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Report of Consensus Panel 6 from the 12th International Workshop on Waldenstrom's Macroglobulinemia on Diagnosis and Management of Transformed Waldenstrom's Macroglobulinemia

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ABSTRACT

Histological transformation (HT) in Waldenström's macroglobulinemia (WM) is a rare complication and despite growing literature in the last years, no consensus recommendations exist. Consensus Panel 6 (CP6) of the 12th International Workshop on Waldenström's Macroglobulinemia (IWWM-12) was convened to review the current data on transformed WM and make recommendations on its diagnosis and management. The key recommendations from IWWM-12 CP6 included: (1) in case of suspected HT, tissue biopsy is the gold standard for diagnosis; (2) the initial work-up should comprise ^{18}FDG-PET/CT for the evaluation of disease extent and, for patients with clinical suspicion or for high-risk patients (CNS-IPI, multiple and/or specific extranodal involvements), cerebrospinal fluid examination and brain MRI; (3) standard dose chemoimmunotherapy (CIT) such as R-CHOP (rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone) or R-CHP + polatuzumab vedotin are the preferred front-line regimen; (4) CNS prophylaxis and consolidation with autologous stem cell transplantation (SCT) can be considered according to de novo diffuse large B-cell lymphoma (DLBCL) guidelines; (5) T-cell-engaging therapies (CAR T-cells, bispecific antibodies) should be used in the relapse/refractory setting according to international guidelines for DLBCL and local access to these therapies. Key unanswered questions include the role of *TP53* abnormalities and *CXCR4* mutations on the risk of HT, the prognostic role of clonal relationship between WM and HT, the optimal front-line therapy (addition of novel agents to CIT, dose-intensive CIT, consolidation with autologous SCT), and the sequence of T-cell-engaging therapies. International collaboration and consideration of and inclusion in clinical trials is critical to address these issues in a rare patient population.

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Introduction

Histological transformation (HT) in Waldenström's macroglobulinemia (WM) is a rare but serious complication with poor outcomes [1–3]. Despite an increase in related literature in recent years, no consensus recommendations have been established. Consensus Panel 6 (CP6) convened at the 12th International Workshop on Waldenström's Macroglobulinemia (IWWM-12) seeks to address the key gaps in knowledge, review current data on transformed WM, and provide recommendations on its diagnosis and management.

1. Which WM patients are at risk for developing transformed WM?

HT in WM is a rare complication, occurring in less than 5% of patients. Two studies have reported a similar incidence of HT in WM. In the Dana Farber Cancer Institute (DFCI) report, 20 patients with transformed WM were identified from a cohort of 1466 WM patients, with 5-, 10- and 15-year cumulative incidence rates of 1%, 2.4% and 3.8% [1]. In the Mayo and Reims study (50 of 1147 patients with HT), the 5-, 10- and 15-year cumulative incidence rates were 2.4%, 4.7% and 5.7% [2]. Similar results have also been reported recently from the Surveillance, Epidemiology, and End Results-17 (SEER-17) database which included 36 transformed lymphoplasmacytic lymphoma (LPL)/WM out of 1622 LPL/WM patients with a cumulative incidence of 2.2% at a median follow-up of 7.7 years [3].

While the median time to transformation from the diagnosis of WM is ~ 4.3 to 4.5 years, HT can occur at anytime during the course of the disease (at diagnosis, in patients responding to WM therapy and as late as 20 to 25 years after the diagnosis of WM) [1,2,4]. About 15% to 25% of patients are treatment-naïve at the time of HT [2,4].

The role of prior therapy, in particular multiple and historically used treatments, have been implicated to be a risk factor of WM transformation in some retrospective studies [5]. This risk seems independent of nucleoside analogs. In the randomized WM1 trial comparing fludarabine and chlorambucil in the frontline treatment of WM, the 6-year cumulative incidence of HT was 8% in the fludarabine arm and 11% in the chlorambucil arm [6].

MYD88 wild-type genotype has been associated with a higher risk of HT (15% of $MYD88^{WT}$ vs 1% of $MYD88^{L265P}$ WM patients) and a shorter time to HT (HR 7.9, $P = .001$) [2,7]. It is plausible that the increased risk of HT could be linked to several mutations present in $MYD88^{WT}$ patients affecting nuclear factor-ĸB signaling, DNA damage repair, and epigenomic regulators, which has also been reported in DLBCL [8]. On univariate analysis, an elevated LDH at diagnosis of WM is associated with a shorter time and higher risk of HT. No other clinical or biological baseline characteristics have been found to be a predictor of HT [2].

- Current available data suggest that the $MYD88^{WT}$ genotype is the only risk factor identified for developing HT, and is also associated with a shorter time to HT.
- The panel suggests that the role of *TP53* abnormalities and *CXCR4* mutations should be assessed in future studies on risk factors for developing HT.
- The panels also highlights that all current data on risk factors for transformed WM have been established in the chemoimmunotherapy era and there is paucity of data in patients treated in the BTK inhibitor era. Whether contemporary therapies have a lower risk of HT or not remains to be determined.

2. What should be the initial work-up in WM patients with suspected histological transformation (HT)?

HT should be suspected in patients with WM who develop constitutional symptoms, rapidly enlarging lymphadenopathy, extranodal involvement (ie bone, CNS, testis, skin), and/or elevated LDH levels [1,2,9]. In some cases, a decreased in serum IgM level may be observed [9].

Surgical excisional biopsy is highly recommended and is considered the gold standard for diagnosis of HT [10,11]. A fine-needle aspiration is not adequate to establish a diagnosis of HT. A core-needle biopsy may be an acceptable alternative, in elderly and/or unfit patients, sites not amenable for excision and/or emergency therapy required. Surgical and core-needle biopsies should be directed by targeting sites of highest avidity on a ^{18}FDG-PET/CT Table 1.

All HT diagnoses should be reviewed by an expert hematopathologist. The recommended immunohistochemical panel should include B-cell markers (CD20, CD79a ± PAX5), CD10, BCL6, MUM1, MYC, BCL2, Ki67 and EBER. The cell-of-origin subtypes (germinal center B-cell [GCB] and activated B-cell [ABC]) should be included in the histological report and can be determined according to institutions' standards (gene expression profiling or immunohistochemistry with the Hans algorithm) [12,13]. The panel suggests performing FISH testing of *MYC* and *BCL2* (and *BCL6*) rearrangements if possible. While data are lacking on the prevalence of high grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* rearrangements in transformed WM, it should be noted that in contrast to most cases of HGBL where *MYC* and *BCL2* rearrangements are of GCB profile, in transformed WM about 80% to 85% of are of non GCB subtype based on the Hans algorithm [9].

The panel recommends repeating BM examination if cytopenias are present to determine if the BM is infiltrated by the underlying WM, the DLBCL component or other etiology.

^{18}FDG-PET/CT should be performed at diagnosis of HT for evaluating disease extent and as a baseline reference for further assessment of the response, as well as identifying an optimal site to biopsy. The median SUVmax in a study of 24 patients with transformed WM was 15 (range, 4-38), contrasting with a mean SUVmax of 2.9 in 35 patients with nontransformed WM [9,14].

CNS involvement is frequent in transformed WM, affecting approximately a quarter of patients with HT or relapsed disease [15]. For CNS evaluation, the panel proposes cerebrospinal fluid (CSF) examination and brain MRI in case of clinical suspicion of CNS involvement in patients with neurological symptoms or for high-risk patients according to the CNS international prognostic index (CNS-IPI) [16]. CSF examination should ideally include cytomorphology analysis, flow cytometry and molecular diagnostics (Ig gene rearrangement and/or $MYD88^{L265P}$ mutation).

- The panel recommends that all patients undergo baseline ^{18}FDG-PET/CT for disease extent evaluation and for assessment of response using the Deauville score and the Lugano classification.
- Tissue biopsy is the gold standard to diagnose HT in WM and may be directed by clinical or radiologic features (ie, by site of increased avidity on ^{18}FDG-PET/CT).
- The panel encourages clinicians to be aware of the risk of CNS involvement in transformed WM and to consider extensive CSF examination and brain MRI in the initial work-up for high-risk patients.
- Subsequent therapy for the DLBCL component should be proposed only to patients who have had an inadequate response per the Lugano criteria and should not be based on serum IgM levels reflecting the underlying WM component.

3. Should clonal relationship testing be performed in all cases of HT?

Table 1
Summary of the key recommendations from the IWWM-12 consensus panel 6 on diagnosis and management of transformed WM.

Risk factors, clinical presentation and diagnosis
1. WM patients with *MYD88* wild-type genotype are at higher risk of HT.
2. HT should be suspected in patients with WM who develop constitutional symptoms, rapidly enlarging lymphadenopathy, extranodal involvement, and/or elevated LDH levels.
3. Surgical excisional biopsy is considered the gold standard for diagnosis of HT.
4. All HT diagnoses should be reviewed by an expert hematopathologist.
5. The cell-of-origin subtypes (GCB and ABC) should be included in the histological report and can be determined according to institutions' standards (GEP or IHC with the Hans algorithm).
6. In case of cytopenias, repeating BM examination at HT to determine if the BM is infiltrated by the underlying WM, the DLBCL component or other etiology is recommended.
7. ^{18}FDG-PET/CT should be performed at diagnosis of HT for evaluating disease extent and as a baseline reference for assessment of the response.
8. CSF examination and brain MRI should be performed in case of clinical suspicion of CNS involvement or for high-risk patients according to the CNS-IPI.
Management
1. CIT such as R-CHOP or R-CHP + polatuzumab vedotin are the preferred first-line regimen for HT.
2. CNS prophylaxis in transformed WM should follow institutional and/or international guidelines for DLBCL. If CNS prophylaxis is used, HD-MTX is the preferred option.
3. No consensus was found on the role of autologous HSCT in consolidation after first-line treatment.
4. T-cell-engaging therapies (CD19-directed CAR T-cells and CD20xCD3 bispecific antibodies) should be proposed according to DLBCL guidelines and specific access to these therapies.
Future directions
1. The role of *TP53* abnormalities and *CXCR4* mutations should be evaluated in future studies on risk factors for developing HT.
2. Clonal relationship between WM and DLBCL should be tested and its prognostic value analyzed.
3. The role of the addition of BTK inhibitors or BCL2 inhibitors to CIT and the role of more intensive CIT regimens should be investigated.
4. The high efficacy reported with CAR T-cells in transformed WM should be evaluated in more patients with a longer follow-up.
5. The role of bispecific antibodies needs to be studied, in particular in patients with disease R/R to auto-HSCT and/or CAR T-cells, or ineligible to auto-HSCT and/or CAR T-cells.

Abbreviations: ABC = activated B-cell; BM = bone marrow; CAR T-cells = chimeric antigen receptor T-cells; CIT = chemoimmunotherapy; CNS = central nervous system; CR = complete response; CSF = cerebrospinal fluid; DLBCL = diffuse large B-cell lymphoma; GCB = germinal center B-cell; GEP = gene expression profiling; HD-MTX = high-dose methotrexate; HSCT = hematopoietic stem-cell transplantation; HT = histological transformation; IHC = immunohistochemistry; IPI = international prognostic index; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; R/R = relapsed/refractory; WM = Waldenström's macroglobulinemia.

DLBCL can be clonally related to WM or occur as a new clone independent of WM. This was shown in a study of 4 cases evaluating *MYD88*^{L265P} mutation and immunoglobulin gene heavy chain variable regions [17]. More recently, next generation sequencing (NGS)-based clonality analysis has been performed in a cohort of 13 patients and DLBCL was found to be clonally related to WM in 77% of cases [18]. This seems to be in line with chronic lymphocytic leukemia where about 80% of Richter syndromes (RS) are clonally related to the underlying indolent disease, however impact on outcomes in setting of transformed WM are unknown [19].

- While choice of frontline treatment of HT is likely not impacted, the panel concurred that it is worth assessing clonal relationships between WM and DLBCL, based on feasibility at centers, in particular for patients with treatment-naïve WM, as it might impact subsequent therapy.

4. What are the preferable chemoimmunotherapy regimens in frontline treatment for HT?

The panel acknowledges the paucity of evidence to support recommendations based upon the existing data for treatment of transformed WM. No dedicated prospective trials have been conducted specifically for transformed WM. Unfortunately, these patients are often excluded from clinical trials or represent a minority of patients among transformed indolent lymphomas. Retrospective studies report the most frequent frontline regimen used in HT is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)-like chemoimmunotherapy (CIT), with overall response (OR) rates of 61% to 79%, complete response (CR) rates of 48% to 77%, and short median progression free-survivals (PFS) of 7 to 10 months [1,2,4].

There are limited data or no data on more intensive CIT regimens, such as R-DA-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) or ACVBP (doxorubicin, cyclophosphamide, vinblastine, bleomycin, and prednisone).

The role of adding novel agents (BTK inhibitors, BCL2 inhibitors) to CIT or maintenance therapy is unclear [20,21].

- Since there is no consensus on a preferred regimen, the panel recommends following de novo DLBCL guidelines with the use of R-CHOP or R-CHP + polatuzumab vedotin, based on individual geographic/institutional standards [22].
- Prior therapy for WM can influence choice for frontline treatment for HT; in the unlikely situation in which R-CHOP-like CIT might have been used, algorithms utilizing nonanthracycline based therapy for de novo DLBCL can be used [23].
- The panel encourages enrollment in clinical trials if available and the development of prospective trials specifically dedicated to this population.

5. What is the place of CNS prophylaxis in frontline treatment? and which CNS prophylaxis if used?

As mentioned above, CNS involvement is frequent in transformed WM [16]. The 3-year rate of CNS relapse was 11%, similar to that observed in DLBCL patients with a high-risk CNS-IPI, and associated with a poor survival (5.6 months after CNS relapse) [15,16]. Factors associated with a higher risk of CNS relapse are involvement of kidney/adrenal glands and presence of *MYD88*^{L265P} mutation. A trend towards a higher risk of CNS relapse was observed for involvement of $\geq$2 extranodal sites.

The benefit of prophylaxis in reducing CNS recurrence in de novo DLBCL is unclear and remains controversial. There is some evidence that intrathecal therapy is ineffective and recent large retrospective studies have reported lack of benefit with high-dose methotrexate (HD-MTX) [24–29]. However, it should be noted that in these retrospective studies in DLBCL, subgroup analyses were underpowered to demonstrate benefit in individual ultra high-risk groups, even in the most recent studies with larger cohorts of patients.

- No consensus has emerged on the role of CNS prophylaxis in transformed WM and the panel suggests following institutional and/or international guidelines which variably consider recommending CNS prophylaxis for high-risk patients, i.e. high CNS-IPI (4-6), multiple and involvement of specific extranodal sites (kidney, adrenal, bone marrow, uterus, breast, testis) [30,31].
- If CNS prophylaxis is used, HD-MTX is the preferred option. To avoid toxicities and/or R-CHOP delays, its delivery can be deferred beyond cycle 1 or preferentially after R-CHOP completion [28,32].

6. What is the role of autologous stem cell transplantation in transformed WM?

The role of high-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation (HSCT) as consolidation therapy after first-line treatment is often considered in transformed indolent lymphomas. Data on its use are limited to retrospective studies of small patient cohorts with heterogeneous populations in terms of the antecedent histology, the timing of HSCT, or the conditioning regimen [33–37]. Due to the rarity of the data in transformed WM, the question of autologous HSCT as consolidation after first-line treatment remains controversial. Additionally, many patients with transformed WM are unfit or ineligible for autologous HSCT due to age, comorbidities, or lack of an adequate response therapy. The largest study is an analysis of a retrospective international database reporting 3-year rates of 44% for PFS, 57% for overall survival (OS), 54% for cumulative incidence of relapse and 2% for nonrelapse mortality (n = 46) [38]. The major independent factor associated with better PFS and OS was achieving a CR at the time of auto-HSCT. Twenty-four patients received auto-HSCT after first-line therapy for HT. When compared to patients in CR after first-line but not receiving HSCT, PFS rates were similar but a trend towards better OS was observed in the auto-HSCT group, possibly explained by the higher rate of WM relapses without DLBCL in this group.

The panel discussed various scenarios: (1) untreated vs heavily pretreated patients with prior WM, (2) clonally related vs clonally unrelated DLBCL, (3) PR vs CR after induction therapy.

- Since there is a paucity of data for this rare complication in a rare disease, the panel was unable to offer conclusive recommendations.
- The panel does not endorse the role of an autologous HSCT after front-line treatment in patients in CR with untreated WM prior to HT.
- At relapse, if CAR T-cell therapy is not available, autologous HSCT may be a reasonable option in chemosensitive fit patients according to local practice.

7. What is the role for T-cell engaging therapies (CAR-T or bispecifics) in relapsed/refractory transformed WM?

T-cell-engaging therapies (CD19-directed CAR T-cells and CD20xCD3 bispecific antibodies) have transformed the therapy landscape of DLBCL and have been approved in the second and third-line settings, respectively [39–41]. In the pivotal studies on glofitamab and epcoritamab, previous treatment with CAR T-cell therapy (30 to 40% of patients) does not appear to impair clinical activity and outcomes [40–41]. The same seems true for patients treated with CAR T-cells and previously exposed to bispecific antibodies [42]. However, the optimal treatment sequencing with CAR-T and bispecifics in DLBCL is unknown, and data in transformed WM with T-cell-engaging therapies are very limited and based on a handful of patients.

The first case report on CAR T-cells in transformed WM reported a patient who achieved CR for 12 months at the time of publication [43]. In the TRANSCEND study with lisocabtagene maraleucel, 18 patients had nonfollicular transformed indolent lymphoma including 2 transformed WM (1 achieving a PR) [44]. The largest study on CAR T-cells in transformed WM is a series of 23 patients from the DESCAR-T registry (the French registry on CAR T-cells, 19 patients) and 2 US centers (4 patients) [45]. Patients received a median of 3 lines of treatment for WM and DLBCL, including 8 patients (35%) who had undergone prior auto-HSCT. Fourteen patients received axicabtagene-cileucel and 9 tisagenlecleucel. The best ORR was 96% and the best CRR 87%, with 1-year PFS and OS rates of 73.4% and 80.5%, respectively, and no unexpected toxicity (74% of CRS including 9% of grade 3-4 and 39% of ICANS including 9% of grade 3-4). In a recently published study comparing CAR T-cells in de novo DLBCL and transformed indolent lymphomas (n = 338), 13 patients had transformed WM [46]. Patients in CR at time of CAR T infusion were not included in this study. The best ORR was 77%, the best CRR 62% and the 1-year PFS 30.8%.

No data exist on bispecifics in transformed WM. In the pivotal studies, only transformed follicular lymphomas were included with glofitamab study, and 40 patients with transformed indolent lymphomas in the epcoritamab study but with no information on the antecedent histology [40–41].

- Given the limited experience and very small number of patients and paucity of data on sequencing CAR-T and bispecifics, the panel could not endorse recommendations and proposed that DLBCL guidelines be followed, taking into account specific access issues based on geographies.

8. Should we treat differently according to MYD88 mutational status or clonal relationship or prognostic factors?

DLBCL with *MYD88*^{L265P} mutation are typically non GCB DLBCL. Frontline treatment with R-CHP + polatuzumab vedotin could be considered in these cases [22]. As outlined in questions 2 and 5, the risk of CNS relapse should be evaluated in patients with *MYD88*^{L265P} mutation, and CNS prophylaxis considered.

As discussed in question 3, the prognostic impact of clonal relationship in transformed WM is unknown, precluding any recommendation on treatment.

The 3 variables independently associated with inferior 2-year OS in transformed WM were elevated LDH, platelet count $< 100 \times 10^9$/L and any previous treatment for WM [4]. However, no recommendation can be made regarding choice of therapies based on these variables, with the exception of the unlikely situation of prior therapy with R-CHOP for WM.

Conclusion

HT from WM continues to be challenging and the Consensus Panel 6 (CP6) convened at the 12th International Workshop on Waldenström's Macroglobulinemia (IWWM-12) attempted to offer some guidelines on various aspects including diagnosis, prognosis and therapy. Key unanswered questions remain such as the role of *TP53* abnormalities and *CXCR4* mutations on the risk of HT, the prognostic role of clonal relationship between WM and HT, the optimal front-line therapy (addition of novel agents to CIT, dose-intensive CIT, consolidation with autologous SCT), and the sequence of T-cell-engaging therapies. International collaboration and consideration of and inclusion in clinical trials is critical to address these issues in a rare patient population.

Declaration of competing interest

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CRediT authorship contribution statement

ED, RA, SPT, CB, JVM prepared, reviewed and/or submitted key questions for this consensus panel. Questions were reviewed, modified and/or supplemented by all members of the consensus panel who met at the 12th International Workshop on WM. ED and RA wrote the first draft, which was submitted to panel members for review and commentary. The consensus panel was composed of individuals with experience in the care of WM patients, who attended the 12th International Workshop on WM, and who volunteered to be on this consensus panel. All authors critically reviewed the draft and approved the final version.

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