GUIDELINES FOR DIAGNOSIS AND TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

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Table 2. Clinical stages and TTM

Rai stages

STAGE	DESCRIPTION	RISK
0	Lymphocytosis, in peripheral blood > 15 x 10^9/L and > 40% in bone marrow	Low
I	Stage 0 with enlarged lymph node (nodes)	Intermediate
II	Stage 0-I with splenomegaly, hepatomegaly or both	Intermediate
III*	Stage 0-II with hemoglobin < 110 g/L	High
IV*	Stage 0-III with platelets < 100 x 10^9/L	High

*immune cytopenias do not fit in this stage definition

Binet stages

STAGE	DESCRIPTION	RISK
A	Hemoglobin ≥ 100 g/L and platelets ≥ 100 x 10^9/L and < 3 involved regions**	Low
B	Hemoglobin ≥ 100g/L and platelets ≥ 100 x 10^9/L and ≥ 3 involved regions	Intermediate
C*	Hemoglobin < 100g/L and/or platelets < 100 x 10^9/L and any number of involoved regions	High

*immune cytopenias do not fit in this stage definition

**The five lymphoid areas comprise: uni or bilateral cervical, axillary and inguinal lymphoid, hepatomegaly and splenomegaly

TTM-score

COMPARTMENT	REPRESENTATIVE	SIZE	RISK
TM_1 – BM and PB	Lymphocyte count (peripheral blood)	$\sqrt{\lvert ly \rvert}\ x\ 10^9$/L	<9 Low
TM_2 - Ly nodes	Diameter of largest palpable node	cm	9-15 intermed
TM_3 - spleen	palpable spleen(below left costal margin)	cm	>15 High
TTM :		TM_1+TM_2+TM_3	Continuous variable

Legend: |ly| - absolute number of lymphocytes; TTM – Total Tumor Mass score

Note: if the largest lymph node is found by imaging (US or CT), those values should be used for TM_2

Tumor Mass Distribution (TD) is calculated as quantitative parameter according to formula: $TD = \frac{TM_1}{TTM}$.

Doubling Time of TTM (DT) is calculated as quantitative parameter according to formula: $DT = \frac{M\ x\ TTM_{beg}}{TTM_{end} - TTM_{beg}}$

where TTM_{beg} is size of TTM at the beginig of period M, TTM_{end} is TTM size at the end of period M; M is interval between TTM_{beg} and TTM_{end} in months.

M should be at least 3 months.

Electronic calculator is available online at http://www.krohem.hr

Table 6 FIRST LINE TREATMENT OF CLL (KROHEM v1 2017)

Stage	% [a]	Molecular cytogenetics	% [b]	General condition	% [b]	First line of treatment
						Standard [c]
Asymptomatic ; Binet:A-B ; Rai 0-II; TTM<9 (15)	33	Irrelevant		Irrelevant		Nothing (W&I)
Binet C, Rai III-IV; TTM>15; or symptomatic disease (indication for treatment met)	67	No del(17p) / TP53 mut	93	Fit	32	FCR (1) [d] B + R [e] Ibrutinib (1)
				Unfit	61	Chl + Obi (1) Chl + R Chl + Ofa B + R Ibrutinib (1)
		Del(17p) / TP53 mut	7	Irrelevant	7	Ibrutinib Idelalisib + R HDMP+R A [f]

Clinical trials are highly recommended for all subsets, we strongly believe that they improve the level of care.

[a] Projected percentages are based on compiled data from western countries and Croatia.

[b] Percentages of patients with distinct general condition and molecular genetics groups refer to treated patients. Fit patients are less than 65 years of age and with CIRS score less than 6. Younger patients with CIRS score of 6 and more and patients with 65 years or more (regardless of CIRS score) qualify as unfit.

[c] Standard treatments are in order of preference, all are 2A or less according to NCCN consensus, treatments with higher grade are marked (1).

[d] In patients with hipermutated IGHV and no 11q.

[e] for les fit patients.

[f] Alemtuzumab is withdrawn from market, but can be obtained free of charge from producer upon request

FCR (fludarabine, cyclophosphamide and rituximab); B = bendamustin; Chl = chlorambucil; R = rituximab; Obi = obinutuzumab; Ofa = ofatumumab; A = alemtuzumab; HDMP (high dose methylprednisolone).

Table 7 TREATMENT OF RELAPSED/REFRACTORY CLL (KROHEM V1 2017)

<table>
<tr><th rowspan="2">Relapse</th><th rowspan="2">% [a]</th><th rowspan="2">Molecular cytogenetics</th><th rowspan="2">%</th><th rowspan="2">General condition</th><th rowspan="2">%</th><th colspan="3">Salvage treatment</th></tr>
<tr><th colspan="2">Standard [b,c]</th><th>Extended / Maintenance</th></tr>
<tr><td rowspan="3">Early (< 2 years)
Refractory disease (< 1 year)</td><td rowspan="3">30</td><td rowspan="2">No del(17p) / TP53mut</td><td rowspan="2">22</td><td>Fit</td><td>7</td><td rowspan="2">Ibrutinib (1)
Idelalisib + R (1)
Venetoclax (1)[c]
HDMP + R
Ofa</td><td>FCR [d]
B+R [d]
F + A [e]</td><td>→AlloSCT
→antiCD20 [g]</td></tr>
<tr><td>Unfit</td><td>15</td><td>B + R
Chl + antiCD20 [d]</td><td>→antiCD20 [g]</td></tr>
<tr><td>Del(17p) / TP53mut</td><td>8</td><td>Fit & Unfit</td><td>8</td><td colspan="2">Ibrutinib (1)
Idelalisib + R (1)
Venetoclax (1)[f]
HDMP + R
A [e] ± R</td><td>→AlloSCT (fit)
→antiCD20 [g]</td></tr>
<tr><td>Late (> 2 years)</td><td>70</td><td></td><td>70</td><td>Fit & Unfit</td><td></td><td colspan="3">Repeat first line (or choose from above)</td></tr>
</table>

The guidelines for salvage treatment are more complex than in first line treatment. It should take into consideration additional criteria depending on type of treatment in first line, and on the observed duration of response. Clinical trials are highly recommended for all subsets, we strongly believe that they improve the level of care.

[a] Projected percentages of early and late relapses are based on KB Dubrava data for 2015 and 2016. Percentages of unfit patients and patients with del(17p) tend to increase. Fit patients = less than 65 years of age and with CIRS score less than 6. Younger patients with CIRS score of 6 and more and patients with 65 years or more qualify as unfit.

[b] Standard treatments are in order of preference, but for each individual patients the decision should be based on integration on clinical data and patients' preference. All treatments are 2A according to NCCN consensus, treatments with higher grade are marked (1).

[c] in patients who are unsuitable for or have failed a B-cell receptor signaling pathway inhibitor and chemo-immunotherapy.

[d] if not in 1st line.

[e] Alemtuzumab is withdrawn from market, but can be obtained free of charge from producer upon request.

[f] in patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor.

[g] ofatumumab is found to significantly prolong PFS in responsive patients in second or third response to chemoimmunotherapy, approved by FDA.

FCR (fludarabine, cyclophosphamide and R); B = bendamustin; Chl = chlorambucil; R = rituximab; Obi = obinutuzumab; Ofa = ofatumumab; A = alemtuzumab; Allo SCT = allogeneic stem cell transplantation; HDMP (high dose methylprednisolone); antiCD20 (ofatumumab or obinutuzumab or rituximab).