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Treatment of mantle cell lymphoma: Current approach and future directions

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Abstract

Although mantle cell lymphoma has been described as "moderately aggressive" it has become clear that it carries a worse long-term prognosis than other subtypes of non-Hodgkin's lymphoma. In recent years, this has prompted numerous clinical trials of novel and more aggressive therapies in hopes of impacting these poor outcomes. These include more intensive combination chemotherapy regimens, monoclonal antibody therapy in conjunction with other treatments or conjugated to radioactive isotopes, high-dose chemotherapy followed by autologous or allogeneic stem cell transplantation, and newer targeted therapies based on increasing understanding of the molecular pathways of this malignancy.

Keywords: Mantle cell lymphoma; Clinical trials; Non-Hodgkin's lymphoma

Mantle cell lymphoma (MCL) is a distinct non-Hodgkin's lymphoma (NHL) subtype first put forward by an international consensus panel [1] in 1992 and then incorporated into the REAL-WHO classification system in 1994 [2]. It comprises a group of subtypes including those previously classified as centrocytic, lymphocytic or diffuse small-cleaved cell lymphoma. This subtype represents approximately 4–6% of all non-Hodgkin lymphomas [3,4] with an incidence of 2–3 per 100,000 years and with a median age at diagnosis of 63 years. Diagnosis is based on histologic, immunophenotypic,

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cytogenetic and molecular criteria, most importantly the characteristic t(11;14) (q13;q32) translocation which places the immunoglobulin heavy chain locus upstream of the BCL1 gene causing overexpression of its gene product—cyclin D1. In a series of 81 patients diagnosed from 1988 to 1990 MCL carried the worst 5-year failure free survival rate of any of the major subtypes (∼11%) and median overall survival of less than 3 years [5].

Because of this poor prognosis there has been an ongoing search for improved treatments. In contrast to the more common aggressive lymphomas (e.g. diffuse large B-cell lymphoma (DLBCL)) there is not one regimen that has demonstrated superiority or equivalence compared to multiple alternatives, hence there is little agreement amongst clinicians regarding appropriate first-line therapy. The purpose of this review is to consider the rationale and available data for commonly used treatment regimens and to survey promising future therapies currently being developed and tested.

1. Diagnosis

Selection of appropriate treatment regimens for patients with MCL and the pursuit of continually better regimens relies upon uniformity of diagnostic criteria for this entity. Clinically, MCL has a male predominance and a tendency for extra-nodal involvement including the bone marrow, spleen and GI tract (particularly the colon). The histologic pattern may be diffuse, nodular, mantle-zone, or a combination of the three with some reports suggesting a better prognosis for those with a mantle-zone pattern [6]. The malignant cell type of classic MCL is composed of small to medium sized lymphocytes with irregular nuclei and condensed chromatin, though there also exists a broad spectrum of morphologic features ranging from small cell to blastoid types and these may reflect distinct biologic characteristics. Patients can present de novo or during the course of their disease with a blastoid variant composed of medium size rounded nuclei with dispersed chromatin, scant cytoplasm and a high mitotic index, resembling lymphoblasts. Interestingly, one series found that although this "transformation" was found in 32% of patients during the course of disease, 70% of autopsy specimens revealed some site of blastoid disease [7].

The immunophenotype of MCL corresponds to mature, naïve pre-germinal center B cells with expression of CD19, CD20, CD22, CD79A, IgM and/or IgD. They are usually $CD5^+$ and $CD43^+$, but $CD10^-$ and $CD23^-$. Though there are exceptions, this basic schema can be helpful in distinguishing between the common small B-cell NHL subtypes (see Table 1).

The most distinctive aspects of MCL are its numerous genetic aberrations that are important both in its diagnosis and in its pathophysiology. The most pathognomonic of these is t(11;14) (q13;q32) translocation. Other well-described mutations include loss of the ataxia telangiectasia mutated (ATM) gene (frequently through 11q deletion), deletions of 9p21 and 17p13 (thought to be important for the loss P16 and P53, respectively) and 8q22–24 amplification (thought to be important for its consequent over-expression of c-myc) [8]. The t(11;14) translocation juxtaposes the BCL1 gene to the B-cell immunoglobulin transcription enhancer and results in the over-expression of cyclin D1 and cell-cycle dysregulation. In approximately 50% of cases the translocation occurs in one identified region called the major translocation cluster. In most of these cases PCR can be used to diagnose and (more importantly) to follow response to treatment at the molecular level. Generally fluorescence in situ hybridization (FISH) assessment for the translocation is the gold standard when definitive genetic testing is required. This technique is 95% sensitive for the specific translocation and can be performed on paraffin fixed specimens.

Table 1
Immunophenotype of small B-cell NHL subtypes [73]

	SLL/CLL	MCL	Follicular	MZL
CD20	+	+	+	+
CD5	+	+	−	−
CD23	+	−	−	−
CD43	+	+	−	+
CD10	−	−	+	−

Abbreviations: SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; MZL, marginal zone lymphoma.

2. Prognosis

There are numerous clinical and pathologic parameters of negative prognostic significance including: age, poor performance status [9], splenomegaly, nodal (as opposed to non-nodal leukemic) disease [10], anemia, non-mantle zone histology [6], blastoid morphology, high mitotic index [11], topoisomerase IIα [12], cyclin D1 [13] and c-myc [14] over-expression. More recently, it has been shown that specifically V_H3-21 gene rearrangement (compared to other gene rearrangements) correlates with an improved prognosis [15]. Also, RNA expression profiling, has identified gene sets, which can prognosticate MCL patients more accurately than clinical parameters (such as morphology) [16]. In the latter study, genes associated with a high proliferation index were associated with aggressive disease and a shorter survival. In this study, patients could be stratified into subsets with median survival differences of greater than 5 years. Certainly some of these parameters will be helpful in the future to guide appropriate therapy for each patient; however, there has been no evidence so far that higher risk groups have greater benefit from more aggressive treatment regimens.

3. Treatment approaches

Considering the poor prognosis of all current therapies there is currently no standard treatment for the disease. Treat-

Table 2
Summary of mantle cell lymphoma treatment options

Treatment	*N*	ORR (%)	CR (%)	PFS/EFS[a]	OS	Median follow-up
CHOP [28]	60	75	7	19 m	82%	18 m
R-CHOP [28,29]	62	94	34	20 m	84%	18 m
	40	96	48	16.6 m		25 m
HCVAD (>65 years) [20]	25	92	68	15 m	92%	17 m
R-HCVAD [31]	97	100	87	64%[a]	82%	3 y
HCVAD-ASCT [21]	45	94	38	1°: 72%[a]	1°: 92 %	3 y
				2°: 17%[a]	2°: 25 %	
ASCT [38] 1° therapy	62	98	81	39 m	83%	3 y
ASCT (GELA)[37] 1° and 2° therapy	24	100	79	55%[a]	68%	3 y
ASCT–R-HDS [46] 1° therapy	28	100	100	79%[a]	89%	35 m
ASCT (EORTC) [40] 1° and 2° therapy	195	88	67	33%	50 %	5 y
Bexxar®-ASCT [58] 2° therapy	16	100	91	61%	93 %	3 y
Allo BMT [49] 2° therapy	16	100	86	55%	55%	3 y
NMA-allo [52,52] 2° therapy	18	100	94	82%[a]	86%	26 m
	33	85	75	60%[a]	65%	24.6 m

CHOP: cyclophosphamide, adriamycin, vincristine, prednisone; R: rituximab; HCVAD: high-dose cytarabine, cyclophosphamide, vincristine, adriamycin, dexamethasone; 1° therapy: initial treatment; 2° therapy: treatment of relapsed or refractory disease; HDS high-dose cyclophosphamide, high-dose cytarabine, high-dose melphalan and high-dose mitoxantrone plus melphalan; NMA: non-myeloablative.

[a] For those timepoints measuring EFS where events are usually defined as progression or death from any cause.

ment options are varied and in general the more aggressive approaches improve progression free survival (PFS) however, no therapy to date is curative. Various approaches are summarized in Table 2.

3.1. Chemotherapy

Though available data have not suggested an optimal first line treatment for MCL, the standard of care has developed from the understanding that the clinical course of MCL is aggressive; treatments have been similar to those for other aggressive lymphomas. An anthracycline-based approach has been standard although most randomized clinical studies have not proven a survival advantage attributable to the inclusion of anthracycline [17–19].

Before the introduction of the monoclonal antibody rituximab, the most commonly used first line regimen was cyclophosphamide, adriamycin, vincristine and prednisone (CHOP), which has shown complete response (CR) rates ranging 20–80%, median failure free survival (FFS) of 10–16 months, and median overall survival (OS) of 3 years. Other approaches have used dose intensified, CHOP-like regimens. Several trials at the MD Anderson Cancer Center have utilized the intensive leukemic regimen hyper-CVAD (a dose intense, hyper-fractionated CHOP-like combination in combination with high-dose methotrexate (MTX) and cytosine arabinoside (ara-C)) both as primary and as salvage therapy. The number of cycles of therapy has varied from four to eight depending on whether or not stem cell transplant was included as primary treatment. In a study of primary therapy for 25 patients over age 65 years, overall response rates (ORR) of 92%, CR rates of 68% and median duration FFS of 15 months were reported [20]. Another study of 45 patients with advanced stage MCL (50% previously treated) received four cycles of hyper-CVAD and patients that achieved a CR went on to autologous stem cell transplant (ASCT) or allogeneic transplant. The ORR was 93.5% with 38% of patients achieving a CR [21]. Previously untreated patients had a 3-year OS and event free survival (EFS) of 92% and 72%, respectively, significantly higher than CHOP-treated historical controls with 3-year OS and EFS rates of 25% and 17%. Although it is difficult to dissect the impact of hyper-CVAD from that of the preparative regimen for ASCT (cyclophosphamide and total body irradiation) it does seem that this intensified regimen is at least as effective for primary or salvage therapy as its predecessor. It must be emphasized these results represent single-institution data and have not been validated by other centers or in a randomized study.

Another approach has been to incorporate regimens used in salvage therapy of other lymphoma subtypes as part of a primary treatment regimen for mantle cell. In a phase II, trial of 28 patients with aggressive MCL, four cycles of CHOP induced CR in only 7%. Remarkably, for those patients with a partial response, the addition of DHAP to CHOP in a sequential fashion induced a complete response in 84% of the remaining patients compared to CHOP alone [22].

Despite the lack of randomized studies evaluating the different treatment regimens for MCL, it appears that newer, more intensive approaches may result in superior ORR compared to CHOP or CHOP-like therapy. The superiority of these regimens may be due to the use of high-dose AraC, which is therefore being tested in ongoing clinical trials.

Whether the improved remission rates translate into improved survival is unclear as the median follow-up of all these studies in short (<3 years). Patients should be enrolled on clinical trials in order to evaluate these new approaches.

3.2. Rituximab

Because MCL is a B-cell malignancy that expresses CD20, the anti-CD20 antibody (Ab), rituximab, has been studied

as a single agent in mantle cell lymphoma with response rates of 20–40% [23–26]. As in other lymphoma subtypes, it has also been studied as longer term maintenance therapy. A randomized trial followed 61 MCL patients who did not progress during rituximab induction therapy assigned to either maintenance (every 2 months for four treatments) rituximab or observation [27]. In this trial, maintenance therapy showed a statistically non-significant trend towards increased EFS of 12 months versus 6 months. More commonly, rituximab has been studied in combination with chemotherapy such as CHOP (i.e. R-CHOP). A prospective study by the German Lymphoma Study Group (GLSG) randomized untreated patients with advanced disease to conventional CHOP or R-CHOP. Responding patients received six cycles of CHOP or R-CHOP followed by a second randomization to α-interferon maintenance or a myeloablative consolidation followed by ASCT (depending on the patient's age). Of the 122 patients evaluated prior to transplant, R-CHOP was resulted in a significantly superior ORR and CR rates compared to CHOP alone: 94% versus 75% ($p = 0.005$) and 34% versus 7% ($p = 0.00024$) [28]. Although the addition of rituximab increased time to treatment failure (TTF) from 14 to 21 months, median PFS and OS were not statistically improved. The lack of an effect on OS is possibly due to the confounding effect of the second randomization.

Similar results were achieved in an earlier phase II study in which R-CHOP yielded ORR and CR rates of 96% and 48% with a median PFS of 16.6 months [29]. However, in the latter study patients obtaining a molecular CR did not have significantly improved PFS.

The GLSG have also recently updated preliminary results of a prospective randomized trial of rituximab in combination with fludarabine, cyclophosphamide, mitoxantrone (FCM) compared to FCM alone in patients with relapsed or refractory MCL. Of 50 patients randomized, R-FCM achieved higher CR and overall median survival times: 29% versus 0% ($p = 0.004$) and 2.5 years versus 0.9 years ($p = 0.031$) [30]. After the superiority of the rituximab arm was demonstrated, an additional 45 patients were assigned to combined immunotherapy and confirmed these promising results.

Rituximab has also been studied in phase II trials with more aggressive regimens such as hyper-CVAD. In 56 untreated patients, R-hyper-CVAD for at least 6 cycles yielded a CR rate of 90% and 2-year FFS and OS were 72% and 90% (median follow-up of 14 months). Subset analysis revealed that patients younger than 65 years treated with R-hyper-CVAD without ASCT did as well historical controls receiving the same hyper-CVAD regimen with ASCT. In a recent update of this trial on 97 patients the 3-year FFS and OS were 64% and 82%, respectively [31]. The toxicity of this regimen, is of concern as five deaths were reported during treatment and four occurrences of myelodysplasia or leukemia developing in patients during CR. More recently, a modified hyper-CVAD regimen that added rituximab induction and maintenance therapy but removed MTX and ara-C was shown to have comparable efficacy as primary therapy with ORR of 85%, CR of 70% and median progression free survival (PFS) and OS not reached after 22.5 months [32]. While the results of this modified approach compare favorably with the original regimen from MD Anderson, longer follow-up along with validation by other centers will be required. Taken together, these data suggest that the addition of rituximab to standard induction regimens appears to result in improved response rates.

Two studies have suggested that post-transplant rituximab increases the clinical and molecular response rate of MCL patients receiving ASCT [33,34]. In one study of advanced stage MCL all patients who received post-transplant rituximab were alive without clinical or molecular relapse at 239 days post-transplant. The treatment was well tolerated and encouraging albeit longer follow-up is needed.

3.3. Autologous stem cell transplant

Myeloablative dose chemotherapy followed by stem cell transplantation can improve survival in other subtypes of lymphoma. This treatment has also been applied to MCL with mixed results [35–37]. Most studies have utilized this approach in patients with relapsed or refractory disease.

Recently, the European MCL Network reported the results of the first prospective randomized trial comparing myeloablative radio-chemotherapy versus α-interferon maintenance therapy in 122 patients that achieved at least a PR after a CHOP-like induction regimen [38]. ASCT consisted of a mobilization regimen of dexamethasone, BCNU, etoposide, ara-C and melphalan (dexa-BEAM) followed by consolidative therapy with total body irradiation (TBI) and high-dose cyclophosphamide (CTX). Compared to the IFN-α arm, patients in the ASCT arm experienced a significantly longer PFS with a median of 39 months versus 17 months ($p = 0.0108$), but no difference in 3-year OS: 83% versus 77% ($p = 0.18$).

Similar outcomes have been described in other mature phase II studies; with a median follow-up of four years, a trial of 25 patients were treated with rituximab plus induction chemotherapy followed by high-dose chemotherapy ± radiotherapy and ASCT [39]. Induction allowed all patients to achieve either CR (36%) or PR (64%) and 3 year OS is 80%.

Data from other trials have also suggested that ASCT is of greater benefit earlier in the course of disease. A retrospective analysis of the European Blood and Bone Marrow Transplant registries of 195 MCL patients treated with ASCT reported OS at 2- and 5-year as 76% and 50% with PFS as 55% and 33%, respectively [40]. Patients who were transplanted in first CR were 33% less likely to die from MCL than patients with chemosensitive disease transplanted later in their course. Results were similar in a retrospective analysis of 69 patients at Stanford and City of Hope who underwent ASCT [41]. Patients who were in first CR at the time of transplant had 3- and 5-year OS/DFS rates of 93%/74% and 77%/50%, respectively. In comparison, the OS/DFS rates at

3 and 5 years for patients who were not in first remission at the time of transplant were 64%/51% and 39%/21%. The median time to relapse in the group transplanted in first CR was 32 months compared to 10.5 months.

As described above, hyper-CVAD remission induction for MCL has yielded 3 year OS and EFS rates were 92% and 72% [21]; these compare favorably with the randomized trial described using CHOP or CHOP-like regimens [38]. A retrospective analysis by Conde et al. evaluated the induction regimens used for MCL [42,43]. An international database of 119 patients with MCL who had received ASCT between 1988 and 2002 was evaluated. The induction regimens were primarily hyper-CVAD and CHOP-like therapy and the estimated 10-year OS and DFS were impressive at 50% and 32%, respectively. Patients receiving hyper-CVAD had a 4-year DFS of 68% compared to 33% in patients treated with other regimens. It should be noted that none of these regimens employed rituximab along with the induction chemotherapy. Though there were differences in baseline characteristics between these two groups, these data suggest the need to evaluate the role of these newer therapies in prospective randomized trials.

3.4. Role of purging

As in other B-cell malignancies, the role of "purging" of the mobilized autologous stem cell product prior to transplant has been examined in MCL. One such approach is the use of ex vivo treatment of stem cell products with anti-CD20 Ab and complement-mediated lysis. A study assessing for minimal residual disease (MRD) at the time of transplant using PCR amplification of the Bcl-1/IgH translocation product showed ex vivo purging to be effective in only 2 of 19 patients [44]. Alternatively, the use of in vivo purging using rituximab has been more promising with evidence of clinical and molecular remissions. The first of these studies demonstrated that stem cell products collected after high-dose cyclophosphamide and cytarabine still had a high rate of MRD versus a parallel cohort that received rituximab after high-dose therapy (60% versus 7%; $p = 0.007$) [45]. The significance of this study for MCL treatment is limited by its inclusion of non-MCL sub-types of NHL. A follow-up study treated 28 MCL patients with cisplatin or doxorubicin-based debulking chemotherapy followed by high-dose sequential therapy with rituximab and ASCT [46]. The 54-month OS and EFS rates were 89% and 79%, respectively as compared to historical controls with 42% and 18%. Again, after cyclophosphamide, cytarabine and rituximab mobilization, 19 out of 19 evaluable patients had stem cell products that were without MRD. Adding cytarabine with rituximab in vivo purging to a CHOP-like regimen compared to the latter regimen alone, showed benefit both in pre-transplant CR rate and post-transplant PCR negativity [47].

Cumulatively these data suggest that in addition to its above noted uses in remission induction and salvage therapy, rituximab also may have an important pre-transplant role both as part of conditioning regimens and for in vivo. Again, none of these studies have a long enough follow-up to assess the impact on overall survival.

3.5. Allogeneic transplantion

Although ASCT has demonstrated prolonged survival for patients with MCL, there has been no evidence of cure with these modalities so more aggressive approaches are still being evaluated. As allogeneic transplantation has demonstrated increased effectiveness in other lymphoma sub-types because of a graft-versus-lymphoma (GVL) effect [48], this approach has been considered for MCL patients refractory to other therapies (or occasionally those in first CR). Along with degree and duration of clinical response, evaluation for evidence of this GVL effect has been an important outcome in such trials. In an early study, 16 patients underwent allogeneic transplant after myeloablative regimens of cyclophosphamide plus TBI (11 patients) or BEAM (3 patients) or a non-ablative preparative regimen consisting of cisplatin, cytarabine and fludarabine [49]. OS and failure-from-progression (FFP) at 3 years were both 55% (28–83%) including a high treatment related mortality of 38%. The suggestion of a GVL effect was evident in several patients who converted to a molecular CR months after the completion of chemotherapy and coincident with the development of graft-versus-host disease (GVHD). Another trial using a myeloablative regimen in 20 MCL patients has reported nine patients alive and disease free 1–9 years post-transplant [50]. This and other [51] reports of long-term DFS raise the question as to whether this approach has curative potential for some patients.

Because MCL occurs more in older patients who are not candidates for myeloablative allogeneic transplants, there has been consideration of non-myeloablative regimens followed by allogeneic transplant (NMA-allo). Early results have been mixed. A recent trial investigated non-myeloablative transplant in 18 patients with MCL who had failed multiple prior chemotherapies including 28% who had failed prior ASCT. CR was achieved in 17 of 18 patients and with a median follow-up of 26 months the estimated 3-year survival rate and current PFS was 85.5% and 82%, respectively [52]. Another study of 33 MCL patients using a non-myeloablative conditioning regimen of fludarabine and 2 Gy TBI followed by related or unrelated allogeneic transplantation demonstrated 2-year OS and DFS of 65% and 60% with a non-relapse mortality of 24% [53]. Still, the outcomes for this approach have been mixed as a larger trial of non-myeloablative chemotherapy followed by allogeneic transplant included 22 patients with MCL and yielded 2-year OS and PFS of 12% and 0% [54].

These data plus other recent retrospective analyses [55,56] suggest that myeloablative conditioning or, in older patients, non-myeloablative conditioning, followed by allogeneic stem cell transplantation is feasible for MCL patients in first CR and after salvage therapy. The high treatment related mortality rates are consistent with results from other lymphoma

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