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Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

Mantle cell lymphoma (MCL) is a less frequent subtype of lymphoid malignancies and represents 6%–9% of malignant lymphoma in Western Europe. The annual incidence of this disease has increased during recent decades to 1–2/100 000 recently. MCL is more common in males than in women with a 3 : 1 ratio.

diagnosis and pathology/molecular biology

Diagnosis should be based on a surgical specimen, preferably a lymph node biopsy. Core biopsies should only be carried out in patients without easily accessible lymph nodes (e.g. retroperitoneal bulk), keeping in mind the heterogeneity of MCL. In the rare cases with leukaemic manifestation only, a bone marrow biopsy may be sufficient if additional diagnostic measures are applied [immunohistochemistry, detection of t(11;14)(q13; q32)]. Fine-needle aspirations are inappropriate for a reliable evaluation of additional risk factors (cytology, cell proliferation).

The histological report should give the diagnosis according to the World Health Organization (WHO) classification and Ki-67 as the most established histomorphological risk factor [1] [I, A]. Most tumours have a classic morphology of small-medium sized cells with irregular nuclei. However, the malignant lymphocytes may present with a spectrum of morphological variants, including small round (resembling chronic lymphocytic leukaemia), marginal zone-like, pleomorphic and blastoid cells. As only the minority of these cases are correctly diagnosed based on classical histology only, review by an expert haematopathologist is advised. Specifically, additional immunohistochemistry for detection of the pathognomonic cyclin D1 overexpression is mandatory.

In the rare cyclin D1-negative cases, detection of Sox-11 may help to establish the diagnosis [2].

Extended gene expression profiling suggests a more favourable clinical course in cases with low cell proliferation; however, this technique is not yet applicable in clinical routine practice. If possible, additional biopsy material should be stored freshly frozen to allow additional molecular (currently still investigational) analyses.

staging and risk assessment

Since treatment may differ depending on the stage of the disease, initial staging should be thorough, particularly in the rare cases with non-bulky stages I and II (Table 1). Initial work-up should include a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy (Table 2). Positron emission tomography-CT (PET-CT) scan is not mandatory, but may be recommended and is especially useful in the rare limited stages I/II, before localised radiotherapy [IV, C]. Gastrointestinal endoscopy is also recommended in these rare cases to detect asymptomatic involvement. Of note, when analysed, the majority of MCL patients will have gastrointestinal involvement.

Central nervous system involvement is rare in asymptomatic patients at diagnosis, but a lumbar puncture may be considered in high-risk cases [at least two of the following risk factors: blastoid variant, elevated lactate dehydrogenase (LDH), impaired performance status] or neurological symptoms [3].

A full blood count, blood chemistry including LDH and uric acid as well as screening tests for human immunodeficiency virus (HIV) and hepatitis B and C are required. Staging is carried out according to the Ann Arbor classification system (Table 1), with mention of bulky disease >5 cm when appropriate.

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Table 1. Ann Arbor classification

Stage	Area of involvement
I (I_E)	One lymph node region or extralymphatic site (I_E)
II (II_E)	Two or more lymph node regions or at least one lymph node region plus a single localised extralymphatic site(II_E) on the same side of the diaphragm
III (III_E, III_S)	Lymph node regions or lymphoid structures (e.g. thymus, Waldeyer's ring) on both sides of the diaphragm with optional localised extranodal site (III_E) or spleen (III_S)
IV	Diffuse or disseminated extralymphatic organ involvement

A, no symptoms; B, unexplained fever of >38°C, drenching night sweats; or loss of >10% body weight within 6 months.

Table 2. Diagnostic work-up

History	B symptoms
Physical examination	Waldeyer's ring, peripheral lymph nodes, liver, spleen
Laboratory work-up	Blood and differential count in leukaemic cases: FACS (CD5/CD20+, CD23/CD200), FISH for t(11;14) recommended
	LDH, uric acid, liver and renal function electrophoresis (optional: immune fixation)
Serology	Hepatitis B, C and HIV serology
Imaging	Chest X-ray
	Abdominal ultrasound
	CT neck, chest, abdomen, pelvis
	MRT only in selected locations (CNS)
	Optional: PET
Bone marrow	Histology (cyclin D1 immunohistochemistry)
	Cytology
	Recommended: FACS, FISH for t(11;14)
	Optional: PCR for IgH rearrangement
Toxicity	Electrocardiogram, cardiac ultrasound (before anthracyclines, ASCT)
	Pulmonary function (before ASCT)
	Creatinine clearance
	Optional: reproductive counselling in young patients

FACS, fluorescence-activated cell sorting; FISH, fluorescence *in situ* hybridisation; LDH, lactate dehydrogenase; HIV, human immunodeficiency virus; CT, computed tomography; MRT, magnetic resonance tomography; CNS, central nervous system; PET, positron emission tomography; PCR, polymerase chain reaction; ASCT, autologous stem-cell transplantation.

For prognostic purposes, a 'Mantle cell lymphoma International Prognostic Index' (Table 3; web-based calculator: www.european-mcl.net/de/clinical_mipi.php) has been established [I, A] [4].

Table 3. Simplified MIPI risk factor

Points	Age (years)	ECOG	LDH (ULN)	WBC (10^9/l)
0	<50	0–1	<0.67	<6.700
1	50–59	–	0.67–0.99	6700–9.999
2	60–69	2–4	1.00–1.49	10.000–14.999
3	>70	–	≥1.50	≥15.000

For each prognostic factor, 0–3 points were given to each patient and points were summed up to a maximum of 11. Patients with 0–3 points in summary were classified as low risk, patients with 4–5 points as intermediate risk and patients with 6–11 points as high risk. ECOG performance status was weighted with 2 points if patients were unable to work or bedridden (ECOG 2–4). LDH was weighted according to the ratio to the ULN. Thus, for an ULN of 240 U/l, the limits were 180, 240 and 360 U/l.

MIPI, mantle cell lymphoma international prognostic index; ECOG, Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ULN: upper limit of normal range; WBC: white blood count.

The evaluation of the Ki-67 proliferative antigen is the most applicable method to evaluate cell proliferation, and is considered the most established biological risk factor in MCL. As the reproducibility of quantitative scores among pathologists may vary, a standardised method has been suggested [5].

indolent subtype of MCL

Most patients with MCL follow an aggressive clinical course. However, a subset of patients may exhibit a more indolent evolution. These cases are commonly characterised by a non-nodal leukaemic presentation with only bone marrow involvement, and splenomegaly [6]. In addition, cases with low Ki-67 (≤10%) tend to have a more indolent course. SOX-11 negativity may also identify cases with more indolent clinical behaviour. However, its role is controversial and additional p53 mutations may cause an aggressive clinical evolution [7] (Figure 1).

Unfortunately, there are no markers to definitely predict indolent behaviour, but a short watch-and-wait period under close observation seems to be appropriate in suspected indolent cases with low tumour burden [III, B] [9].

treatment

first line

stage I–II. In the small proportion of patients with limited non-bulky stages I–II, radiotherapy (involved field, 30–36 Gy) has been suggested to achieve long-term remissions [10]. In contrast, in a randomised study, all patients with early-stage MCL relapsed within 1 year [11]. Thus, a shortened conventional chemotherapy induction followed by consolidating radiation (similar to diffuse large-cell lymphoma) may be most appropriate in these cases [IV, B].

In stage I–II patients with large tumour burden or adverse prognostic features, systemic therapy as indicated for advanced stages would be appropriate in most cases; a radiation consolidation may be considered, depending on tumour location and anticipated side-effects [IV, B].

stage III–IV

induction: In all symptomatic patients and asymptomatic cases with high tumour burden, therapy should be initiated at diagnosis [I, A]. The current therapeutic approach is based on clinical risk factors, symptoms and patient characteristics (Figure 2).

elderly patients: Based on a median age of 65 years at first diagnosis, the majority of patients do not qualify for dose-intensified regimens. Three prospective first-line trials, a salvage trial and a systematic meta-analysis support an improved overall response, progression-free survival (PFS) and overall survival (OS) if rituximab was added to chemotherapy (Table 4) [I, A] [12].

Rituximab in combination with chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine should be used [I, B] [13, 18]. R-CVP

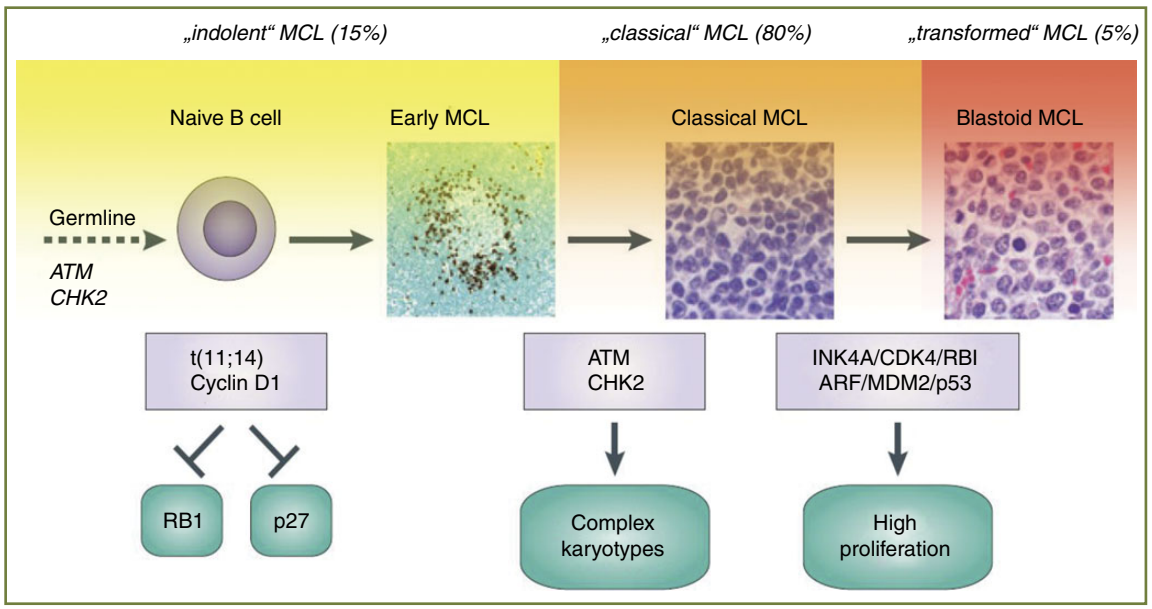

Figure 1. Molecular pathogenesis of mantle cell lymphoma. Reprinted from [8]. Reused with permission. Copyright 2014 American Society of Clinical Oncology. All rights reserved.

Young patient (≤65)	Elderly patient (>65) First line treatment	Compromised patient
Dose-intensified Immuno-chemotherapy (R-CHOP + R-high dose Ara-C (alternating or sequential) =>ASCT)	Conventional Immuno-chemotherapy (e.g. R-CHOP, BR) ↓ Rituximab maintenance radioimmunotherapy	Watch and wait ? R-Chlorambucil BR
1. Relapse		
High tumour load: Immuno-chemotherapy (e.g. BR, R-DHAP) ↓ Allo-transplant Radioimmunotherapy Rituximab maintenance	Immuno-chemotherapy (e.g. BR, R-FC) Targeted approaches ↓ ASCT Radioimmunotherapy Rituximab maintenance	Immuno-chemotherapy (e.g. BR) Targeted approaches
Higher relapse		
Targeted approaches: Temsirolimus, Bortezomib*, Ibrutinib, Lenalidomide* (preferable in combination) Repeat previous therapy (long remissions)		

R, rituximab; CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; B, bendamustine; FC, fludarabine/cyclophosphamide; ASCT, autologous stem-cell transplantation; *currently not registered in this indication in the European Union (EU).

Figure 2. Therapeutic recommendations. Modified from [8]. Reused with permission. Copyright 2014 American Society of Clinical Oncology. All rights reserved.

Table 4. Published clinical studies investigating first-line conventional immunochemotherapy in mantle cell lymphoma

Author	Study features	Evaluable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (months)	2-years OS
Conventional immunochemotherapy						
Lenz et al. [13]	Phase III, randomised	112	CHOP versus R-CHOP	75 (7) versus 94 (34)	21 versus 14 (TTF)	76% versus 76%
Herold et al. [14]	Phase III, randomised	90	MCP versus R-MCP	63 (15) versus 71 (32)	18 versus 20	52% versus 55% (4-year OS)
Gressin et al. [15]	Phase II	113	Rituximab–VADC	73 (46)	16 (no ASCT) 58 (ASCT)[a]	62% (3-year OS)[a]
Sachanas et al. [16]	Phase II	20	Rituximab–chlorambucil	95 (90)	89% (3-year PFS)	95% (3-year OS)
Kluin-Nelemans et al. [17]	Phase III, randomised	485	Induction: R-CHOP versus R-FC	86 (34) versus 78 (40)	28 versus 28 (TTF)	62% versus 47% (4-year OS)
			Maintenance: rituximab versus interferon alpha	–	58% versus 29% (4-year DOR)	79% versus 67% (4-year OS)
Rummel et al. [18]	Phase III, randomised	514 (94 MCL)	R-CHOP versus rituximab–bendamustine	91 (30) versus 93 (40)	21 versus 35	No differences

Data derived from the overall population of the study, not exclusively from patients with MCL.

[a]Forty-nine patients received ASCT consolidation.

R, rituximab; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; FC, fludarabine, cyclophosphamide; MCP, mitoxantrone, procarbazine, lomustine; ASCT, autologous stem-cell transplantation; VADC, vincristine, doxorubicin, oral dexamethasone, chlorambucil; TTF, time to failure; DOR, duration of response; ORR, overall response rate; CR, complete response.

(cyclophosphamide, vincristine and prednisone) combination results in inferior response rates and PFS [19]. Purine analogue-based schemes [R-FC (fludarabine and cyclophosphamide) or R-FM (fludarabine and mitoxantrone)] are also discouraged due to early failures and long-lasting myelosuppression [17] [I, D].

In frail patients, a less intense immunochemotherapy [chlorambucil, VADC (vincristine, doxorubicin, oral dexamethasone, chlorambucil) or PEP-C (prednisone, etoposide, procarbazine, cyclophosphamide)] may be considered, aiming primarily at palliation [II, B]. However, targeted therapy exhibiting a low toxicity profile may be used in this population.

Antibody monotherapy [rituximab, radioimmunotherapy (RIT)] achieves only moderate response rates and is therefore not recommended [III, B] [20].

In patients with positive hepatitis B serology, prophylactic antiviral medication is strongly recommended [I, A] [21].

consolidation/maintenance: Rituximab maintenance significantly improves PFS and even OS after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) (75% versus 58% after 3 years, $P < 0.0001$) [I, A] [17].

RIT consolidation also prolongs PFS after chemotherapy, but its benefit seems to be inferior in comparison to rituximab maintenance [II, B] [22].

younger patients: Although no curative treatment is available for MCL so far, an intensive approach, e.g. by ASCT, has been demonstrated to induce higher response and survival rates in fit patients, independent of the addition of rituximab [I, B] [23, 24] (Table 5).

In addition, a randomised trial confirmed that a cytarabine-containing induction achieves a significantly improved median time to treatment failure ($P = 0.038$) and a trend for median OS ($P = 0.045$) [I, B] [25]. In contrast, an induction based on high-dose cytarabine alone achieves only insufficient response rates [III, D] [34]. Therefore, a rituximab containing induction of CHOP and high dose Ara-C followed by high dose consolidation and ASCT is recommended.

In a retrospective study comparison of the Nordic, HOVON and MCL younger protocols, total body irradiation (TBI) before ASCT was confirmed to be beneficial only in partial response (PR) patients [II, B] [35]. In contrast, the benefit of RIT has not been demonstrated in inter-study comparisons.

An upfront, dose-intensified approach (R-Hyper-CVAD, rituximab in combination with fractionated cyclophosphamide, vincristine, anthracycline and dexamethasone) with alternating high-dose methotrexate/cytarabine cycles also achieved very high response and survival rates in phase II studies, but its feasibility is hampered by a significant therapy-associated toxicity [II, C] [31–33].

The role of rituximab and lenalidomide maintenance after autologous transplantation is currently being investigated by the randomised LyMa [36] and MCL 0208 trials, respectively.

So far, there are no data to support the application of allogeneic transplantation as part of front-line treatment [II, D] [37].

relapsed disease

A repeated biopsy is strongly recommended to identify prognostically important features of MCL.

Selection of salvage treatment depends on efficacy of prior regimens. In early relapses (<12–24 months), a non-cross-resistant scheme should be preferred (bendamustine or high-dose-Ara-C

Table 5. Published clinical studies investigating first-line dose-intensified therapy in mantle cell lymphoma

Author	Study features	Evaluable patients	Therapeutic regimen	ORR% (CR%)	Median PFS (years)	Median OS (years)	Dropout rate	TRM	Secondary tumours rate
ASCT-based regimens									
Dreyling et al. [23]	Phase III, randomised	122	R-CHOP + TBI + ASCT versus R-CHOP + TBI + interferon-α	98 (81) versus 99 (37)	3.3 versus 1.4	NR (83% 3-year OS) versus NR (77% 3-year OS)	13% versus N/A	5% versus 0%	5%
Hermine et al. [25]	Phase III, randomised	455	R-CHOP + TBI + ASCT versus R-CHOP/R-DHAP + HD-araC + ASCT	98 (63) versus 99 (61)	3.8 versus 7.3	6.8 versus NR	N/A	4%	N/A
Damon et al. [26]	Phase II	77	R-CHOP + methotrexate + HD-araC/ etoposide + ASCT	88 (69)	NR (56% 5-year PFS)	NR (64% 5-year OS)	13%	3%	N/A
Van't Veer et al. [27]	Phase II	87	R-CHOP + HD-araC + ASCT	70 (64)	NR (36% 4-year PFS)	NR (66% 4-year OS)	30%	5%	N/A
Geisler et al. [28]	Phase II	160	R-Maxi-CHOP + HD-araC + ASCT	96 (54)	7.4	NR (64% 10-year OS)	9%	5%	4%
Delarue et al. [29]	Phase II	60	R-CHOP/R-DHAP + HD-araC + ASCT	100 (96)	6.9	NR (75% 5-year OS)	18%	1.5%	18%
Touzeau et al. [30]	Retrospective	396	Different ASCT-based schedules	83 (77)	NR (67% 3-year PFS)	NR (83% 3-year OS)	N/A	2.5%	6%
Non-ASCT-based regimens									
Romaguera et al. [31]	Phase II, monocentric	97	R-Hyper-CVAD	97 (87)	4.6	NR (64% 10-year OS)	29%	8%	5%
Merli et al. [32]	Phase II, multicentric	60	R-Hyper-CVAD	83 (72)	NR (73% 5-year PFS)	NR (61% 5-year OS)	63%	6.5%	1.5%
Bernstein et al. [33]	Phase II, multicentric	49	R-Hyper-CVAD	86 (55)	4.8	6.8	39%	2%	4%

R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; DHAP, dexamethasone, HD-araC, high dose Ara-C (cytarabine), Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, anthracycline, dexamethasone; TBI, total body irradiation; ASCT, autologous stem-cell transplantation; NR, not reached; TRM, treatment-related mortality.

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containing regimens, e.g. R-BAC after CHOP or vice versa) [38]. Rituximab should be added if the previous antibody-containing scheme achieved >6–12 months duration of remission [IV, B].

In cases of early relapses or in refractory cases, newer targeted approaches should be strongly considered (Figure 2). Currently, temsirolimus is the only compound registered for relapsed MCL in the EU based on a randomised trial [39]. Among the compounds registered in the United States (bortezomib, ibrutinib and lenalidomide), ibrutinib achieves the highest response rates but longer follow-up is warranted [40–42] (Table 6).

Targeted approaches in combination with immunochemotherapy have been suggested but are still investigational.

Rituximab maintenance has a favourable safety profile and prolongs PFS and OS in relapsed disease [I, A] [59]. However, such a second-line maintenance treatment has not been investigated in patients relapsing after front-line maintenance [IV, D].

RIT consolidation seems to result in extended remission durations [55], especially in elderly patients with comorbidities not eligible for dose intensification [IV, B].

High-dose chemotherapy with ASCT may be considered in patients relapsed after conventional first-line therapy. However,

Table 6. Published clinical studies investigating molecular targeted approaches in relapsed mantle cell lymphoma

Author	Study features	Evaluable patients	Therapeutic regimen	ORR% (CR %)	Median PFS (months)	Median OS (months)
Proteasome inhibitors						
Goy et al. [40]	Phase II	141	Bortezomib	33 (8)	6.7 (TTP)	23.5
Lamm et al. [43]	Phase II	16	Bortezomib, rituximab, dexamethasone	81 (44)	12.1	38.6
Kouroukis et al. [44]	Phase II	25	Bortezomib, gemcitabine	60 (11)	11.4	N/A
mTOR inhibitors						
Witzig et al. [45]	Phase II	34	Temsirolimus	38 (3)	6.5 (TTP)	12
Ansell et al. [46]	Phase II	27	Temsirolimus	41 (4)	6 (TTP)	14
Hess et al. [39]	Phase III, randomised	54	Temsirolimus 175 mg/75 mg	22 (2)	4.8	12.8
		54	Temsirolimus 175 mg/25 mg	6 (0)	3.4	10
		53	Investigator's choice	2 (2)	1.9	9.7
Ansell et al. [47]	Phase II	69	Temsirolimus, rituximab	59 (19)	9.7	29.5
Renner et al. [48]	Phase II	35	Everolimus	20 (6)	5.5	N/A
Immunomodulatory drugs						
Zinzani et al. [41]	Phase II	57	Lenalidomide	35 (12)	8.8	NR
Goy et al. [49]	Phase II	134	Lenalidomide	28 (8)	4	19
Wang et al. [50]	Phase II	44	Lenalidomide, rituximab	57 (36)	11.1	24.3
Zaja et al. [51]	Phase II	33	Lenalidomide, dexamethasone	52 (24)	12	20
Harel et al. [52]	Retrospective	58	Thalidomide ± bortezomib ± rituximab	50 (21)	NR (1-year TTF 29%)	NR (62% 1-year OS)
Ruan et al. [53]	Phase II	22	Metronomic prednisone, etoposide Procarbazine, cyclophosphamide, rituximab, thalidomide	73 (32)	10	NR (45% 2-year OS)
Antibody-based approaches						
Wang et al. [54]	Phase II	32	^{90}Y-ibritumumab tiuxetan	31 (16)	6 (EFS)	21
Ferrero et al. [55]	Phase II	15[b]+ 30[b]	^{90}Y-ibritumumab tiuxetan	40 (20) 72 (38)	3.7 8.9	13.8 32.2
Morschhauser et al. [56]	Phase II	40 (15 MCL)	GA-101	27 (13)	2.7[a]	N/A
BCR signalling inhibitors						
Wang et al. [42]	Phase II	111	Ibrutinib	68 (21)	13.9	NR (58% 1.5-year OS)
Kahl et al. [57]	Phase I	16	Cal-101	62 (N/A)	3 (DOR)	N/A
Various						
Davids et al. [58]	Phase I	32 (8 MCL)	ABT-199	100 (0)	N/A	N/A

[a]Data derived from the overall population of the study, not exclusively from patients with MCL. Six patients received the schema as first-line therapy.
[b]Fifteen patients received the antibody as relapse monotherapy, 30 patients as consolidation after salvage treatment.
mTOR, mammalian target of rapamycin; BCR, B-cell receptor; ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; TTP, time to progression; NR, not reached; TTF, time to failure; EFS, event-free survival; DOR, duration of response.

Table 7. Recommended follow-up

Examination	Details	Year 1–2	Year 3–5	Year >5
History	B symptoms	Every 3 months	Twice annually	Annually
Physical examination	Particular: peripheral lymph nodes, liver, spleen	Every 3 months	Twice annually	Annually
Laboratory work-up	Blood and differential count	Every 3 months	Twice annually	Annually
	LDH	Every 3 months	Twice annually	Annually
Imaging	Abdominal ultrasound	Optional: 3–6 months	Optional: every 6–12 months	If progress suspected
	CT neck, chest, abdomen, pelvis	Optional: every 3–6 months	Optional: every 6–12 months	If progress suspected
Toxicity	TSH if irradiated	Annually	Annually	Annually

LDH, lactate dehydrogenase; CT, computed tomography; TSH, thyroid-stimulating hormone.

Table 8. Summary of recommendations

- Diagnostic procedures include histomorphology by an expert haematopathologist and mandatory detection of cyclin D1 overexpression or t(11;14)(q13;q32)
- Clinical (MIPI) and biological (Ki-67) prognosticators should be applied in clinical routine to estimate the clinical behaviour
- In localised stages: discuss conventional chemotherapy followed by radiotherapy (30–36 Gy)
- In advanced stages
  - Younger patients: high-dose cytarabine-containing regimens plus rituximab with dose intensification (e.g. autologous stem-cell transplantation)
  - Elderly patients: conventional immunochemotherapy (R-CHOP, R-B) followed by rituximab maintenance
- In relapse
  - (Combined) targeted approaches (bortezomib, ibrutinib, temsirolimus, lenalidomide) should be considered
  - In younger patients, an allogeneic transplantation should be discussed among possible options

Table 9. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [65].

the benefit seems to be minor in this setting [60], and there is no role for a second autograft at relapse.

In younger patients, allogeneic stem-cell transplantation is potentially curative and has achieved long-term remissions, even in patients following early relapse and with refractory disease. Based on the advanced age of most patients, a dose-reduced conditioning is appropriate [IV, B] [61]. Haplo-identical bone marrow transplantation achieves high response rates but is still experimental in MCL.

response evaluation

Radiological tests should be carried out mid-treatment and following the completion of chemotherapy. Patients who achieve less than a PR should be considered for early salvage regimens. Patients achieving a PR may convert to a complete response after post-induction treatment.

PET-CT for response evaluation is optional [62].

The independent prognostic role of minimal residual disease (MRD) applying patient-specific primers has been confirmed in numerous studies [63, 64]. However, because of limitations of applicability and the need for qualified and standardised laboratories, its use is advised in clinical trials but not recommended in clinical routine except the setting of donor lymphocyte infusion post allograft.

personalised medicine

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

The selection of optimal treatment is mainly based on clinical and biological risk factors, symptoms and tumour load (Figure 2). PET- and MRD-based tailored treatments are currently evaluated in studies but are not yet routine clinical practice.

New agents (especially inhibitors of Bruton's tyrosine kinase as well as PI3 kinases and BCL-2) are currently being investigated [42].

follow-up and long-term implications

The following recommendations are based on consensus rather than on evidence (see Table 7):

- History and physical examination, blood counts and routine chemistry every 3 months for 2 years, every 4–6 months for 3 additional years and subsequently once a year [V, D].
- Annual evaluation of thyroid function in patients with irradiation of the neck.
- Optional CT scan (or chest X-ray/ultrasound examinations to reduce radiation exposure) every 3–6 months for 2 years and every 6–12 months up to 5 years. However, there is no strong evidence to support a regular radiological follow-up. PET-CT should not be used for surveillance. These recommendations are driven by the concern to minimise radiation exposure.
- Some studies suggest that pre-emptive treatment may be efficient. However, MRD screening may be carried out but should not guide therapeutic strategies outside clinical studies.

note

A summary of recommended treatment strategies outside clinical studies is provided in Figure 2, and a summary of recommendations is provided in Table 8. Levels of evidence and grades of recommendation have been applied using the system shown in Table 9. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

MD has reported scientific advisory boards for Bayer, Celgene, Gilead, Janssen and Pfizer; support of academic trials for Celgene, Janssen, Mundipharma, Pfizer and Roche; speaker's honoraria: Celgene, Janssen, Mundipharma, Pfizer and Roche. CG has reported scientific advisory boards for Roche, Celgene, Janssen and GlaxoSmithKline; support of academic trials by Celgene and Janssen. SR: advisory boards for Johnson & Johnson, Pharmacyclics, Roche, Napp and Celgene. OS: advisory boards for Roche and Takeda; research grants from Roche and Janssen. JW: advisory boards for Celgene, Roche, Mundipharma, Takeda, Bayer, Boehringer Ingelheim, Janssen and Amgen; research grants from Roche, Celgene, GlaxoSmithKline and Mundipharma; speaker's honoraria for Roche, Mundipharma, Celgene and Takeda. ML has reported speaker's bureau for Celgene, Janssen-Cilag, Roche, Bayer, Amgen and Mundipharma; research contracts from Celgene, Pfizer, Mundipharma and Roche; funds received from Amgen, Roche and Italfarmaco. SL, OH and HK have reported no potential conflicts of interest.

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