

# **GUIDELINES FOR DIAGNOSIS AND TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA**

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## 5.12 FIRST LINE TRETMENT OF CLL (KROHEM v1 2015) 07-05-2015

Stage	%*	General condition	%	Molecular cytogenetics	%	First line of treatment	
						Standard **	Alternative ***
Asymptomatic ; Binet:A-B ; Rai 0-II; TTM<9 (15)	33	Irrelevant		Irrelevant		Nothing (W&W)	Clinical trial
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	Clinical trial
				Del(17p)	3	Ibrutinib Idelalisib + Rituximab FCR HDMP + Rituximab → AlloSCT (elective)	Clinical trial CHOP + R DHAP + R HDDex + R OFAR
		Unfit	67	No del(17p)	62	Chlorambucil + Obinutuzumab (1) Chlorambucil + Rituximab Chlorambucil + Ofatumumab Bendamustin**** + Rituximab	Clinical trial FCR reduc CVP + R, HD Chlorambucil ± Pred
				Del(17p)	5	Ibrutinib Idelalisib + Rituximab FCR reduc HDMP + Rituximab	Clinical trial

\*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.

\*\*Standard treatments are in order of preference, all are 2A according to NCCN consensus, treatments with higher grade are marked (1).

\*\*\*Clinical trials are highly recommended, since we strongly believe that they improve the level of care.

\*\*\*\*Bendamustin is not yet approved in Croatia (but is approved in majority of EU countries).

FCR (fludarabine, cyclophosphamide and rituximab ); R = rituximab; Allo SCT = allogeneic stem cell transplantation; HDMP (high dose methylprednisolone); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); DHAP (dexamethasone, cytarabine and cisplatin (CDDP)); HDDex (high-dose dexamethasone); OFAR (oxaliplatin, fludarabine, cytarabine, rituximab); CVP (cyclophosphamide, vincristine, prednisone); HD Chlorambucil (high dose continuous chlorambucil).

### 5.13 TREATMENT OF RELAPSED/REFRACTORY CLL (KROHEM v1 2015) 07-05-2015

Relapse	%* (FCR)	General condition	%	Molecular cytogenetics	%	Salvage treatment	
						Standard **	Alternative ***
Early (< 3 years) Refractory disease (< 1 year)	30	Fit	9	No del(17p)	7	Ibrutinib (1) Idelalisib + Rituximab FCR (>18 months w/o DP) Bendamustin**** + Rituximab Fludarabin + Alemtuzumab***** (>12 months w/o DP) HDMP + Rituximab Ofatumumab	Clinical trial CHOP + R DHAP + R OFAR →AlloSCT
				Del(17p)	2	Ibrutinib Idelalisib + Rituximab HDMP + Rituximab Alemtuzumab ± Rituximab	Clinical trial →AlloSCT CHOP + R
		Unfit	21	No del(17p)	15	Ibrutinib (1) Idelalisib + Rituximab FCR reduc Bendamustin**** + Rituximab Chlorambucil + antiCD20 (not received in first line) HDMP + Rituximab	Clinical trial Fludarabin + Alemtuzumab***** CVP + Rituximab
				Del(17p)	6	Ibrutinib Idelalisib + Rituximab HDMP + Rituximab	Clinical trial
Late (> 3 years)	70	Fit & Unfit	70			Repeat first line (or choose from above)	Clinical trial

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. Therefore, the operational definition of early relapse may be defined as PFS < expected median for given therapy (ChI+R=12, ChI+Obi=24, FCR=36 months).

\*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.

\*\*Standard treatments are in order of preference, all are 2A according to NCCN consensus, treatments with higher grade are marked (1).

\*\*\*Clinical trials are highly recommended, we strongly believe that they improve the level of care.

\*\*\*\*Bendamustin is not yet approved in Croatia (but is approved in majority of EU countries).

\*\*\*\*\*Alemtuzumab is withdrawn from market, but can be obtained free of charge from producer upon request.

FCR (fludarabine, cyclophosphamide and rituximab ); R = rituximab; Allo SCT = allogeneic stem cell transplantation; HDMP (high dose methylprednisolone); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); DHAP (dexamethasone, cytarabine and cisplatin (CDDP)); HDDex (high-dose dexamethasone); OFAR (oxaliplatin, fludarabine, cytarabine, rituximab); CVP (cyclophosphamide, vincristine, prednisone); HD Chlorambucil (high dose continuous chlorambucil).