Evaluation and Management of Disease Transformation in Waldenström Macroglobulinemia

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KEYWORDS

- Diffuse large B-cell lymphoma • Waldenström macroglobulinemia
- Histologic transformation • *MYD88*^{L265P} mutation

KEY POINTS

- Histologic transformation should be suspected in patients with WM that develop constitutional symptoms, rapidly progressive lymphadenopathy, extranodal involvement, sudden rise in LDH levels, and/or decreased serum IgM levels.
- Tissue biopsy is mandatory to diagnose histologic transformation and may be directed by clinical or radiologic features (ie, by site of rapidly enlarging lymph nodes, or by site of increased avidity on ^{18F}FDG-PET/CT).
- Histologic diagnosis is required to confirm transformation to high-grade lymphoma. Most transformation events are caused by DLBCL variants, but rarely other aggressive lymphomas may occur.
- Treatment with intermediate-dose chemoimmunotherapy, such as R-CHOP, is the preferred option. CNS prophylaxis with HD-MTX should be considered if feasible and consolidation with autologous SCT should be discussed in fit patients responding to chemoimmunotherapy. If available, enrollment in clinical trials should be recommended.

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INTRODUCTION AND HISTORICAL PERSPECTIVES

Waldenström macroglobulinemia (WM) can undergo histologic transformation (HT) into aggressive lymphoma, usually diffuse large B-cell lymphoma (DLBCL) of the activated B-cell (ABC) subtype.

This phenomenon was first reported by Wood and Frenkel[1] in 1967 in a patient with WM who developed multiple lymphoblastic lymphosarcomatous masses. Initial case reports described HT in WM as "reticulum cell sarcoma" or "immunoblastic sarcoma."[2–6] A case series of 16 patients highlighted common features, such as rapid growth of lymph nodes, physical deterioration, decrease in serum monoclonal IgM level, and a poor prognosis with a median survival of 2 months.[7]

More recent retrospective studies have reported survival of approximately 1.5 to 2.7 years with chemoimmunotherapy (CIT).[8–10] Patients with HT often present with high rates of extranodal involvement and high International Prognostic Index (IPI) scores. The importance of *MYD88* status in conferring risk for HT and as a prognostic factor after HT has been reported in multiple studies.[10–12] CIT treatments used in de novo DLBCL are less successful in HT with reported median survival after HT of 16 months to 2.7 years,[10,11] resulting from refractory disease or relapse, and a high frequency of central nervous system (CNS) involvement.[11,13] Clinical trials are difficult to conduct in such a rare disease; however, novel agents may be trialed in these patients. The role of stem cell transplantation (SCT) is not established.

DISCUSSION

Epidemiology and Risk Factors

HT to aggressive B-cell lymphoma is estimated to occur in 1% to 4% of patients with WM.[9,10] Two large centers in the United States have reported 5-, 10-, and 15-year cumulative incidence rates of transformation of 1%, 2%, and 4%; and 2%, 5%, and 6%. The 6-year cumulative incidence of HT was reported to be 8% in the fludarabine arm and 11% in the chlorambucil arm in the randomized WM1 trial, which compared fludarabine and chlorambucil.[14] The median time to transformation is reported to be 4.3 to 4.6 years.[8–11] About 15% to 25% of patients are reported to be treatment-naive at the time of HT.[8–10]

The high rate of HT in patients treated with nucleoside analogues found in some retrospective studies[15] has not been confirmed in the randomized WM1 trial.[14] The risk of HT in patients treated with Bruton tyrosine kinase (BTK) inhibitors is unknown.[16–19]

Data on risk factors for development of HT in WM are sparse. The $MYD88^{WT}$ genotype has been shown to be independently associated with a higher risk of HT.[10,12] HT occurred in 15% of $MYD88^{WT}$ compared with only 1% in $MYD88^{L265P}$ mutated patients, with a 10-year cumulative incidence of 20% and 1%, respectively.[12] Another study reported that $MYD88^{WT}$ was associated with a shorter time to HT (hazard ratio, 7.9; $P = 0.001$) (**Fig. 1**); furthermore, it was the only factor associated with an increased risk of HT in a multivariate analysis (odds ratio, 7; $P = 0.003$).[10] There are several mutations reported in $MYD88^{WT}$ patients affecting nuclear factor-κB signaling (*TBL1XR1*, *NFKBIB*, *NFKBIZ*, *NFKB2*, *MALT1*, *BCL10*), DNA damage repair (*TP53*, *ATM*, and *TRRAP*), and epigenomic regulators (*KMT2D*, *KMT2C*, and *KDM6A*), many of which are also reported in DLBCL; these are hypothesized to contribute to the increased risk of HT.[20]

Clinical Features

Patients with WM who develop rapidly enlarging lymphadenopathy, progressive constitutional symptoms, physical decline, rise in serum lactate dehydrogenase (LDH) levels, and/or extranodal involvement should be suspected to have HT. Most

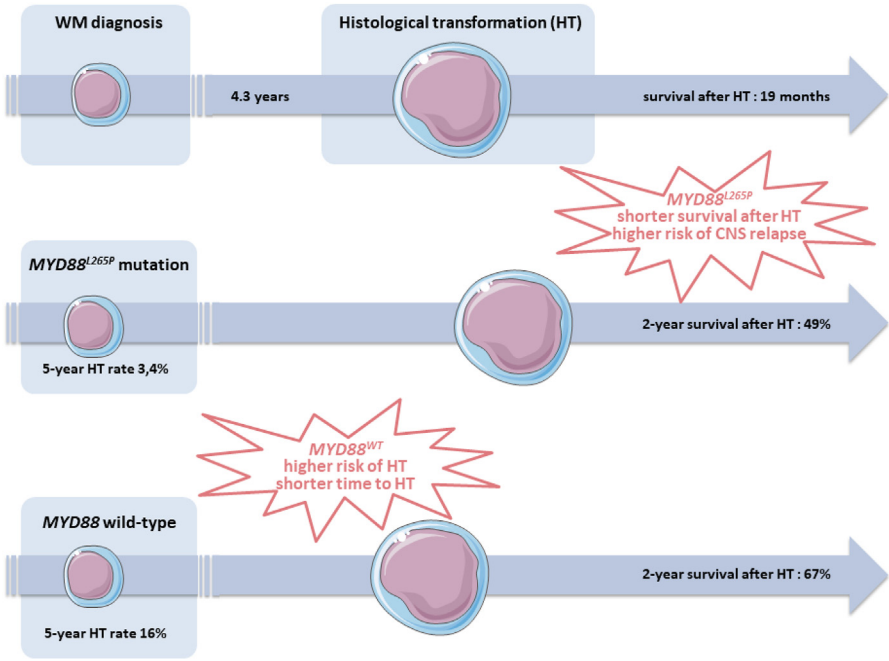

Fig. 1. Schematic representation of HT in WM. Transformation rates, time to HT, and survival after HT according to *MYD88* status. (*From* Durot et al.[65])

patients with HT present with advanced Ann Arbor stage disease and high IPI score. Transformed WM is often associated with a decrease in serum IgM levels.[8,10] This may be because of HT developing while patients are responding to treatment of underlying WM and/or be related to a process of dedifferentiation. Extranodal involvement, which is rare in WM (4.4%), is a common feature in HT, and is reported to occur in 70% to 90% of patients (**Table 1**).[8–10,21] Although skeletal bone and bone marrow are the most common sites of involvement, there is a high frequency of CNS, testis, and skin involvement.[8,13,22] The de novo DLBCL counterpart of transformed *MYD88*-associated sites (CNS, testis) is now a distinct entity, called "large B-cell lymphomas of immune-privileged sites" in the recent World Health Organization Classification of hematolymphoid tumors.[23] It includes aggressive tumors of ABC phenotype, characterized by concomitant *MYD88* and *CD79B* mutations and poor prognosis.[24]

Diagnosis

Histologic confirmation of high-grade lymphoma with a tissue biopsy is the gold standard to diagnose HT. The choice of the site of biopsy may be directed by clinical features (ie, site of rapidly increasing lymphadenopathy), or preferably, by high maximum standardized uptake value (SUVmax) on ^{18}fluorodeoxyglucose-PET/computed tomography (^{18F}FDG-PET/CT).[8,25] The median SUVmax in a study of 24 transformed patients with WM was 15 (range, 4–38) and 71% presented with an SUVmax greater than 10[8], contrasting with 35 patients with nontransformed WM, in which 77% had positivity on ^{18F}FDG-PET/CT with a mean SUVmax of 3 (range, 1–8).[26] Further studies are needed in WM to evaluate positive and negative predictive values of ^{18F}FDG-PET/CT in HT diagnosis.

Table 1
Summary of the main published retrospective studies on HT in WM

Study	Garcia et al,[7] 1993	Lin et al,[27] 2003	Castillo et al,[9] 2016	Zanwar et al,[10] 2020	Durot et al,[8] 2017
Number of patients	16 (including 14 from literature review)	12	20	50	77
Incidence of HT (%)	NA	13	2.4 at 10 y	4.7 at 10 y	NA
Treatment naive before HT (%)	7	25	25	15	21
Median time from WM diagnosis to HT (y)	4	3.7	4.4	4.5	4.6
Male sex (%)	69	33	60	66	65
Median age at HT	NA	68	70	66	71
Extranodal involvement (%)	NA	100	84	72	91
Elevated LDH (%)	NA	80	67	53	72
Front-line treatment of HT					
R-CHOP-like (%)	NA	33	80	80	85
HyperCVAD (%)	NA	58	0	0	0
Rituximab-containing regimen (%)	NA	42	85	69	83
Autologous SCT (%)	NA	8	30	NA	15
Overall response rate (%)	NA	NA	NA	73	61
Complete response (%)	NA	NA	77	53	48
Progression-free survival (mo)	NA	NA	NA	10	9
Survival after HT (mo)	2	75 died within 10 mo	32	38	16

Abbreviations: CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; NA, not available; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
From Durot et al.[65]

Histology

Although most transformation events are associated with the emergence of DLBCL variants,[8–10,27] cases of anaplastic large-cell lymphoma, T-cell lymphoma, plasma cell proliferation and Epstein-Barr virus-associated DLBCL, lymphomas intermediate between DLBCL and Burkitt lymphoma, or aggressive lymphomas, not otherwise specified have also been described.[28]

The histologic appearance of DLBCL is characterized by large B cells with frequent mitotic figures, resembling centroblasts (75% of cases) or immunoblasts (25% of cases).[27] Ki67 is high with a positive expression in 80% to 90% of the malignant cells.[8,9] Using the Hans algorithm,[29] about 80% to 90% of cases are classified as non-germinal center B-cell subtype.[8,10] CD20 is positive in 95% of patients using immunohistochemistry, CD10 in 7% to 10%, BCL6 in 34% to 78%, MUM1 in 78% to 100%,

BCL2 in 86% to 89%, and MYC in 44% to 7%.[8–10] Most transformed WM (83%–100%) are negative for Epstein-Barr virus-encoded RNA in situ hybridization.[8–10,27] *MYC* gene rearrangement is seen in 11% to 38% of patients by fluorescence in situ hybridization,[8,10] but cases with *MYC* and *BCL2* and/or *BCL6* rearrangements ("double-hit" or "triple-hit" lymphomas) are not seen; a series of seven cases reported no cases that were found using fluorescence in situ hybridization.[30]

Biology and Clonal Evolution

Most (80%) high-grade transformation (ie, Richter syndrome) in chronic lymphocytic leukemia are clonally related to the underlying indolent condition.[31] In transformed WM, analysis of light-chain expression is reported to be similar in WM and transformed lymphoma cells in 75% to 100% of cases.[8,10] Using *MYD88*^{L265P} mutation and immunoglobulin gene heavy chain variable region analysis, an Australian study on four cases of transformed and paired antecedent WM samples showed that DLBCL can be clonally related to WM or occur as a new clone independent of WM (synchronous de novo DLBCL).[32] More recently, MYD88L265P mutation, immunoglobulin gene heavy chain variable region rearrangement analyses, and next-generation sequencing were reported in seven patients who presented with lymphoplasmacytic lymphoma and DLBCL, with DLBCL being the first malignancy in some cases.[30] Three mechanisms of DLBCL development have been proposed: (1) "true" transformation with sequential mutation acquisition from WM to DLBCL, (2) clonal identity with a common origin but divergent evolution of WM and DLBCL, and (3) different lymphomas. A branching model of evolution has also been described with a transformed clone that did not evolve from the same subclone responsible for progression.[33]

There is limited understanding of the biology of transformation of WM to DLBCL. Whole-exome sequencing in four patients with WM who transformed to DLBCL showed genetic heterogeneity and complexity.[33] HT is associated with a much higher frequency of mutations and time of transformation is inversely related to mutation burden. Possible driver mutations within a high proportion of tumor cells that are conserved during transformation are identified. Additional and recurrent mutations are gained at HT including *PIM1*, *FRYL*, *PER3*, *PTPRD*, and *HNF1B*. *CD79B* mutations are postulated to be biomarkers predicting HT, being found mutated in three of the four evaluated cases.[33]

Prognosis

The outcome of patients with transformed WM is generally poor with overall survival (OS) after HT reported to vary from 16 to 38 months (see **Table 1**).[8–11] Zanwar and colleagues[10] reported a hazard ratio of 5.1 for death (95% confidence interval, 3.8–6.8; $P < 0.001$) and Castillo and colleagues[9] reported a much shorter median OS from diagnosis of WM to all-cause death of 9 versus 16 years for HT and non-HT patients.

Durot and colleagues,[8] in their cohort of 77 patients with transformed WM, showed that two or more lines of treatment of WM, prior rituximab exposure, time to transformation 5 or more years from WM diagnosis, elevated serum LDH, and less than partial response (PR) to DLBCL treatment were associated with shorter OS after transformation in univariate analysis. Time to transformation 5 or more years and elevated serum LDH retained significance in multivariate analysis. Longer time to transformation is also reported to adversely affect prognosis in Richter syndrome,[34] and outcome in transformed follicular lymphoma is worsened by previous therapy[35]; but there are conflicting data on the prognostic value of time to transformation in follicular lymphoma.[35,36] Concurrent diagnosis of indolent lymphoma and DLBCL has been reported to be associated with comparable outcomes to de novo DLBCL.[37] However,

because there were only two cases of transformed lymphoplasmacytic lymphoma in the cohort and no cases of transformed WM, there are no data on how prognosis of HT in WM compares with DLBCL.[37]

The best evidence on prognosis in WM with HT comes from an international collaborative study in the form of a validated prognostic index, called the transformed Waldenström International Prognostic Index (tWIPI).[11] A training cohort of 133 patients was used to develop the index; three variables including high serum LDH (scored with 2 points), platelet count less than 100×10^9/L, and previous treatment of WM (both scored with 1 point each) were noted to be independently predictive of 2-year survival after HT. Three risk groups were defined: low-risk (0–1 point; 24% of patients), intermediate-risk (2–3 points; 59%), and high-risk (4 points; 17%), with 2-year survival rates of 81%, 47%, and 21%, respectively. This model was validated in an independent cohort of 67 patients and displayed high discrimination and calibration properties (Harrell C-index of 0.75 in the training cohort and 0.79 in the validation cohort).

In Richter syndrome, patients with clonally unrelated DLBCL, which accounts for 20% of cases, experience longer survival, comparable with patients with de novo DLBCL.[31] The clonal relationship between WM and DLBCL was not reported in the largest retrospective studies that analyzed clinical outcomes, precluding any conclusion of potential prognostic value of clonal relationship in transformed WM.[8–11]

MYD88 mutation status at time of WM seems to have a prognostic impact on survival after HT (see **Fig. 1**).[11] In the tWIPI study, *MYD88* mutation status was known in 64 patients. Patients with $MYD88^{L265P}$ mutation had a significantly lower 2-year survival rate after HT compared with patients with $MYD88^{WT}$ disease (49% vs 67%; $P = 0.018$). This finding, which is consistent with previous studies in de novo DLBCL,[38,39] requires confirmation in a larger cohort. The presence of $MYD88^{L265P}$ mutation has also been associated with a higher incidence of CNS relapse in transformed WM (17% vs 0% for $MYD88^{WT}$ patients).[13] In this study, the median survival after CNS relapse was 6 months.

Treatment Options

Given the rarity of the disease, there have been no prospective trials in transformed WM. Patients with transformed WM are usually excluded from clinical trials or represent a minority of patients among transformed indolent lymphomas. The recommendations on the treatment of transformed WM are therefore drawn from retrospective studies and from transformation of other indolent lymphomas. It should be kept in mind that patients can also be treated with palliative intent, reflecting the underlying comorbidities and frailty of this population.

Chemotherapy

Treatment of transformed WM usually mirrors DLBCL and involves use of CIT. Data on response rates and outcomes are based on retrospective studies. The most frequent frontline regimen used in HT is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)-like CIT, which has been reported in 62% to 85% of cases, with overall response rates of 61% to 79%, complete response (CR) rates of 48% to 77%, and short median progression-free survival of 7 to 10 months (see **Table 1**).[8,10]

Data on more aggressive CIT regimens, such as R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) or ACVBP (doxorubicin, cyclophosphamide, vinblastine, bleomycin, and prednisone), are limited. In the study by Lin and colleagues,[27] 7 of 12 patients were treated with hyper-CVAD (fractioned cyclophosphamide, vincristine, doxorubicin, and dexamethasone), of which six died

within the first 5 months; one patient was alive at 8 months after consolidation with BEAM (carmustine, etoposide, cytarabine, and melphalan) and autologous SCT (autoSCT). Other therapies used in frontline setting are DHAP (dexamethasone, cytarabine, and cisplatin), ICE (ifosfamide, cyclophosphamide, and etoposide), and GEMOX (gemcitabine and oxaliplatin).[8]

Autologous stem cell transplantation

High-dose chemotherapy consolidation followed by autoSCT in first CR (CR1) can be considered in fit patients with transformed indolent lymphomas, because of the poor prognosis associated with HT; however, it should be recognized that this is not based on strong evidence.[40–45] The retrospective studies available in transformed indolent lymphoma are mainly in transformed follicular lymphoma and have heterogeneous populations including patients in first or later remission and variable treatment regimens.[41–45] There are few WM patients with HT in these reports. There have been two case reports of transformed WM treated with allogeneic SCT[40] and only one WM case in a recent study of 49 patients investigating autoSCT in first remission.[46]

In the setting of transformed WM, a study reported one patient treated with hyper-CVAD followed by BEAM (carmustine, etoposide, cytarabine, and melphalan) conditioning and autoSCT.[27] In another cohort, 6 out of 20 patients received autoSCT with no survival benefit ($P = 0.13$).[9] This may be partly related to the fact that five patients underwent autoSCT at HT relapse and only one while in CR1. Another study did not find survival benefit in patients who underwent autoSCT ($P = 0.4$); however, only a few patients (3 out of 50) received it as consolidation after frontline therapy.[10] Ten (13%) of 77 patients underwent autoSCT, including seven after first-line treatment of HT in another series,[8] with a plateau emerging with use of autoSCT in patients responsive to frontline therapy (median OS not reached vs 4.5 years for responding non-autoSCT patients), although this was not statistically significant ($P = 0.33$).

Given that a randomized trial to elucidate the role of autoSCT in transformed WM is not likely to be feasible because of the rarity of the diagnosis, the role of consolidative autoSCT as part of frontline therapy for transformed WM in eligible patients remains unclear. Nevertheless, most patients with transformed WM are unfit (because of age or comorbidities) or do not achieve adequate response to proceed to autoSCT.

Central nervous system prophylaxis

Relapse within the CNS occurs in 2% to 5% of DLBCL cases and is associated with poor prognosis with median OS of 5 to 6 months.[47–49] The incidence of CNS relapse in transformed WM has been recently reported, with a 3-year rate of 11%, which is similar to that observed in the CNS-IPI high-risk group.[13,47] Patients with kidney/adrenal involvement and/or *MYD88*^{L265P} mutation have a higher incidence of CNS relapse. Optimal CNS prophylaxis in these situations remains unknown because there is some evidence that intrathecal therapy is ineffective[50] and recent studies have reported lack of benefit with high-dose methotrexate (HD-MTX).[51,52] If HD-MTX is considered, recent studies in DLBCL suggest its delivery could be deferred beyond cycle 1 of R-CHOP (on Day 1 and especially before Day 10) or even until R-CHOP completion to avoid toxicities and/or R-CHOP delays.[53,54]

Novel agents

BTK inhibitors,[16–19] and BCL2 inhibitors, such as venetoclax,[55] show efficacy in WM and likely represent potential therapeutic options in transformed WM, given that expression of BCL2 is seen in 90%, and *MYD88*^{L265P} mutation in 67% of cases. R-CHOP with concomitant ibrutinib showed improvement in event-free survival, progression-free survival, and OS in patients aged less than 60 years in a phase 3

study in ABC DLBCL.[56] However, patients older than 60 years showed increased toxicity with this regimen. Efficacy and safety of venetoclax associated with R-CHOP in the phase 2 CAVALLI study showed increased myelosuppression and potentially improved outcomes in BCL2+ subgroups.[57]

Chimeric antigen receptor T cells

CD19-targeted chimeric antigen receptor (CAR) T-cell therapies can lead to durable responses in relapsed/refractory (R/R) DLBCL, including transformed follicular lymphomas.[58,59] These therapies were initially used in third-line treatment of R/R DLBCL; however, their role as second-line treatment has now been established.[60,61] In R/R WM, efficacy of CD19-directed CAR T-cell therapy has been reported in three heavily pretreated patients, none of whom had transformed WM.[62] Abramson and colleagues[63] described use of lisocabtagene maraleucel in DLBCL transformed from indolent lymphoma. Eighteen patients had nonfollicular transformed indolent lymphomas, including two transformed WM; however, individualized data were not available from the study.[63] The potential effectiveness of CAR T-cell therapy in R/R transformed WM has recently been demonstrated in a case report of a 71-year-old man who received two prior lines of treatment of WM before HT. R-CHOP in

Table 2
Key points on clinical presentation, diagnosis, prognosis, and treatment of HT in WM

Clinical presentation	High frequency of extranodal involvement, in particular skeletal bone, bone marrow, and *MYD88*-associated sites (CNS, testis, skin) Advanced stage and high IPI score Elevated LDH Decrease in serum IgM spike
Diagnosis	Suspect HT in case of physical deterioration in patients with WM, rapid growth of lymph nodes, extranodal involvement, and/or rise in LDH level Tissue biopsy required for diagnosis of HT Tissue biopsy may be directed by ^{18F}FDG-PET/CT
Prognosis	Poor outcome after HT Prognosis index (tWIPI) based on 3 predictors of 2-y survival after HT: elevated LDH (2 points), platelet count <100 $\times$ 10^9/L (1 point), and any previous treatment of WM (1 point) Presence of $MYD88^{L265P}$ mutation: lower 2-y survival after HT and higher risk of CNS relapse
Treatment	Treatment with similar regimens used in de novo DLBCL (R-CHOP-like regimen) ORR 61%–79% CR 48%–77% PFS 7–10 mo Insufficient data on more aggressive chemoimmunotherapy regimens Use of second-line chemoimmunotherapy regimens, such as RICE, are reasonable options for those rare patients that may have received anthracyclines for WM CNS prophylaxis should be considered (HD-MTX) Autologous SCT as consolidation in fit patients responding to induction chemotherapy should be considered Insufficient data on allogeneic SCT, novel agents, CAR T cells

Abbreviations: CAR, CD19-targeted chimeric antigen receptor; CR, complete response; ^{18}FDG-PET/CT, ^{18}fluorodeoxyglucose-PET/computed tomography; HD-MTX, high-dose methotrexate; ORR, overall response rate; PFS, progression-free survival; tWIPI, transformed Waldenström International Prognostic Index.

From Durot et al.[65]

combination with ibrutinib was used at HT. He then failed R-DHAP + autoSCT and was treated with axicabtagene ciloleucel following cytoreduction with fludarabine and cyclophosphamide, which induced CR on PET/CT and bone marrow biopsy, which was maintained at 1 year.[64] More data on use of this therapy for HT are needed.

SUMMARY

This paper details the clinical presentation, diagnosis, prognosis and treatment of histological transformation in WM (**Table 2**). The outcome of patients with transformed WM in retrospective studies remains poor. Whether increasing use of novel agents, such as BTK inhibitors or CAR T-cell therapy in WM, will change the frequency and outcomes of HT in WM remains unknown.

A deeper understanding of the biology and the pathophysiology of the disease, and prospective studies using novel therapies, are needed to improve clinical outcomes. This is particularly relevant for elderly, frail patients who are not fit for intermediate-dose CIT and stem cell transplant. International collaborations are required to deepen the understanding of this rare condition.

CLINICS CARE POINTS: RECOMMENDATIONS FOR MANAGEMENT OF HISTOLOGIC TRANSFORMATION IN WALDENSTRÖM MACROGLOBULINEMIA

Recommendations for optimal management of HT in WM are limited by the lack of prospective data and are therefore drawn from retrospective studies.

- HT should be suspected in patients with WM that develop constitutional symptoms, rapidly progressive lymphadenopathy, extranodal involvement, sudden rise in LDH levels, and/or decreased serum IgM levels.
- Tissue biopsy is mandatory to diagnose HT and may be directed by clinical or radiologic features (ie, by site of rapidly enlarging lymph nodes, or by site of increased avidity on ^{18}FDG-PET/CT).
- Histologic diagnosis is required to confirm transformation to high-grade lymphoma. Most transformation events are associated with the emergence of DLBCL variants, but other aggressive lymphomas may occur rarely.
- Treatment with intermediate-dose CIT, such as R-CHOP, is the preferred option. CNS prophylaxis with HD-MTX should be considered if feasible and consolidation with autologous SCT should be discussed in fit patients responding to CIT. If available, enrollment in clinical trials should be recommended.

AUTHORSHIP

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