GUIDELINES FOR DIAGNOSIS AND TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

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KROHEM B-CLL
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5.12 FIRST LINE TRETMENT OF CLL (KROHEM v1 2016) 23-04-2016

Stage	% [a]	General condition	%	Molecular cytogenetics	%	First line of treatment	
						Standard [b]	Alternative [c]
Asymptomatic ; Binet:A-B ; Rai 0-II; TTM<9 (15)	33	Irrelevant		Irrelevant		Nothing (W&W)	
Binet C, Rai III-IV; TTM>15; or symptomatic disease (indication for treatment met)	67	Fit	33	No del(17p)	30	FCR (1) Bendamustin + Rituximab	
				Del(17p)	3	Ibrutinib Idelalisib + Rituximab* → AlloSCT (elective)	FCR HDMP + Rituximab
		Unfit	67	No del(17p)	62	Chlorambucil + Obinutuzumab (1) Chlorambucil + Rituximab Chlorambucil + Ofatumumab Bendamustin + Rituximab Ibrutinib (1)**	FCR reduc. CVP + R, HD Chlorambucil ± Predn.
				Del(17p)	5	Ibrutinib Idelalisib + Rituximab*	HDMP + Rituximab

[a] Percentages are based on compiled data from western countries and Croatia. Percentages of patients with distinct general condition and molecular genetics groups refer to treated patients. Fit patients are less than 70 years of age and with CIRS score less than 6. Younger patients with CIRS score of 6 and more and patients with 70 years or more (regardless of CIRS score) qualify as unfit.

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

[c] Clinical trials are highly recommended for all subets, since we strongly believe that they improve the level of care.

*Pending on regulator decision.

**Ibrutinib is approved for first line therapy by FDA, but not yet by EMA.

FCR (fludarabine, cyclophosphamide and rituximab); R = rituximab; Allo SCT = allogeneic stem cell transplantation; HDMP (high dose methylprednisolone); CVP (cyclophosphamide, vincristine, prednisone); HD Chlorambucil (high dose continuous chlorambucil).

5.13 TREATMENT OF RELAPSED/REFRACTORY CLL (KROHEM v1 2016) 23-04-2016

Relapse	% [a] (FCR)	General condition	%	Molecular cytogenetics	%	Salvage treatment	
						Standard [b]	Alternative [c]
Early (< 3 years) Refractory disease (< 1 year)	30	Fit	9	No del(17p)	7	Ibrutinib (1) Idelalisib + Rituximab (1)* FCR (if not in 1st line) Bendamustin + Rituximab HDMP + Rituximab Ofatumumab	CHOP + R DHAP + R OFAR Fludarabin + Alemtuzumab*** antiCD20 maintenance (2B)**** →AlloSCT
				Del(17p)	2	Ibrutinib Idelalisib + Rituximab* HDMP + Rituximab Alemtuzumab*** ± Rituximab Venetoclax**	→AlloSCT CHOP + R antiCD20 maintenance (2B)****
		Unfit	21	No del(17p)	15	Ibrutinib (1) Idelalisib + Rituximab (1)* Bendamustin + Rituximab FCR reduc Chlorambucil + antiCD20 (not received in first line) HDMP + Rituximab	Fludarabin + Alemtuzumab*** CVP + Rituximab antiCD20 maintenance (2B)****
				Del(17p)	6	Ibrutinib Idelalisib + Rituximab* HDMP + Rituximab Venetoclax**	antiCD20 maintenance (2B)****
Late (> 3 years)	**70**	Fit & Unfit	70			Repeat first line (or choose from above)	

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. The operational definition of early relapse may be defined as PFS < expected median for given therapy (F=12, Chl+R=12, Chl+Obi=24, BR=24, FCR=36 months).
[a] Percentages are based on best FCR published data (Tam CS et al, Blood 2014;124:3059). With less efficient treatments the likelihood of relapse percentage in first 3 years considerably increases. Also the percentages of unfit patients and patients with del(17p) tend to increase. Fit patients = less than 70 years of age and with CIRS score less than 6. Younger patients with CIRS score of 6 and more and patients with 70 years or more qualify as unfit; [b] Standard treatments are in order of preference, all are 2A or less according to NCCN consensus, treatments with higher grade are marked; [c] Clinical trials are highly recommended for all subsets, we strongly believe that they improve the level of care.
*Pending on regulator decision; **Venetoclax is approved for second line therapy by FDA, but not yet by EMA; ***Alemtuzumab is withdrawn from market, but can be obtained free of charge from producer upon request; **** 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); R = rituximab; Allo SCT = allogeneic stem cell transplantation; HDMP (high dose methylprednisolone); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); DHAP (dexamethasone, cytarabine and cisplatin (CDDP)); OFAR (oxaliplatin, fludarabine, cytarabine, rituximab); CVP (cyclophosphamide, vincristine, prednisone: antiCD20 (ofatumumab or obinutuzumab or rituximab).