Mise à jour des recommandations ELN pour le traitement et le suivi de la LMC

L VERONESE

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REVIEW ARTICLE

Chronic myelogenous leukemia

European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

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Qui ?

Panel d'experts internationaux de la LMC (n=34)
Europe, USA, Asie

Patients impliqués

Comment ?

6 réunions entre 2015 et 2019 (pendant ASH, ELN etc…)
5 séries de questions clés soumises aux experts
Consensus adopté si > 75% des experts ; certains points restent en discussion
Financement par ELN

Pourquoi ?

Evolution des thérapeutiques
Identification de stratégies permettant **l'arrêt de traitement par ITK** et l'obtention d'une TFR (=treatment free remission)

DIAGNOSTIC

Table 1 Diagnostic work-up, baseline.

Physical examination with particular reference to spleen and liver size
Complete blood cell count with microscopic differential
Bone marrow aspirate for cytologic examination and cytogenetics; core biopsy if dry tap
Chromosome banding analysis (CBA)
Fluorescence in-situ hybridization (FISH) only in case of Ph-negativity
Qualitative reverse transcriptase polymerase chain reaction (PCR) for the detection of BCR-ABL1 transcripts and identification of the transcript type
Electrocardiogram
Standard biochemical profile with hepatitis B-serology

Blastose ? (CP – AP – BP)

Bandes G

Identification du transcrit (2-4% transcrits atypiques)
Quantification initiale non indispensable

SCORE PRONOSTIQUES INITIAUX

Table 2 Prognostic scores at baseline and comparison of Sokal [21] and ELTS [24] scores.

(a) Score calculation

Score	Calculation	Definition of risk groups
Sokal	Exp 0.0116 × (age—43.4)	Low risk: <0.8
	+0.0345 × (spleen—7.51)	Intermediate-risk: 0.8–1.2
	+0.188 × [(platelet count/700)^2—0.563]	High-risk: >1.2
	+0.0887 × (blood blasts—2.10)	
ELTS	0.0025 × (age/10)^3	Low risk: <1.5680
	+0.0615 × spleen size	Intermediate risk:1.5680–2.2185
	+0.1052 × peripheral blood blasts	High-risk: >2.2185
	+0.4104 × (platelet count/1000)$^{-0.5}$	

(b) Risk strata proportions and outcome

	Low risk		Intermediate risk		High risk	
$n = 5154$	Sokal	ELTS	Sokal	ELTS	Sokal	ELTS
%	38	55	38	28	23	13
10-year OS	89%	88%	81%	79%	75%	68%
6-year LRD	3%	2%	4%	5%	8%	12%

3 scores : Sokal, Euro, and EUTOS

ELTS = new EUTOS Long Term Survival (ELTS)
Pour patient sous ITK
Impact moindre de l'âge sous ITK (vs chimio)
⇒ Utilisation **recommandée** par l'ELN
⇒ Calculateur en ligne

Autres facteurs de risque identifiés (moindre réponse / progression) :

-myélofibrose
-**ACA de haut risque**
+8,
+Ph
i(17q)
+19
−7/7q-
11q23
or 3q26.2 aberrations
and complex aberrant karyotypes

DEFINITIONS DES REPONSES

Table 4 Milestones for treating CML expressed as BCR-ABL1 on the International Scale (IS).

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

For patients aiming at TFR, the optimal response (at any time) is BCR-ABL1 ≤0.01% (MR^4).

A change of treatment may be considered if MMR is not reached by 36–48 months.

NA not applicable, *ACA* additional chromosome abnormalities in Ph+ cells, *ELTS* EUTOS long term survival score.

[a]Loss of MMR (BCR-ABL1 >0.1%) indicates failure after TFR

Tous les 3 mois au minimum
Même après MMR

Réponse moléculaire profonde RMP

Table 3 Reference gene numbers required for scoring molecular response [29, 31].

	MMR	MR^4	$MR^{4.5}$	MR^5
Minimum sum of reference gene transcripts	10,000 ABL1[a] 24,000 GUSB[a]	10,000 ABL1 24,000 GUSB	32,000 ABL1 77,000 GUSB	100,000 ABL1 240,000 GUSB
BCR-ABL1 transcript level on the IS[b]	≤0.1%	≤0.01%	≤0.0032%	≤0.001%

[a]Minimal sensitivity for accurate quantification.

[b]International Scale, IS.

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Même après MMR

to assess eligibility for treatment discontinuation. Cytogenetics, by CBA of marrow cell metaphases, may be useful when performed, but alone is not sufficiently sensitive to monitor response. However, cytogenetics should be done in patients with atypical translocations, rare or atypical BCR-ABL1 transcripts that cannot be measured by qPCR, treatment failure/resistance to exclude ACA, and with progression to AP or BP. FISH monitoring may be needed in patients with atypical transcripts.

« emergence of additional chromosome abnormalities in Ph+ cells (ACA) raise concerns for progression of disease »

Faire caryotype si :
Translocation atypique
Transcrit rare / atypique
Echec / résistance
Progression vers AP ou BP

TRAITEMENT

PREMIERE LIGNE

-(hydrea)

-ITK => 4 molécules approuvées (EMA et FDA) :

imatinib (Glivec* ou gé)

dasatinib (Sprycel*)

nilotinib (Tasigna*) } 2G-ITK

bosutinib (Bosulif*)

radotinib (Supect) en corée du sud*

DEUXIEME LIGNE

-en cas d ’échec / résistance

-en cas d’intolérance / complication liée au ttt

Choix fondé sur

-présence de mutations du domaine kinase de BCR-ABL (NGS>Sanger)

-comorbidités / terrain

3G-ITK : ponatinib (Iclusig*)

Approuvé pour T315i ou intolérance/résistance ≥ 2 ITK

Table 5 Recommended tyrosine kinase inhibitors in case of BCR-ABL1 resistance mutations.

T315I	Ponatinib
F317L/V/I/C, T315A	Nilotinib, bosutinib[a], or ponatinib
V299L	Nilotinib or ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, bosutinib[a], or ponatinib

[a]There are limited data available regarding mutations associated with clinical resistance to bosutinib in vivo. Some in vitro data suggest that the E255K and, to a lesser extent, the E255V mutation, might be poorly sensitive to bosutinib.

Place du PEG-IFNα ?

TRAITEMENT

Survie globale
Espérance de vie normale pour la plupart des patient LMC PC

↓

Obtention d'une RMP stable (MR4 ou MR4.5)

↓

Arrêt de traitement et obtention d'une TFR

Table 7 Cumulative incidence of deep molecular response (MR^4 and $MR^{4.5}$) with imatinib, nilotinib, and dasatinib by 5 and 10 years.

Study		5 years (%)	10 years (%)
CML-Study IV[a], [36, 37]	Imatinib MR^4	68	81
	Imatinib $MR^{4.5}$	53	72
ENESTnd[b], [41, 52]	Nilotinib MR^4	66	73
	Nilotinib $MR^{4.5}$	54	64
	Imatinib MR^4	42	56
	Imatinib $MR^{4.5}$	35	45
Dasision[c], [40]	Dasatinib $MR^{4.5}$	42	NA
	Imatinib $MR^{4.5}$	33	NA

DMR rates of these trials cannot be directly compared owing to different methods of trial evaluation.

NA not available.

[a]Imatinib ($n = 1442$).

[b]Nilotinib 300 mg twice daily ($n = 282$), imatinib 400 mg daily ($n = 283$).

[c]Dasatinib 100 mg once daily ($n = 259$), imatinib 400 mg daily ($n = 260$).

TFR

Table 8 Requirements for tyrosine kinase inhibitor discontinuation.

Mandatory:

- CML in first CP only (data are lacking outside this setting)
- Motivated patient with structured communication
- Access to high quality quantitative PCR using the International Scale (IS) with rapid turn-around of PCR test results
- Patient's agreement to more frequent monitoring after stopping treatment. This means monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter.

Minimal (stop allowed):

- First-line therapy or second-line if intolerance was the only reason for changing TKI
- Typical e13a2 or e14a2 BCR–ABL1 transcripts
- Duration of TKI therapy >5 years (>4 years for 2GTKI)
- Duration of DMR (MR^4 or better) >2 years
- No prior treatment failure

Optimal (stop recommended for consideration):

- Duration of TKI therapy >5 years
- Duration of DMR > 3 years if MR^4
- Duration of DMR > 2 years if $MR^{4.5}$

>80% des rechutes moléculaires surviennent dans les 6-8 mois

↓

Reprise du même ITK

3 évolutions péjoratives / >3000 patients inclus ds protocoles

« UNMET NEEDS »

Le taux d'échec augmente avec le nombre de ligne de ttt

Parmi les patients en 2L, 63-72% n'atteignent pas de MMR et 50-56% n'atteignent pas de RCyC

Mutations KD

T315I chez ~15% des patients en échec d'imatinib
Options thérapeutiques limitées

Résistance

Absence de mutation KD chez 2/3 des patients résistants en PC
=> Autres mutations et autres thérapies ciblées ?

Obtention RMP

50-70% des patients n'atteignent pas la MR4.5 en 5 ans
=> Chgt ITK même si MMR?

Coût

80% des patients n'atteindront jamais une TFR
Imatinib ge+++

Sécurité

Effet des ITK à long/très long terme