CELL NHL, T-CELL NHL, AND HODGKIN LYMPHOMA (J AMENGUAL, SECTION EDITOR)

Mantle Cell Lymphoma: Which Patients Should We Transplant?

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Published online: 19 June 2019

Abstract

Purpose of Review Mantle cell lymphoma is a CD5+ non-Hodgkin lymphoma associated with suboptimal outcome. Young, fit patients are generally offered intensive induction followed by autologous hematopoietic cell transplantation (AHCT) in first remission. Some patients may not benefit from this strategy.

Recent Findings Recent studies have investigated the role of AHCT in the modern era. First, an analysis of the National Cancer Database demonstrated improved progression-free survival (PFS) for consolidative AHCT. Second, a multi-center study associated consolidative AHCT with improved PFS even after propensity-weighted analysis. Improved overall survival (OS) for certain subgroups was suggested. Third, patients with p53 mutations derive little benefit from AHCT. Finally, retrospective series suggest certain high-risk patients may be considered for allogenic HCT.

Summary AHCT consolidation in first remission is associated with improved PFS even after adjustment for disease severity. An overall survival benefit has not been definitively shown. Patients with p53 mutations should be treated with novel agents.

Keywords Mantle cell lymphoma (MCL) · Autologous hematopoietic cell transplantation (AHCT) · Allogenic hematopoietic cell transplantation (alloHCT)

Introduction

Mantle cell lymphoma (MCL) is an uncommon hematologic malignancy comprising approximately 7% of all non-Hodgkin lymphoma (NHL) [1–3]. It is characterized by the t(11,14) (q13;q32) translocation, which leads to overexpression of cyclin D1 [4, 5]. The majority of cases are CD5 positive and cyclin D1 positive by immunohistochemistry, though CD5-negative and cyclin D1-negative patients have been described [6, 7]. Mantle cell lymphoma that is cyclin D1 negative can be identified by microarray profile [8]; SOX-11 positivity is almost universal in these cases [6]. Furthermore, t(11,14)-negative MCL has been described, with translocations involving CCND2 and CCND3 instead of the typical CCND1 [9]. The clinical outcomes of MCL are heterogeneous. While high-risk patients have a median overall survival (OS) of only 37 months and 20% 5-year OS [10–12], an indolent clinical course is seen in some patients, often associated with SOX11-negative and IGHV-mutated B cells [13, 14].

At present, there is no standard of care for upfront management. The initial treatment regimen is based on age, performance status, presence of symptoms, prognostic scoring, and comorbidities (Fig. 1). For patients with indolent clinical behavior, observation is sometimes employed; one report of 97 patients at a single institution found that 31 patients were observed for a range of 4 to 128 months; time to treatment did not predict OS [13]. More recently, a similar observation was reported from the British Columbia Cancer Agency, in which 17% of 440 patients with MCL were initially observed with median time to treatment of 35 months (range 5–79 months) [15•]. Historically, symptomatic patients with MCL were treated with CHOP (cyclophosphamide, vincristine, and prednisone) induction, adding in rituximab after its development, as with other subtypes of NHL [16, 17]. Due to relatively poor outcomes of MCL treated with R (rituximab)–CHOP, more intensive regimens were devised for patients who are young and fit. Based on this data, such patients are

This article is part of the Topical Collection on *B-cell NHL, T-cell NHL, and Hodgkin Lymphoma*

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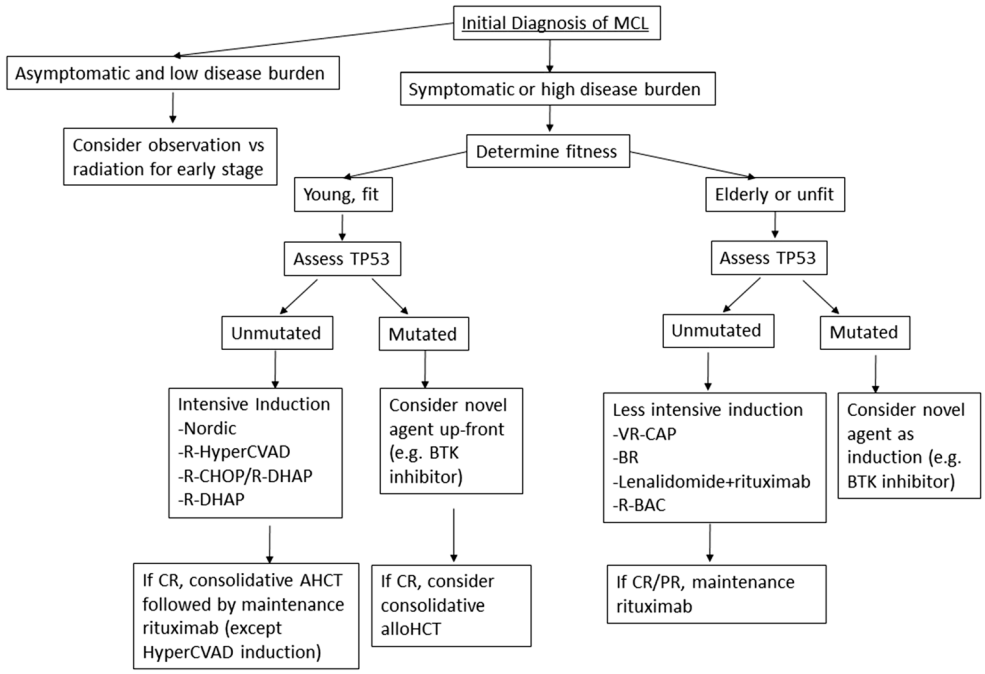

Fig. 1 Algorithm for determination of use of hematopoietic cell transplantation. AHCT, autologous hematopoietic cell transplantation; alloHCT, allogenic hematopoietic cell transplantation; Nordic, dose-intensified rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone alternating with rituximab and high-dose cytarabine; R-HyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-DHAP, rituximab, dexamethasone, high-dose cytarabine, and cisplatin; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicine, and prednisone; BR, bendamustine and rituximab; R-BAC, rituximab, bendamustine, cytarabine

now generally offered intensive induction therapy such as HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) [18, 19], the "Nordic regimen" (dose-intensified rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone alternating with rituximab and high-dose cytarabine) [20], alternating R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) with R-CHOP [21], and R-DHAP alone [22••]. All such intensive strategies incorporate cytarabine, which appears to be an important component of induction with an OS benefit in multiple trials [18, 20, 21]. Following induction, such patients are frequently offered consolidative autologous hematopoietic cell transplantation (AHCT) in first remission. The basis for this strategy is mainly on retrospective data [18, 23–27], and only one single randomized clinical trial in the pre-rituximab era has been performed evaluating AHCT consolidation. This trial randomized patients after induction to consolidative AHCT vs interferon maintenance [28]. An improved progression-free survival (PFS) of 39 vs 17 months was observed. Despite this, no benefit in overall survival was demonstrated. Furthermore, patients were not treated with rituximab, cytarabine-based induction, or rituximab maintenance, drawing questions as to the applicability to today's patients. Additionally, certain intensive cytarabine-containing induction regimens (e.g., R-HyperCVAD) have shown prolonged disease-free survival without using HCT consolidation. A report of 97 patients treated with R-HyperCVAD alternating with cytarabine and methotrexate without consolidative AHCT demonstrated a 3-year freedom from survival of 64% and OS 82% [29, 30]. A recently published retrospective series suggested similar outcomes after R-CHOP followed by consolidative AHCT and R-HyperCVAD without AHCT, with a median PFS of 3.2 and 4.0 years, respectively [30]. Finally, in the era of targeted agents such as bortezomib, lenalidomide, and ibrutinib, any survival benefit gained through aggressive induction therapy might be abrogated by integration of such agents into induction, or by use in later lines of therapy. The benefit of incorporating novel biological agents into upfront therapy regimens was highlighted by the recently updated LYM-3002 trial, a randomized controlled trial of 487 patients with MCL ineligible for transplant, who were randomized to either R-CHOP or VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicine, and prednisone). PFS was previously reported as 24.7 months for VR-CAP vs 14.4 months for R-CHOP [31], and the recent update demonstrated an impressive OS benefit, with median OS 90.7 months for VR-CAP vs 55.7 for R-CHOP [32••]. Lenalidomide with rituximab has also been investigated as upfront therapy in a single arm trial of 38 patients with median age 65 and demonstrated an overall response rate of 92% with estimated 85% 2-year PFS and 97% 2-year OS [33]. A

recently published 5-year update to this original trial confirmed ongoing good outcomes, with 3-year PFS and OS of 80% and 90%, respectively, and minimal residual disease (MRD) negativity in 8/10 patients who had completed at least 3 years of follow-up [34].

Prognostic Scoring

Due to the heterogeneous nature of the disease, several attempts have been made to identify high-risk populations who may benefit from more intensive induction. Efforts to better prognosticate resulted in the creation of the MCL International Prognostic Index (MIPI) that combines age, performance status, lactase dehydrogenase level, and white blood cell count. Patients are divided into low-, intermediate-, and high-risk groups, with median OS of not reached 51 and 29 months respectively [35]. The incorporation of Ki-67, an immunohistochemical marker of cell proliferation, into the MIPI score was shown to further refine prognostication (biological MIPI or $MIPI_B$) [36].

TP53 Mutations

Recently, investigation into the prognostic significance of certain genetic abnormalities has identified TP53 alterations as an important, independent predictor of poor outcome. In a cohort of 183 younger MCL patients, the prognostic significance of TP53 deletions and TP53 mutations (as identified by PCR), as well as NOTCH1 and CDKN2A mutations (also identified by PCR) was assessed. Patients with a TP53 mutation were found to have a median OS of 1.8 years, with half of patients relapsing at 1 year. The benefit of autologous HCT appeared to be minimal in this cohort. Interestingly, after multivariate analysis, only TP53 mutations—but not TP53 deletions (as opposed to mutations), NOTCH1 mutations, and CDKN2A deletions—were associated with worse OS in this analysis [37••]. One recent report identified TP53 mutations in 11 of 15 MCL patients who progressed on ibrutinib therapy, with only 2 patients exhibiting mutations in Bruton's tyrosine kinase (BTK), which raises concern that TP53 mutations may be a resistance mechanism even to novel agents [38]. A novel small molecule, nutlin-3, activates TP53 by targeting murine double minute 2 (MDM2), and has shown activity and synergy with bortezomib in relapsed MCL cell lines [39]. Strategies that integrate novel agents (e.g., ibrutinib, bortezomib, acalabrutinib, lenalidomide, and venetoclax) into induction regimens followed by consolidation with alloHCT in first remission may prove a viable strategy for patients with TP53 alterations, as discussed below [40].

Blastoid/Pleomorphic Variant

The blastoid and pleomorphic variants of MCL have been shown to have an inferior outcome as compared with MCL with typical morphology [41, 42] with significantly worse OS despite similar response rates to induction therapy [43]. Such variants comprise approximately 20% of cases [44, 45], though such a diagnosis can be challenging due to variation in morphology and inter-rater variability [45, 46]. It has been suggested that the difference in outcome may be primarily tied to higher Ki67 staining (which is common in blastoid and pleomorphic variants), rather than morphology itself [47]. p53 mutations are more commonly found in blastoid and pleomorphic variants, and higher incidence of p53 protein overexpression has also been reported; both are predictive or worse outcome [48–51]. Patients with blastoid and pleomorphic variants have a more rapid relapse and worse OS even when treated with intensive induction. Despite this observation, patients are generally offered the same induction strategies as patients with normal variant MCL, mainly due to the lack of clearly superior management strategies. Some experts recommend alloHCT in first remission for patients with blastoid and pleomorphic variant [41], although the benefit has not been clearly demonstrated.

Maintenance Rituximab

Maintenance rituximab after induction chemotherapy with or without consolidation with AHCT has shown an OS benefit in multiple trials. In a randomized trial of 560 transplant-ineligible patients, with the use of maintenance rituximab after R-CHOP or rituximab, fludarabine, and cyclophosphamide (R-FC), 4-year OS was 87% with maintenance rituximab vs 63% with interferon alpha [52]. More recently, rituximab maintenance was shown to improve PFS and OS in younger patients after 4 cycles of D-HAP followed by consolidative HCT. In a recent randomized controlled trial, patients were randomized to 3 years of maintenance rituximab or observation following induction therapy and autologous HCT. Four-year PFS was 83% for maintenance vs 64% with observation, and 4-year OS was 89 vs 80% [22••]. There is no randomized data to suggest the use of maintenance rituximab should be based on MRD status after induction; however, rituximab maintenance does appear to negate the prognostic significance of MRD positivity after induction [53]. Specifically, rituximab maintenance was shown to prolong PFS in both MRD-positive and MRD-negative patients [54]. Additionally, pre-emptive rituximab therapy appears to convert the majority of patients who, despite MRD negativity after induction and consolidative AHCT, convert to MRD positive, thereby again achieving a MRD-negative state [55]. However, information

on whether this strategy translates into improved survival is currently not available.

Role of Consolidative AHCT: Recent Data

As noted above, the use of consolidative AHCT for young, fit patients with MCL is mainly based on retrospective experience showing favorable outcomes compared with historical controls [18, 23–27], with only one single randomized clinical trial that was conducted in the pre-rituximab era [28]. A recently reported analysis of the National Cancer Database sought to define the impact of consolidative AHCT using a population-based study. Over 10,000 patients diagnosed between 2004 and 2012 were analyzed, 17% of whom underwent consolidative AHCT. The authors utilized propensity score matching in an attempt to control for confounding variables. After adjustment, consolidative AHCT was associated with improved OS, with a hazard ratio of 0.46 (95% confidence interval 0.41–0.52, $p < 0.001$) [56•]. Though impressive in scope and reflective of the "real-world" experience, the small number of patients undergoing AHCT and lack of control for poor PS or comorbidities limit the generalizability of this study.

The largest series comes from a retrospective analysis that reported the outcome of over 1000 patients aged 65 and younger with MCL pooled from 25 academic medical centers, with both authors participating [57••]. The majority of patients were treated with intensive induction as well as with AHCT in first remission—44% and 64%, respectively. Patients were excluded if they were not offered AHCT due to poor PS or comorbidities, and a propensity score–weighted (PSW) analysis was performed in an effort to control for inherent bias in the selection of patients for AHCT. After a median of 6.3 years, the median PFS and OS for the entire cohort were 5.2 years and 11.5 years, respectively. A clear benefit in progression-free survival was demonstrated, a finding that persisted after propensity-weighted analysis, with median PFS 49 months without AHCT vs 78 months with AHCT. Although an OS benefit was seen before PSW, this was no longer statistically significant after PSW. However, on subgroup analysis after PSW, certain subgroups appeared to derive the most benefit, including patients with high MIPI scores, those treated with non-intensive induction (CHOP based or bendamustine based), those who did not receive cytarabine with induction, and those with blastoid or pleomorphic morphology. With the caveats of a retrospective review, this publication lends support to the use of AHCT in first remission based on the clear PFS benefit in all subgroups even after propensity-weighted analysis, and suggests a potential OS benefit in certain subgroups (Table 1).

Role of alloHCT: Recent Data

Limited data exists utilizing alloHCT in the management of MCL. An early report of 16 patients demonstrated the graft-vs-tumor effect of alloHCT in patients with MCL [58]. Another retrospective study reported the outcome of 36 patients treated with alloHCT at Moffitt Cancer Center, of which 7 patients were transplanted in first remission. The median PFS and OS were 53 and 86 months, respectively, and 5-year PFS and OS 49% and 54%, respectively [59]. A multicenter trial from the UK analyzed the outcome of 25 patients, all of whom received alloHCT as part of initial therapy. The authors reported a 2-year PFS and OS of 68 and 80%, respectively, and 5-year PFS and OS 56% and 75% [60]. The EBMT Lymphoma Working Party reported their experience with alloHCT in MCL and pooled data from over 600 transplant centers and included 324 patients who were treated with reduced intensity alloHCT between 2000 and 2008. Of these patients, 43% of whom had received > 3 prior therapies. With a median follow-up of 72 months, the cumulative incidence of relapse was 25% at 1 year and 40% at 5 years. PFS and OS were significantly worse for patients with chemorefractory disease at transplant, but not different for patients who were treated with alloHCT in first remission as compared with later line [61].

Limited data suggests alloHCT may be appropriate for patients who relapse after AHCT [62] and for those with TP53 alterations, based on a recent analysis of 42 patients with MCL treated with alloHCT [40]. This study reported no difference in outcome between patients with and without TP53 alterations, raising the possibility that alloHCT may prove a viable strategy for patients with these patients. Finally, expert opinion also recommends consideration of alloHCT for patients with blastoid and pleomorphic variants as noted above [41].

Conclusions and Future Directions

MCL remains an incurable malignancy with no clear standard of care for frontline management. AHCT prolongs PFS for many patients with MCL, but no OS benefit has been clearly demonstrated as yet. With the FDA approval of multiple highly active novel agents (e.g., ibrutinib, bortezomib, acalabrutinib, and lenalidomide) in the relapsed setting, these agents are actively being integrated into earlier lines of therapy; this may lead to diminishing returns for high-dose chemotherapy and abrogate any benefit of consolidative AHCT. Furthermore, the impact of AHCT is likely differential, with some patients deriving great benefit, while others may not experience any benefit at all (Table 2). Refined risk stratification before and after induction therapy may help to inform the decision to transplant or not in first remission. As an example, an ongoing ECOG-ACRIN clinical trial (NCT03267433) seeks to prospectively evaluate the role of AHCT for patients

Table 1 Selected studies evaluating consolidative autologous hematopoietic cell transplantation (AHCT) after induction

Trial	Trial category	Induction	Maintenance therapy	*N*	Outcome
Milpied et al., 1998 [26]	Retrospective	CHOP-like	No	18 (17 auto, 1 allo)	- DFS at 4 yr 48% - OS at 4 yr 80%
Decaudin et al., 2000 [25]	Retrospective	Multiple regimens, no R	No	24	- EFS at 3 yr 55% - OS at 3 yr 68%
Vandenberghe et al., 2000 [23]	Retrospective	Not specified, no R	No	199	- OS 76% at 2 yr and 50% at 5 yr
Dreyling et al., 2005 [28]	Prospective, randomized	CHOP	Yes: randomized to IFN alpha until progression vs observation	122	- Median PFS 39 mo with AHCT vs 17 mo without - 3-yr OS 83% with AHCT vs 77% without
Geisler et al., 2008 [20]	Prospective, non-randomized	R-CHOP alternating with R-high-dose cytarabine	No	160	- PFS at 6 yr 66% - OS at 6 yr 70%
Tam et al., 2009 [24]	Retrospective	Multiple, R with induction in 40%	No	121	- PFS at 6 yr 39% - OS at 6 yr 61%
Le Gouill et al., 2017 [22••]	Prospective, 86% received AHCT (non-randomized)	R-DHAP	Yes—randomized to R for 3 yr vs observation	299	- PFS at 4 yr 68% - OS at 4 yr 78%
Sawalha et al., 2017 [55]	Retrospective, propensity scoring	Multiple	Yes: R (subset)	16,035	- OS: hazard ratio with transplant = 0.46 (95% CI 0.41–0.52)
Gerson et al., 2019 [56•]	Retrospective, propensity-weighted analysis	Multiple	Yes: R (subset)	1029	- PFS: hazard ratio with transplant = 0.70 (95% CI 0.59–0.84) - OS: hazard ratio with transplant = 0.87 95% CI 0.69–1.1)

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; *INF*, interferon; *R*, rituximab; *DHAP*, dexamethasone, high-dose cytarabine, cisplatin; *DSF*, disease-free survival; *OS*, overall survival; *auto*, autologous; *allo*, allogenic; *EFS*, event-free survival; *PFS*, progression-free survival; *CI*, confidence interval; *mo*, months; *yr*, years

who achieve MRD negativity after induction using high-throughput sequencing of the immunoglobulin receptor. If positive, MRD assessment may become an important part of the determination of the appropriateness for individual patients.

Chemotherapy-free induction regimens are already a reality in MCL, and novel combinations of biological are quickly moving to the forefront. Results of such trials, including the chemotherapy-free regimens of ibrutinib plus venetoclax (NCT03112174), lenalidomide plus rituximab (ECOG-E1411 NCT 01415752), and rituximab plus ibrutinib and lenalidomide (NCT 03232307), are eagerly awaited. Finally, with the advent of CD-19-directed chimeric antigen receptors T cells (CART), where early reports indicate promising activity in MCL [63], it may supplant AHCT and alloHCT. While an accepted mainstay of the management of young fit patients

Table 2 Specific populations who may derive benefit/no benefit from consolidative autologous hematopoietic cell transplantation after induction

Population	Potential benefit	Unlikely to benefit	Uncertain
Blastoid/pleomorphic morphology	+		
Less-intensive induction (e.g., R-CHOP, BR)	+		
No cytarabine given with induction	+		
HyperCVAD as induction		+	
High MIPI score	+		
TP53 mutation		+	
Novel agent with induction			+

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; *BR*, bendamustine rituximab; *MIPI*, mantle cell lymphoma international prognostic index; *HyperCVAD*, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine

with MCL for decades, the current role of hematopoietic cell transplantation in MCL is rapidly evolving. Going forward, a more refined approach is warranted for each individual patient, accounting for TP53 mutations, MRD, and use of novel agents in order to appropriately inform the risk and benefit calculation.

Compliance With Ethical Standards

Conflict of Interest James N. Gerson reports that he is on the Advisory board for Seattle Genetics.

Stefan K. Barta reports personal fees from Janssen, grants from Takeda, grants from Merck, grants from Celgene, grants from Bayer, grants and personal fees from Seattle Genetics, personal fees from Curis, and personal fees from Mundipharma.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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