

Monoclonal B-cell lymphocytosis: Recommendations from the Dutch Working Group on CLL for daily practice

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ABSTRACT

Monoclonal B-cell lymphocytosis (MBL) is defined by the presence of small B-cell clones in asymptomatic individuals. Usually, MBL cells are characterised by a chronic lymphocytic leukaemia (CLL) phenotype ('CLL phenotype MBL'); however, an atypical phenotype ('atypical-CLL phenotype MBL') or non-Hodgkin lymphoma phenotype ('non-CLL phenotype MBL') can be found as well. The prevalence of MBL in the general population with an age over 40 years is 3 to 5%. Subjects with MBL develop CLL requiring treatment at a rate of 1 to 2% per year. At the moment official guidelines with respect to MBL are not available in the Netherlands. On the basis of the available data, we will discuss the definitions of MBL, highlight clinical consequences and offer recommendations for daily practice. Individuals with clinically suspected MBL should undergo a complete evaluation by a haematologist. In case of CLL phenotype MBL, further annual follow-up can take place by the general practitioner. If signs of progression occur patients should be referred to a haematologist.

KEYWORDS

MBL, CLL, practical guidelines

INTRODUCTION

Monoclonal B-cell lymphocytosis (MBL), a relatively new entity, is a preclinical haematological syndrome where small B-cell clones with an abnormal immunophenotype are present in the peripheral blood of asymptomatic individuals. In most cases, these clonal cells have an immunophenotype similar to chronic lymphocytic leukaemia (CLL; CLL phenotype MBL). To date, no official

guidelines have been published in (inter)national medical literature. On the basis of available literature we will offer recommendations for daily practice in case of suspected MBL and in case of confirmed MBL.

DEFINITION

Recently, MBL was introduced and defined (*table 1*) in the updated iwCLL (International Workshop on CLL) classification.¹ In preceding years several groups have performed population-based studies and with the advent of more sensitive flow cytometry techniques it was found that a substantial part of the general adult population carries typical monoclonal B-cell clones in their peripheral blood, which was classified as MBL.²⁻⁶ MBL cells are monoclonal B cells which usually express CD5. In 85% of the cases, these clones also express the other typical surface markers of CLL cells ('CLL phenotype MBL'; CD19⁺, CD20^{weak}, CD23⁺, surface Ig (sIg)^{weak} and CD79b^{weak}).¹ Furthermore, a second category of MBL has been called 'atypical-CLL phenotype MBL'. In this category clonal B cells also express CD5, but other markers are differentially expressed as compared with CLL (e.g. CD23 negative or bright expression of CD20, CD79 or sIg). The clonal B cells of the third category of MBL, called 'non-CLL phenotype MBL' lack expression of CD5 and do express phenotypic markers resembling non-Hodgkin lymphomas, such as marginal zone lymphoma or follicular lymphoma (*table 1*). As the clonal B cells of individuals with both CLL and 'CLL phenotype MBL' share an identical immunophenotype, they need to be differentiated based on absolute B-lymphocyte count; CLL is defined by the presence of $\geq 5 \times 10^9/l$ B lymphocytes and MBL is defined by the presence of $< 5 \times 10^9/l$ B lymphocytes with a

Table 1. Diagnostic criteria and nomenclature of MBL (adapted from Shanafelt et al.²)

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|--|--|
| Diagnostic criteria | |
| 1. Documentation of clonal B-cell population by: | kappa:lambda ratio >3:1 of <0.3:1 or >25% of B cells lacking or expressing low-level surface immunoglobulins |
| 2. Presence of a disease-specific immunophenotype ^a | |
| 3. Absolute B-lymphocyte count <5 x 10 ⁹ /l | |
| 4. No other features of a lymphoproliferative disorder: a) absence of B symptoms, b) normal physical exam (no lymphadenopathy or organomegaly), c.) no autoimmune/infectious disease | |
| Subclassification | |
| • CLL phenotype MBL | CLL phenotype: CD5 ⁺ CD19 ⁺ CD20 ^{weak} CD23 ⁺ sIg ^{weak} |
| • Atypical-CLL phenotype MBL | CD5 ⁺ CD19 ⁺ , but CD23 weak or negative or CD20, sIg or CD79b bright |
| • Non-CLL phenotype MBL | CD5 ⁻ CD19 ⁺ CD20 ⁺ |
| ^a In the absence of a disease-specific immunophenotype, a highly skewed kappa:lambda ratio can be the result of a reactive process. | |

characteristic CLL phenotype in peripheral blood.¹ Before the introduction of MBL in the recent iwCLL classification, CLL used to be classified as the presence of characteristic monoclonal B cells in the peripheral blood, with a minimum absolute lymphocyte count (ALC) of 5 x 10⁹/l.⁷ Since the change in the CLL diagnostic criteria from an ALC >5 x 10⁹/l to a B-cell count >5 x 10⁹/l, up to 40% of CLL patients who were previously classified as CLL Rai stage 0 are now diagnosed as MBL.^{8,9} In literature, the terms 'low-count MBL (lcMBL) and 'clinical MBL' (cMBL) have also been introduced² to discriminate cases with extremely low monoclonal B-cell clones (which are only found by population screening) from cases with an asymptomatic lymphocytosis. In the literature, no clear distinction has been made between lcMBL and cMBL on the basis of the number of B lymphocytes, but most lcMBL patients do

have a B-lymphocyte count below 0.5 x 10⁹/l.^{2,10} The risk to develop CLL requiring treatment is clearly increased in cMBL in comparison with healthy age-matched controls and not in lcMBL (see further).

PREVALENCE OF MBL

The reported prevalence of MBL in the general population varies substantially, from 0.6% to even 20% in some studies (table 2).²⁻⁶ These differences are most likely due to both different sensitivity of the flow cytometry approach applied and to the age of the studied population. In an Italian and English study, in which a four-colour flow cytometry (CD5, CD19, kappa and lambda; 2 x 10⁵ analysed cells)¹¹ was used, a prevalence of 3 to 5% was found in the general population with a mean age of 73 years (range 62 to 98 years).^{3,4} A Spanish study, which applied a more sensitive approach (CD5, CD19, CD20, CD23, CD38, kappa and lambda; 5 x 10⁶ analysed cells) reported a prevalence of up to 20% in the general population over 60 years of age (table 2).⁵ There are even recent data suggesting that almost everyone older than 70 years harbours circulating CLL clones at very low numbers.¹² Currently, the consensus on the prevalence of MBL is 3 to 5% in the Western population with an age over 40 years. There is a fourfold increase of MBL in first-degree relatives of CLL patients in comparison with the general elderly population.^{13,14} For young adults aged 16 to 40 years this relative risk is even 17-fold increased.¹⁴

There are less data on the prevalence of MBL in individuals with asymptomatic lymphocytosis. In an English study, a monoclonal B-cell population was found in 60% of the 2000 individuals referred with an asymptomatic lymphocytosis (median age 77 years): 19% with MBL and 46% with CLL.⁴ A comparable study was performed in a Dutch cohort of 520 patients aged over 40 years, who presented with a relative (>60%) or absolute (>6.0 x 10⁶/l) lymphocytosis. In the groups of individuals with an

Table 2. Prevalence of CLL-like MBL in population studies (adapted from Shanafelt et al.²)

| Study group | | | | Flow cytometry | | CLL-like MBL prevalence | |
|---|-------------|------------|---|----------------|----------------------------|-------------------------|--------------------|
| | Source | Median age | N | No. of colours | Events (x10 ⁵) | All ages in study | >60 years |
| US residential population ²⁹ | 53 (40-78) | 1926 | 2 | | Not specified | 0.6% | >0.6% ^a |
| US blood donors ³⁰ | 45 (18-79) | 5141 | 2 | | Not specified | 0.14% | 0.9% |
| UK hospital OPs ^{4*} | 57 (40-90) | 910 | 4 | | 2 | 3.5% | 5.0% |
| Italy, primary care ³ | 74 (65-98) | 500 | 4 | | 2 | 5.5% | 5.5% ^b |
| UK hospital OPs ^{4**} | 74 (60-80) | 1520 | 4 | | 2 | 5.1% | 5.1% ^c |
| Italy, residential population ³¹ | 55 (18-102) | 1725 | 5 | | 5 | 7.4% | 8.9% |
| Spain, primary care ⁶ | 62 (40-97) | 608 | 8 | | 50 | 12.0% | >20% ^a |

^aEstimated from data; ^bage above 65; ^cage range 60-80 years; OPs = outpatients, *without lymphocytosis, ** with lymphocytosis.

absolute lymphocyte count below $4.0 \times 10^9/l$, between 4.0 and $9.0 \times 10^9/l$, and over $9.0 \times 10^9/l$, monoclonal B cells were found in 2% (all MBL), 16% (87% MBL) and 66% (2.8% MBL; 90% CLL) respectively.¹⁵

RISK OF PROGRESSION TO SYMPTOMATIC DISEASE

For CLL-phenotype MBL, it is more relevant to define progression as the risk to develop CLL requiring treatment than the risk to develop CLL,¹⁰ since there is an arbitrary distinction between MBL and CLL Rai stage 0. Based on the larger MBL follow-up studies the annual risk to develop CLL requiring treatment is 1 to 2%^{2,4,16,17} compared with an annual risk for CLL Rai stage 0 patients of 5 to 7%. In other words, the ten-year treatment risk for MBL is 10 to 20% in contrast to 50 to 70% for CLL Rai stage 0 patients.² Since these studies indicate that no plateau phase is reached in the risk of progression to CLL (comparable with multiple myeloma and monoclonal gammopathy of unknown significance (MGUS)) one should question whether these patients need to be monitored in the long term. The only factor known to predict development to CLL is the actual number of B lymphocytes.^{8,10,17} Roughly, MBL patients with a B-lymphocyte count below 1 to $2 \times 10^9/l$ have a low risk to develop progressive lymphocytosis and CLL. In 90% of the cases the extent of the clone stays stable.¹⁰ In an American study only 1.5% (1/64) of the MBL patients with a B-lymphocyte count below $1.5 \times 10^9/l$ progressed to CLL requiring treatment.¹⁷ In patients with more than $3.7 \times 10^9/l$ B lymphocytes (in most cases these subjects have asymptomatic lymphocytosis) the chance to develop CLL is substantial: 72% after 2.6 years,^{10,16} in contrast to 39% after 5.5 years in case of a B-lymphocyte count between 1.2 and $3.7 \times 10^9/l$.¹⁶ Established risk factors for CLL, such as IGVH mutation status, cytogenetic aberrations, ZAP-70 and CD38 expression, are technically difficult to obtain in MBL subjects. So far, these factors have not shown independent prognostic power to predict progression.^{2,4}

Progression to CLL of lcMBL is extremely rare in the experience of researchers in the field.² Since the prevalence of lcMBL can be up to 20% in the general elderly population and only a really small number of individuals develop CLL, the CLL progression risk is not expected to be increased in comparison with the risk in the general population.¹⁷

RISK OF CLL-RELATED MORBIDITY

CLL patients have an increased risk of infection (notably in the later stages of the disease, both due to a diminished humoral immunity and neutropenia caused

by bone marrow infiltration), secondary malignancies and autoimmune diseases (especially autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura).^{18,19} There is little information on CLL-related morbidity in case of MBL. In the studies described earlier with larger patient cohorts,^{4,16,17} the risk of infections, autoimmune haemolysis and secondary malignancies was not investigated. However, in case of cMBL, it is known that lower numbers of circulating B lymphocytes are present in the peripheral blood in comparison with healthy individuals. In most MBL patients with more than $1.0 \times 10^9/l$ circulating monoclonal B lymphocytes there is a complete loss of circulating normal B lymphocytes, comparable with CLL.¹⁰ Whether decreased numbers of circulating normal B lymphocytes in cMBL patients (which does not coincide with lower immunoglobulin levels)¹⁷ results in an increased infection risk is questionable. A very recent cohort study of 520 MBL patients from the Mayo Clinics showed a 6.5-fold increased risk of infection requiring hospital admission in these patients as age-matched healthy controls.²⁰ Furthermore, it is known that MBL patients have a significantly lower risk of infections compared with CLL Rai stage 0 (risk of infection WHO grade 2 to 4: 10.9 per 100 patient-years for MBL and 15.1 per 100 patient-years for CLL).¹⁷ T-lymphocyte abnormalities have also been described in CLL, notably altered function of T lymphocytes.²¹⁻²⁵ Although not extensively investigated, T-lymphocyte dysfunctions do not seem to be prominent in MBL.²⁶ In conclusion, decreased immunity might occur in cMBL patients and awareness for infections is recommended.

RECOMMENDATIONS FOR DAILY PRACTICE

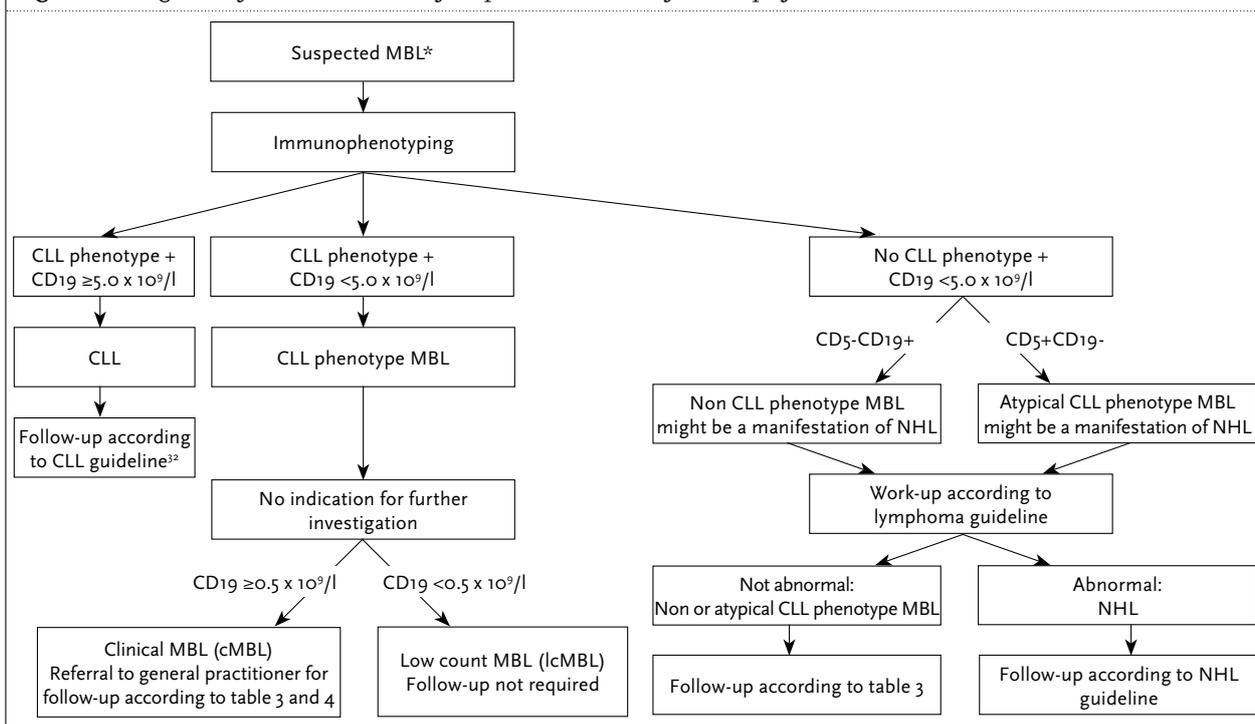
Official Dutch guidelines with respect to MBL are lacking, although recently a report in the *Nederlands Tijdschrift voor Geneeskunde* introduced the entity MBL.²⁷ Based on available literature and international consensus, the Dutch HOVON CLL Working Party formulated the following recommendations for daily practice (see algorithm, figure 1).^{2,28}

How to proceed in case of:

Suspected MBL

The general advice is to avoid screening of healthy individuals outside studies for MBL. However, if a lymphoproliferative disorder is suspected, for example in case of persisting (asymptomatic) lymphocytosis, referral to a haematologist is indicated for further investigation. A thorough medical history, physical examination and complete blood count need to be performed. In case of MBL, B symptoms (fever, weight loss, night sweats

Figure 1. Diagnostic flowchart in case of suspected MBL and follow-up of MBL



*Patients with persistent asymptomatic lymphocytosis without lymphadenopathy at physical examination, cytopenias and B symptoms. CLL = chronic lymphocytic leukaemia; MBL = monoclonal B-cell lymphocytosis; NHL = non-Hodgkin lymphoma.

and fatigue), palpable lymph nodes (>1 cm), hepatosplenomegaly, anaemia and thrombocytopenia need to be absent (table 3 and figure 1). Additional investigation includes peripheral blood smear, absolute B-lymphocyte count and immunophenotyping with at least the following markers: CD5, CD19, CD23, CD20, CD79b, IgM, IgD, IgG, kappa and lambda (table 1). There is no need for a further bone marrow aspirate or imaging in case of CLL phenotype MBL. Moreover, there is no additional value for further determination of prognostic markers such as CD38, ZAP-70, IGVH mutation status or cytogenetic abnormalities.² Furthermore (comparable with MGUS patients) patients need to be reassured that MBL is not in itself a lymphoproliferative disorder, but a pre-leukaemic condition with an increased risk to develop CLL.

In case of atypical-CLL phenotype MBL or non-CLL phenotype MBL, a more thorough evaluation is required due to the possible presence of leukaemic non-Hodgkin lymphoma. In contrast to CLL phenotype MBL, imaging studies and bone marrow biopsy for staging are recommended. Furthermore, fluorescent in situ hybridisation (FISH) analysis for cytogenetic aberrations such as t(11;14) and t(14;18) is advised to exclude mantle cell lymphoma (in atypical-CLL phenotype MBL) and follicular lymphoma (in non-CLL phenotype MBL) respectively. In the absence of these translocations it might be a manifestation of another indolent lymphoma.²

Confirmed CLL phenotype MBL

Although the annual risk of progression to CLL requiring treatment is 1 to 2%, this risk turns out to be strongly dependent on the number of circulating B lymphocytes in the peripheral blood (see earlier). Based on these data it seems reasonable, depending on age and comorbidity, that cMBL patients (CD19 ≥ 0.5 x 10⁹/l) are evaluated annually by their general practitioner. Evaluations need to consist of at least a detailed history (B symptoms), physical examination (lymphadenopathy and organomegaly) and complete blood cell count. The frequency of additional laboratory analysis should be increased to every three to six months when absolute lymphocyte counts increase by more than 5 x 10⁹/l (table 4).²⁸ Patients are advised to be referred to a haematologist in case clinical CLL/lymphoma-related symptoms develop (lymphadenopathy, night sweats, infections, weight loss) or in case one of the criteria mentioned in table 4 is met. These criteria are based on those used by a UK study which investigated the efficacy on the follow-up of CLL phenotype MBL when performed by general practitioners.²⁸ The benefit of Influenza vaccines has not been studied but it is reasonable to consider vaccination.

There is no need to evaluate individuals with lcMBL (CD19 < 0.5 x 10⁹/l), since the risk to develop CLL is not thought to be increased compared with the general population.

Table 3. Recommendations for evaluation and follow-up of MBL in daily practice (adapted from Shanafelt et al.²)

| Recommendations | CLL-like phenotype MBL | Atypical-CLL phenotype and non-CLL phenotype MBL |
|--|------------------------|--|
| Diagnostic evaluation | | |
| WBC count with differential | + | + |
| FISH with probe for t(11;14) and t(14;18) | - | + |
| Imaging | - | + |
| Bone marrow biopsy | - | + |
| CLL prognostic markers | - | - |
| Counselling and follow-up | | |
| Patient counselling on symptoms to watch for | + | + |
| Risk of progression requiring therapy | 1-2% per year | Undefined |
| History | Annual ^a | 3-12 months ^b |
| Physical exam | Annual ^a | 3-12 months ^b |
| CBC count with differential | Annual ^a | 6-12 months ^b |
| CT scan chest/abdomen/pelvis | - | Clinical judgement |

+ = yes; - = no; ^apreferentially by general practitioner; ^bpreferentially by haematologist.
CBC = complete blood cell; WBC = white blood cell.

Table 4. Recommendations for change in frequency of complete blood cell count and clinical referral (adapted from Rawstron et al.²⁸)

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|--|
| Increase frequency of complete blood cell count to 3-6 monthly if: Absolute lymphocytes increase by more than $5.0 \times 10^9/l$ in one year |
| Clinical referral is indicated if: Presence of B symptoms Absolute lymphocyte count $>30.0 \times 10^9/l$ Lymphocyte doubling time less than 1 year Anaemia (Hb <6.5 mmol/l or significantly decreasing Hb) Absolute platelet count $<100 \times 10^9/l$ |

It is recommended that the follow-up of patients with an atypical-CLL phenotype MBL or non-CLL phenotype MBL should be done by a haematologist, since there are limited data on the risk of progression (table 3).

RECOMMENDATIONS FOR DAILY PRACTICE

1. A substantial proportion of the general adult population carries monoclonal B-cell clones in their peripheral blood with a typical CLL immunophenotype.

2. In case of persisting asymptomatic lymphocytosis, there might be a manifestation of MBL and referral to a haematologist is indicated for a thorough evaluation consisting of medical history, physical examination, complete blood cell count and flow cytometry.
3. A distinction between 'CLL phenotype', 'atypical-CLL phenotype' and 'non-CLL phenotype' MBL needs to be made based on immunophenotyping in case of a newly diagnosed MBL.
4. Clinical MBL patients ($CD19 \geq 0.5 \times 10^9/l$) need to be evaluated at least annually with a complete blood cell count including white blood cell differentiation, since there is a reasonable chance to develop CLL requiring treatment.
5. Patients need to be reassured that MBL is a pre-leukaemic condition with an increased risk to develop CLL, but is not in itself a lymphoproliferative disorder.
6. Low-count MBL ($CD19 < 0.5 \times 10^9/l$) subjects do not need to be further evaluated, since the chance to develop CLL is not increased compared with the general population.

7. Patients with CLL phenotype MBL can be referred annually to their general practitioner for further evaluation, but follow-up of patients with atypical-CLL phenotype and non-CLL phenotype MBL should be performed by a haematologist.
8. There is no additional value for further determination of prognostic markers such as CD38, ZAP-70, IGHV mutation status and cytogenetic abnormalities in case of MBL. The only known prognostic marker in MBL is the absolute number of B lymphocytes.

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