ELN European LeukemiaNet

UPDATE 2013

European LeukemiaNet Recommendations for the Management of Chronic Myeloid Leukemia (CML)

Baccarani et al, Blood 2013;122:872-884

Response definitions for any TKI first line, and 2nd line in case of intolerance, all patients (CP, AP, and BC)

Time	Optimal response	Warning	Failure
Baseline		High risk Major route CCA/Ph+	
3 mos.	BCR-ABL^{IS} ≤10%* Ph+ ≤35% (PCyR)	BCR-ABL^{IS} >10%* Ph+ 36-95%	No CHR* Ph+ >95%
6 mos.	BCR-ABL^{IS} <1%* Ph+ 0% (CCyR)	BCR-ABL^{IS} 1-10%* Ph+ 1-35%	BCR-ABL^{IS} >10%* Ph+ >35%
12 mos.	BCR-ABL^{IS} ≤0.1%* (MMR)	BCR-ABL^{IS} 0.1-1%*	BCR-ABL^{IS} >1%* Ph+ >0%
Then, and at any time	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

Treatment recommendations

Line	Event		TKI, standard dosage[1]					Transplantation				
Chronic phase												
								Search for		alloSCT		
			Imatinib 400 mg/qd	Nilotinib 300 mg/bid	Dasatinib 100 mg/qd	Bosutinib 500 mg/qd	Ponatinib 45 mg/qd	HLA type + sibs	unrelated donor	consider	recommended	Chemotherapy
1st	Baseline		X	X	X			X[2]				
2nd	Intolerance to 1st TKI		Any other TKI approved 1st line									
	Failure 1st line of	imatinib		X[8]	X	X	X	X				
		nilotinib			X	X	X	X	X	X		
		dasatinib		X[8]		X	X	X	X	X		
3rd	Intolerance to/failure of two TKI		Any remaining TKI								X	
Any	T315I mutation						X	X	X	X		
Accelerated or blast phase												
In newly diagnosed, TKI naïve patients	start with		X[3]		X[4]			X	X			
	no optimal response, BP										X[7]	X[5]
TKI pre-treated patients			Any other TKI				X[6]				X[7]	X[5]

[1]choice of the TKI consider tolerability and safety, and patient characteristics (age, comorbidities), [2]only in case of baseline warnings (high risk, major route CCA/Ph+), [3]400 mg/bid, [4]70 mg/bid or 140 mg/qd, [5]may be required before SCT to control disease and to make patients eligible to alloSCT, [6]in case of T315I mutation, [7]only patients who are eligible for alloSCT, not in case of uncontrolled, resistant BP, [8]400 mg bid in failure setting qd: Once daily bid: Twice daily

Other definitions

CCA	Clonal chromosome abnormalties
CCA/Ph+	CCA in Ph+ cells which define failure if newly arisen
CHR	Complete hematologic response: Platelet count < 450 x 10^9 /L; WBC count <10 x 10^9 /L; Differential: no immature granulocytes, basophils <5%; no palpable spleen
High risk	Evaluated by Sokal-Score (>1.2), Euro-Score (>1,480) or EUTOS-Score (>87)
Major route CCA/Ph+	Major route CCA/Ph+ are trisomy 8, 2nd Ph+ [+der(22)t(9;22)(q34;q11)], isochromosome 17 [i(17)(q10)], trisomy 19, and ider(22)(q10)t(9;22)(q34;q11)
Mutations	BCR-ABL kinase domain point mutations (not to be confused with ABL1 polymorphisms), Mutational analysis by conventional Sanger sequencing is recommended in case of progression, failure and warning.

Timing of Cytogenetic and Molecular Monitoring

At diagnosis	CBA, FISH in case of Ph- (for cryptic or variant translocations), qualitative PCR (transcript type)
During treatment	RQ-PCR every 3 months until MMR has been achieved, then every 3 to 6 months and/or CBA at 3, 6, and 12 months until CCyR has been achieved, then every 12 months. Once CCyR is achieved, FISH on blood cells can be used.
Failure, progression	RQ-PCR, mutational analysis, and CBA. Immunophenotyping in blast phase.
Warning	Molecular and cytogenetic tests more frequently. CBA in case of myelodysplasia or CCA/Ph-

CBA: Chromosome banding analysis of marrow cell metaphases at least 20 metaphases analysed

Response definitions to 2nd line therapy in case of failure of imatinib (can be used provisionally, NOT for the response to 3rd line treatment).

Time	Optimal response	Warnings	Failure
Baseline		No CHR Loss of CHR on imatinib Lack of CyR to 1st line TKI High risk	
3 mos.	BCR-ABL^{IS} ≤10%* Ph+ <65%	BCR-ABL^{IS} >10%* Ph+ 65-95%	No CHR, or Ph+ >95%, or New mutations
6 mos.	BCR-ABL^{IS} ≤10%* Ph+ <35% (PCyR)	BCR-ABL^{IS} ≤10%* Ph+ 35-65%	BCR-ABL^{IS} >10%* Ph+ >65%* New mutations
12 mos.	BCR-ABL^{IS} <1%* Ph+ 0 (CCyR)	BCR-ABL^{IS} 1-10%* Ph+ 1-35%	BCR-ABL^{IS} >10%* Ph+ >35%* New mutations
Then, and at any time	MMR or better	CCA/Ph- (-7 or 7q-) or BCR-ABL^{IS} >0.1%	Loss of CHR, or Loss of CCyR or PCyR New mutations Loss of MMR** CCA/Ph+

*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

Definition of response

Optimal response	Best long-term outcome No indication for a change of treatment.
Failure	Patient should receive a different treatment to limit the risk of progression and death
Warning	Characteristics of disease and response to treatment require more frequent monitoring to permit timely changes in therapy, in case of treatment failure.