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UCCH / UCCSH Pathway

Guideline
Morbus Waldenström

Version Nov/2023

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According to WHO classification of lymphoid neoplasms, 4th edition

Lymphoma and Multiple Myeloma board members

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Legend of Colours

= Therapeutic procedure

= Clinical or diagnostical condition

= Diagnostic procedure

= Clinical trial

= Supportive measure

= Referral

TB

= Tumorboard (including post tumorboard interaction with patient that follows the principles of shared decision-making)

Pathway page 1: Work up

Work up	Remarks
History	• B-symptoms? • Hyperviscosity syndrome? - blood clotting disorders as well as thromboembolism? - neurological symptoms (including dizziness, ataxia, vigilance effects) - eye symptoms (visual disturbances, visual loss) - cardiac symptoms (including angina pectoris)? • Signs of cryoglobulinemia - Raynaud's syndrome with circulatory disorder in those areas which are exposed to cold, e.g. fingers, toes, nose, cheeks, ears
Clinical examination	• Splenomegaly, hepatomegaly, lymphadenopathy? • Opthalmological examination in case of visual disturbances: funduscopy
Laboratory	• Differential blood count • BSG, LDH, β_2-microglobulin • GOT, GPT, AP, γ-GT, bilirubin, creatinine, uric acid • Quick/INR, PTT • Electrophoresis, clonal protein, whole protein • Quantitative immunoglobulines (IgG, IgA, IgM) in serum • Immunofixation in serum and urine • Free kappa- and lambda- light chain in serum, incl. kappa/lambda ratio • 24h-urine for quantification of protein- (including albumin excretion) and light chain- excretion • proBNP (screening cardiac amyloidosis) • HBV, HCV, HIV screening
Histology	Lymphoplasmocytic lymphoma (LPL)
Bone marrow aspirate & biopsy	Obligatory bone marrow infiltration due to lymphoplasmocytic lymphoma (LPL)
Molecular genetics	• MYD88, CXCR4 mutation status * • Differentiation from other indolent NHL
Imaging	• Abdominal sonography • Chest and abdominal CT
Echocardiography	• if indicated by clinical symptoms or suspicion of amyloidosis

Supportive measures see Pathway page 5

WHO-Definition

The Waldenström disease is defined by the histopathological diagnosis of lymphoplasmocytic lymphoma (LPL) with monoclonal IgM gammopathy and infiltration of the bone marrow by the LPL.

* *MYD88*^{L265P} is found in over 90% of patients with Waldenström's disease.
CXCR-4 (chemokine receptor type 4) mutation is found in approximately 30% of all patients.

The genotypes may influence the patient's response to the BTK inhibitor ibrutinib.

Treon SP, Tripsas CK, Meid K, et al.: Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med 372:1430-1440, 2015. DOI:10.1056/NEJMoa1501548
Treon SP, Xu L, and Hunter Z: MYD88 Mutations and Response to Ibrutinib in Waldenstrom's Macroglobulinemia. N Engl J Med 373:584-586, 2015. DOI:10.1056/NEJMc1506192
Treon SP, Xu L, Yang G, et al.: MYD88 L265P somatic mutation in Waldenstrom's macroglobulinemia. N Engl J Med 367:826-833, 2012. DOI:10.1056/NEJMoa1200710

Pathway page 2: First line therapy

Symptomatic findings?

- Constitutional findings
- Hyperviscosity syndrome (rare associated with IgM <50 g/l)
- Symptomatic lymphadenopathy or bulky disease ≥5 cm (ESMO-Guideline)
- Symptomatic hepatomegaly and/or splenomegaly
- Cryoprecipitate
- Amyloidosis
- Cold agglutinins associated autoimmune hemolytic anemia (AIHA)
- Peripheral neuropathy refers to anti-MAG (Myelin-associated Globulin)-antibodies
- Hb <10 g/dl, Tz <100 Mrd/l (ESMO-Guideline)
- IgM >60 g/l (ESMO-Guideline)

TB

No → **Watch and wait**

Yes → **Hyperviscosity?**

Yes → **Plasmapheresis** +

No

Standard therapy

- **Ibrutinib + Rituximab**[1]
- **DCR** = Dexamethason, Cyclophosphamid, Rituximab (6 course), Rituximab formal off-label

Optional if medically fit

- **R–Bendamustin** (3-6 course)[2,3] ,off label

Optional if medically unfit

- **Rituximab mono-therapy**[4]
- **Zanubrutinib**
- **Ibrutinib**[5]
- **Bortezomib + Rituximab**[6] ,off label use‘

[1] Ibrutinib in combination with Rituximab: response rate 92% (Ibrutinib-R) vs 47% (R-mono), independent of MYD88/CXCR –status (Dimopoulos MA et al, N Engl J Med 2018 Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström’s Macroglobulinemia)

[2] Cave: prolonged cytopenias

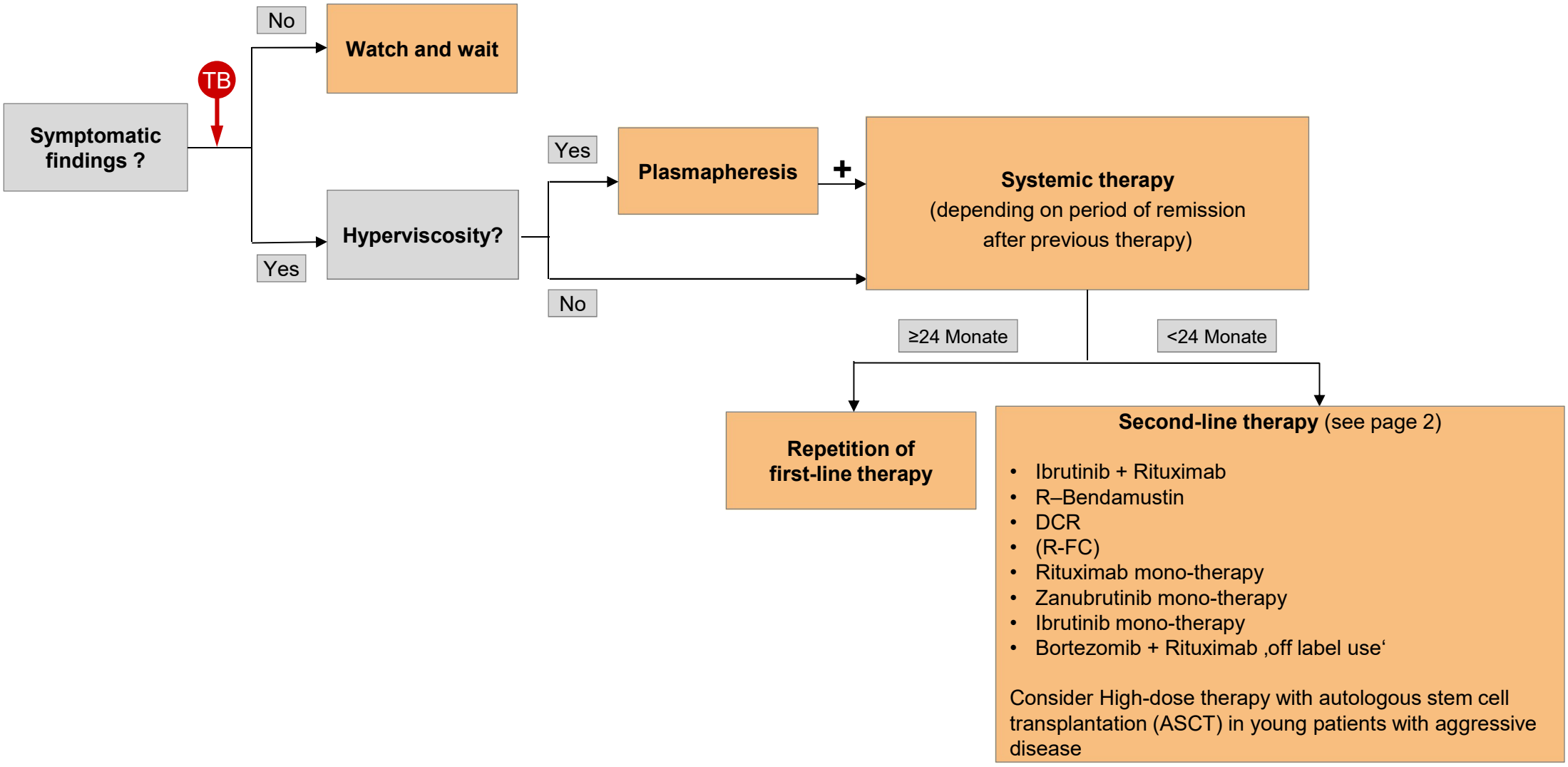
[3] R-FC (Rituximab, Fludarabin, Cyclophosphamid) consider not to be first choice cause of prolonged cytopenias

[4] Rituximab mono-therapy: response rate 20 – 50 %, delayed response median > 4 months partially. Cave: „flare phenomenon“ (temporary increase of IgM) with risk of critical hyperviscosity. In case of IgM- rates > 50 g/l implement plasmapheresis before starting Rituximab

[5] Ibrutinib mono-therapy: lack of effectiveness in case of wild-type MYD88; consider to survey MYD88-status before starting Ibrutinib

[6] First-line therapy Bortezomib in combination with Rituximab obtain response rate of > 80%. Bortezomib is most effective in case of high paraprotein

Pathway page 3: relapsed disease



Pathway page 4: therapy protocols

Ibrutinib-Rituximab [1]			
Rituximab	375mg/m^2	Inf.	day 1 in week 1-4 and than day 1 in week 17-20 (a total of 8x)
Ibrutinib	420mg	p.o.	continous till progressive disease or toxicity

BR-protocol (repeat day 29, 3-6 courses) [2]			
Bendamustin	90mg/m^2 consider 70mg/m² in elderly/frail pat	Inf	day 1, 2
Rituximab	375mg/m^2	Inf	day 1
DRC-protocol (repeat day 22, 6 courses) [3]			
Dexamethason	20mg	Inf	day 1
Rituximab	375mg/m^2	Inf	day 1
Cyclophosphamid	100mg/m^2	p.o. 2xdaily	day1-5

1 Meletios A. Dimopoulos, N Engl J Med 2018 Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobul
2,3 Quelle: Taschenbuch Onkologie 2020/2021

Pathway page 5: Supportive measures

Information about hereditary risk

Relatives of first degree have a 20-fold increased risk of developing Waldenström's disease and a 3 to 5-fold increased risk of developing other non-Hodgkin's lymphomas or MGUS compared to the normal population.

Supportive measures

At each stage of the process or whenever indicated:

- Offer contact to self help group (hand out leaflet)
- Offer psychooncological support
- Offer complementary medicine support
- Offer social service
- Consider palliative care and/ or intervention