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Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

The incidence of chronic myeloid leukemia (CML) ranges between 10 and 15 cases/10^6/year (age adjusted) without any major geographic or ethnic differences [1]. The median age at diagnosis ranges between 60 and 65 years in Europe, but is considerably lower in countries where the population is younger. The prevalence of CML is steadily rising due to the very substantial prolongation of survival that has been achieved with targeted therapy [2].

molecular biology and pathology

The translocation of the ABL gene from chromosome 9 to 22 t (9;22)(q3.4;q1.1) leads to the formation of a new, hybrid, fusion gene (BCR-ABL) that codes for an oncoprotein (P210, more rarely P190 or P230) that is located in the cytoplasm and has a strong, constitutively activated, tyrosine kinase activity, resulting in the activation of several downstream signals that transform hematopoietic stem cells [3]. BCR-ABL-positive cells are genetically unstable and are prone to develop multiple and heterogenous genomic abnormalities, resulting in the transformation of the leukemic phenotype from chronic to acute, hence leading to the progression from chronic (CP) to accelerated and blast phases (AP, BP) [1]. One important event associated with progression is the development of point mutations in the kinase domain (KD) of the BCR-ABL gene, leading to resistance to the tyrosine kinase inhibitors (TKI) [4, 5].

Bone marrow (BM) biopsies taken from untreated patients at diagnosis [6] show increased cellularity due to proliferation of the granulocytic series that turns in different stages of maturation, although myelocytes and segmented forms predominate. No substantial features of dysplasia are found. Eosinophils may be prominent. Blasts must account for <5% of the whole examined population. Megakaryocytes are smaller than normal with hypolobulated nuclei ('dwarf megakaryocytes'). Although their number may be normal or slightly decreased, in ~50% of cases there is moderate to extensive megakaryocytic proliferation. Moderate to marked reticulin fibrosis is encountered in ~30% of cases [6]. Pseudo-Gaucher cells and sea-blue histiocytes are usually observed. Notably, the BM picture undergoes important changes, particularly following long-term treatment. These consist in reduction of the granulocytic cellularity, normalization of megakaryopoiesis, regression of fibrosis, and increase in apoptosis associated with decrease in proliferative activity.

The recognition of disease progression from CP to BP is relevant for prognosis and treatment. However, the clinical and morphologic boundaries between these stages are sometimes vague. Immunohistochemistry with a large panel of antibodies raised against CD34, TdT, myeloid, monocytic, erythroid, B and T-lymphoid cell markers gives objective support to the morphologic interpretation, by also allowing the distinction between myeloid (70%–80%) and lymphoid (20%–30%) blast crisis [6].

diagnosis/assessment of prognosis

The symptoms are not specific, including weight loss, asthenia, small fever, sweats, and malaise, and are not frequent, since in ~40% of cases the diagnosis is fortuitous, being based on abnormal blood counts and differential. Physical findings consist mainly or only in splenomegaly, in slightly >50% of patients. The hallmark of diagnosis is leukocytosis with basophilia and with immature granulocytes, mainly metamyelocytes, myelocytes and promyelocytes, and few or occasional myeloblasts. Severe anemia is rare. Thrombocytosis is frequent. Blood counts and differential are very important for the calculation of a prognostic risk (Table 1) [7–9] and for the distinction between chronic, accelerated and blast phases (Table 2) [6, 10, 11].

The diagnosis must be confirmed by cytogenetics showing t (9; 22)(q3.4;q1.1), and by reverse transcriptase polymerase chain reaction (RT-PCR) showing BCR-ABL transcripts. Cytogenetics must be performed by chromosome banding analysis (CBA) of marrow cell metaphases [12, 13]. If marrow

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cells cannot be obtained, CBA can be substituted by interphase fluorescence in situ hybridization (I-FISH) of blood cells, using dual color dual fusion probes that allow the detection of BCR-ABL+ nuclei. CBA is required, because it is necessary to detect additional chromosome abnormalities. FISH is not required, but it may become necessary to detect some variant translocations [14]. Qualitative RT-PCR is performed on RNA extracted by freshly collected BM or blood cells. It identifies the transcript type, either e14a2 or 13a2 (also known as b3a2 and b2a2), or much more rarely e19a2, or e1a2, indicating the BCR-ABL protein weight (P210, rarely P230 or P190). Real time, quantitative, PCR (RT-Q-PCR measuring BCR-ABL transcripts level as BCR-ABL % on the International Scale) is not required baseline. It will be necessary, later on, for monitoring the response to treatment [15–17]. These recommendations for the baseline diagnostic work-up are summarized in Table 3.

management, treatment, and monitoring

The treatment of CML was historically based on busulfan, that should no longer be used, then on hydroxyurea, that is still used for a short and quick pretreatment phase in case of marked leukocytosis or thrombocytosis [1]. Interferon-α (IFNα) became the gold standard in the 90s and for a decade, before the introduction of tyrosine kinase inhibitors (TKI) [18]. Imatinib was the first TKI to be used and is still the gold standard of first-line treatment worldwide [19–24]. More recently, the second-generation TKI nilotinib and dasatinib have been tested and approved for second-line [25, 26], then also for first-line treatment [27–31]. Current treatment recommendations are reported in Table 4.

These recommendations are based on the assessment of the response (Table 5) and on the definition of the response (Table 6). The response to TKI can be classified as optimal,

Table 1. The relative risk of a patient with CML can be calculated using simple clinical and hematologic data provided that they are collected prior to any treatment

	Sokal et al. [7]	EURO [8]	EUTOS [9]
Age (years)	0.116 (age—43.4)	0.666 when age >50	NA
Spleen size (cm)	0.345 × (spleen—7.51)	0.042 × spleen	4 × spleen
Platelet count (×109/l)	0.188 × [(platelet/700)^2 − 0.563]	1.0956 when platelet ≥1500	NA
Blood blast cells (%)	0.887 × (blast cells—2.10)	0.0584 × blast cells	NA
Blood basophils (%)	NA	0.20399 when basophils >3%	7 × basophils
Blood eosinophils (%)	NA	0.0413 × eosinophils	NA
Relative risk	Exponential of the total	total × 1000	Total
Low	<0.8	≤780	≥87
Intermediate	0.8–1.2	781–1480	NA
High	>1.2	>1480	>87

There are three systems: Sokal et al. [7], that was developed in 1984, in the era of conventional chemotherapy; EURO [8], that was derived in 1998 from IFNα-treated patients, and EUTOS [9], that has derived more recently (2011) from imatinib-treated patients. The EUTOS risk score is simpler, and in imatinib-treated patients have a prognostic value greater than Sokal and EURO.
Spleen is measured by manual palpation and expressed as maximum distance below costal margin.
NA: not applicable; CML: chronic myeloid leukemia; IFNα: interferon-α.

Table 2. Clinical and hematologic criteria for the definition of AP and BP according to WHO [6] and to ELN [11]

	Accelerated phase		Blast phase	
	WHO [6]	ELN [11]	WHO [6]	ELN [11]
Spleen	Persisting or increasing splenomegaly unresponsive to therapy	/	/	/
WBC	Persisting or increasing WBC (>10 × 10^9/l) unresponsive to therapy	/	/	/
Blast cells[a]	10%–19%	15%–29%	≥20%	≥30%
Basophils[a]	>20%	>20%	/	/
Platelet count	>1000 × 10^9/l uncontrolled by therapy	/	/	/
	<100 × 10^9/l unrelated to therapy	Yes	/	/
CCA/Ph+	Present	Present	/	/
Extramedullary involvement[b]	/	/	Present	Present

The criteria of AP are different, reflecting the difficulty of making the diagnosis of this transitory phase. The criteria of BP differ only for the percent of blast cells. Only one of the listed criteria is sufficient for the diagnosis of AP or BP.
CCA/Ph+ = clonal chromosome abnormalities in Ph+ cells.
[a]In peripheral blood or in BM.
[b]Excluding liver and spleen, including lymph nodes, skin, CNS, bone, and lung.
AP: accelerated phase; BP: blast phase; WHO: World Health Organization; ELN: European LeukemiaNet; BM: bone marrow.

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Table 3. Recommendations for the diagnostic workup and for assessing and monitoring the response to treatment

	Baseline (diagnostic workup)	To assess the response	To monitor the response and the treatment
Blood counts and differential	Yes	Every 15 days until a CHR has been achieved	Every 3 months
Bone marrow, cytology	Yes	No	No
Bone marrow, Karyotype (CBA)	Yes	At 3 and 6 months, then every 6 months, until a CCgR has been achieved	Every 12 months, once a CCgR has been achieved, only if molecular response cannot be assured
Blood, I-FISH	No	No	Only if CBA of marrow cell metaphases cannot be performed, and molecular response cannot be assessed
Blood, RT-PCR (qualitative)	Yes	No	No
Blood, RT-Q-PCR (quantitative, BCR-ABL %)	No	Every 3 months until a major molecular response has been achieved	Every 6 months, once a MMR has been achieved
Mutational analysis	Only in AP or BP	No	Only in case of failure (see Table 6)

There are no prospective studies providing evidence for these recommendations, but they are strongly supported by expert opinions and by the design of all main studies [1, 6, 10, 11, 14, 15, 16, 19–32, 36–39].
CBA: chromosome banding analysis; I-FISH: interphase fluorescence in situ hybridization; CCgR: complete cytogenetic response; CHR: complete hematologic response; AP: accelerated phase; BP: blastic phase; RT-PCR: reverse transcriptase polymerase chain reaction; RT-Q-PCR: quantitative reverse transcriptase polymerase chain reaction; MMR: major molecular response.

Table 4. Treatment recommendations

Chronic phase	
First line	Imatinib 400 mg, or nilotinib 300 mg × 2, or dasatinib 100 mg
Second line	In case of intolerance, switch to another TKI, taking into consideration the side effects of the first TKI, and comorbidities
	In case of failure of imatinib, switch to nilotinib, or dasatinib, taking into consideration the presence and the type of BCR-ABL KD mutation
	In case of failure of nilotinib or dasatinib, switch to dasatinib or nilotinib, taking into consideration the presence and the type of BCR-ABL KD mutation. Consider alloHSCT
Third line	In case of failure of two or three TKI, consider alloHSC
Accelerated/blastic phase	
TKI naïve	Imatinib 600 or 800 mg, or nilotinib 400 mg × 2 or dasatinib 140 mg, and consider alloHSCT
TKI pretreated	Switch to another TKI, consider chemotherapy and alloHSCT

For all recommendations for CP, the level of evidence is I (evidence from at least one large randomized, controlled trial of good methodological quality) and the grade is A (strong evidence for efficacy with a substantial clinical benefit, strongly recommended). However, the choice among the three currently available tyrosine kinase inhibitors (TKI) is based on a low level of evidence, which does not allow any strong recommendation to be made. For all recommendations for AP and BP, the level of evidence is III/IV (prospective and retrospective cohort studies) and the grade is B (strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended). Experimental treatments are under active investigation in first, second, and third lines.
TKI: tyrosine kinase inhibitors; alloHSCT: allogeneic hematopoietic stem cell transplantation; KD: kinase domain.

Table 5. Assessment of responses

CHR
WBC <10 × 10^9/l, no immature granulocytes, basophils <5%, platelet count <450 × 10^9/l, spleen non-palpable
CgR
Complete CgR, no Ph+ metaphases by CBA, or <1% BCR-ABL+ nuclei by I-FISH
Partial CgR, 1%–35% Ph+ metaphases by CBA
Minor CgR, 36%–65% Ph+ metaphases by CBA
Minimal CgR, 66%–95% Ph+ metaphases by CBA
No CgR, >95% Ph+ metaphases by CBA
MR
Major MMR when the BCR-ABL transcript level is ≤0.1% on the International Scale
Complete MR when the BCR-ABL is undetectable by RT-Q-PCR. The transcript level can be below 0.01% or 0.0032%, or 0.001%, depending on the sensitivity of the assay

The CgR is assessed on marrow cells by standard CBA. The molecular response is assessed on blood, buffy coat, cells, by RT-Q-PCR and is expressed as BCR-ABL^{IS} % according to the International Scale. The definition of these responses is based on expert consensus [1, 6, 10, 11].
CHR: complete hematologic response; WBC: white blood cell; CgR: cytogenetic response; CBA: chromosome banding analysis; I-FISH: interphase fluorescence in situ hybridization; MR: molecular response; MMR: major molecular response.

meaning that continuing treatment the survival is predicted to be normal or close to normal; and failure, meaning that treatment must be switched to a second-generation TKI, or allogeneic hematopoietic stem cell transplantation (alloHSCT). Between optimal and failure, there is a gray zone that was

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Table 6. Definition of the response to first-line therapy with TKI (imatinib, nilotinib, and dasatinib)

	Optimal = continue the treatment	Warning = monitor more carefully some patients may benefit of a change of treatment	Failure = change the treatment
3 months	Ph+ ≤95%, or BCR-ABL <10%		Ph+ >95%, or BCR-ABL >10%
6 months	Ph+ ≤35%, or BCR-ABL <10%	Ph+ 35%–65%	Ph+ >65%, or BCR-ABL >10%
12 months	Ph+ 0, or BCR-ABL ≤1%		Ph+ ≥1%, or BCR-ABL >1%
Any time		Loss of MMR	Loss of CHR loss of CCgR, mutations

These definitions are a provisional adaptation of the original ELN definitions of the response to first-line therapy with imatinib [11]. Operationally, 'optimal' means to continue the treatment, 'failure' to change the treatment, and 'warning' to monitor more carefully and to be ready to consider a change of treatment.

TKI: tyrosine kinase inhibitors; MMR: major molecular response; CHR: complete hematologic response; CCgR: complete cytogenetic response; ELN: European LeukemiaNet.

defined 'suboptimal' [10, 11]. Now the term suboptimal may be better replaced by the term 'warning', meaning that the response must be monitored more carefully and that the patient may be eligible for potentially better treatments.

The choice of the treatment, particularly the decision of moving from one treatment to another, strongly depends on the response to treatment, particularly on the degree of the cytogenetic response (CgR), and on the detection of BCR-ABL KD point mutations [32].

cytogenetic monitoring

Cytogenetic monitoring (Table 3) must be performed by CBA of marrow cell metaphases, reporting the number of Ph+ metaphases relative to the number of metaphases analyzed, that must be at least 20 [10, 11, 32]. The CgR is defined complete (CCgR) with 0% Ph+ metaphases, partial (PCgR) with 1%–35% Ph+ metaphases, minor with 36%–65% Ph+ metaphases, minimal with 66%–95% Ph+ metaphases, and none if >95% of metaphases are Ph+ [10, 11]. I-FISH can substitute for CBA if marrow cells cannot be sampled or if a sufficient number (20) of marrow cell metaphases cannot be evaluated [11, 14]. However, based on I-FISH, one cannot assess the degree of CgR, (minimal, minor, partial) but can establish only if the CgR is complete (<1% BCR-ABL+ nuclei out of at least 200 nuclei) [14]. The CgR must be assessed at 3 and 6 months, then at least every 6 months, until a CCgR has been achieved, then at least every 12 months, unless a regular molecular monitoring cannot be assured [11].

molecular monitoring

A quantification of BCR-ABL mRNA, performing RT-Q-PCR from 20 ml EDTA-anticoagulated peripheral blood, is required every 3 months (Table 3). This method represents the most sensitive tool for the assessment of the disease status, particularly of minimal residual disease [11]. BCR-ABL transcript levels should be expressed according to the International Scale (BCR-ABL^{IS} %) [15] to guarantee comparability of results among different laboratories. Therefore, local methods require thorough optimization and harmonization with reference laboratories [16, 17]. Intervals can be prolonged from 3 to 6 months after repeated achievement of a major molecular response (BCR-ABL^{IS} ≤0.1%, 3 log reduction from standardized baseline). Significant rises of BCR-ABL transcript levels (5–10 fold beyond major molecular response, MMR) during long-term therapy are early indicators for treatment failure or non-adherence. The achievement of very deep molecular responses (4–5 log reduction) during TKI treatment is the prerequisite for therapy interruptions within controlled trials [33].

More than 90 different point mutations in the KD of BCR-ABL that impair TKI binding have been reported in patients who develop resistance to imatinib [4, 5, 34]. Importantly, only a small, definite subset of them retains insensitivity also to dasatinib and/or nilotinib. In particular, V299L, T315A, and F317L/V/I/C are resistant to dasatinib. Y253H, E255K/V, and F359V/C/I are resistant to nilotinib [34–36]. T315I is resistant to both nilotinib and dasatinib. Although mutations account for <50% of failures, the knowledge of BCR-ABL mutation status is a valuable piece of information to be integrated in the decision algorithm aimed at tailoring the best therapeutic strategy for each TKI-resistant patient. Recommendations as to when mutation analysis should be performed have recently been compiled by European LeukemiaNet (ELN) [34] and are reported below:

- During first-line therapy with imatinib, the analysis is due in case of failure and in case of an increase in BCR-ABL transcript levels leading to a loss of major molecular response.
- During second-line therapy with dasatinib or nilotinib, the analysis is due in case of hematologic or cytogenetic failure.
- In case of AP or BP, the mutational analysis is always due.

In any case, mutation analysis should be performed by direct sequencing. More sensitive strategies should remain confined to a research area.

discussion and conclusions

These guidelines are based on a number of high quality reports of phase 2 and phase 3 studies, single-arm, and randomized, that have been published in peer-reviewed journals over the last 10 years [19–31, 36–39], and on the recommendations that were shared by an expert panel that was appointed by ELN [10, 11]. The definition of the responses, and the guidelines for monitoring the response to treatment, are not based on studies that were specifically designed for these purposes, but reflect

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expert opinions [1, 10, 11, 14–17, 32, 34], and the design of almost all the important clinical trials [19–31, 36–39].

For treatment and recommendations for CP, the evidence is always based on at least one large randomized, controlled trial, or a phase 2 single-arm study of good methodologic quality, providing strong evidence for efficacy with a substantial clinical benefit (level of evidence I, grade A). However, there is not yet sufficient evidence to make specific recommendations on which TKI should be used first line. For treatment recommendations in AP and BP [1, 10, 11, 35], the level of evidence is lower, III/IV, based mainly on phase 2 single-arm studies and retrospective analysis, so that the grade B is also lower (moderate evidence for efficacy, with a limited clinical benefit, generally recommended).

Overall, based on the three TKI that are currently available, the progression-free survival is projected at 80%–90%, and overall survival at 85%–95%, after >5 years, with a tendency to a true plateau. The use of second-generation TKI front-line has the potential of reducing the rate of progression to AP and BP. AlloHSCT has the potential to cure, but is currently limited to the patients who are resistant to TKI [35]. The combination of TKI with IFNα [24, 36–38], as well as the use of other second- or third-generation TKI, like bosutinib [39], that has an efficacy profile similar to nilotinib and dasatinib, or ponatinib [40], that is active also in case of T315I mutation, are still investigational.

The gold standard of first-line treatment is still imatinib, 400 mg daily (Table 5). In this setting, the choice of a higher dose of imatinib (600 or 800 mg daily) or of a second-generation TKI must be balanced between 'pros' (more potency, more rapid response, deeper molecular response) and 'cons' (shorter period of observation, higher cost). For second-line treatment, the choice can be guided by the type of the adverse events which caused the switch, and by the results of mutational analysis. However, these choices are based on a low level of evidence. The treatment of accelerated and blast phase is still orphan. Switching to other TKI, using chemotherapy or testing investigational treatments are all of limited help. AlloHSCT is still the most valid option, but it should be offered before the disease has become blastic [1].

The goal of the treatment is to prevent progression, so as to ensure a normal survival. For that goal, TKI treatment should be continued indefinitely. However, there are data suggesting that in the patients where the disease is no longer molecularly detectable (so-called complete molecular remission), the treatment can be safely discontinued [33]. The number of these patients is small, but is predicted to increase with the use of second-generation TKI. Treatment discontinuation, that is particularly important for the quality of life [41], is an important achievement and will probably become the major and more important end point of next clinical studies.

Progress in treatment of CML has been such that the disease should no longer be considered fatal and incurable, as it was for more than one century. The very name of leukemia could be now disputed, because leukemia is still synonymous with fatality for the public. This great success has a price, including not only the cost of the treatment, and of monitoring, but also the availability of well trained, fully dedicated medical personnel with the capacity of understanding and solving the problems of this rare disease, of interpretating the results of sophisticated laboratory techniques, of managing very expensive drugs, and of interacting with the patients, who must be aware of all the aspects of the disease and its treatment, from the potential of a fatal outcome to the potential of cure, and must be assisted in all aspects of family and social life.

conflict of interest

Prof. Baccarani has reported that he has received honoraria from Novartis, Bristol-Myers Squibb, Pfizer and Ariad, for participation to advisory boards and as a speaker at scientific and educational meetings. Dr. Pileri has reported: Takeda-Millennium (member of the Scientific Board); Celgene (Histopathology Trial Reviewer); TopoTarget (Histopathology Trial Reviewer). Prof. Müller has reported: Novartis (research support, honoraria), Bristol-Myers Squibb (research support, honoraria); Ariad (honoraria). Dr. Soverini has reported: Consultancy and speaker's honoraria: Novartis, Bristol-Myers Squibb and Ariad. Prof. Dreyling has reported: Consultancy/Honoraria: Celgene, Janssen, Mundipharma, Pfizer, Roche; Research funding to the institution: Celgene, Janssen, Pfizer, Mundipharma, Roche. Dr. Steegmann has reported: research sponsored by Bristol-Myers Squibb and Novartis; speakers' bureau for Novartis, Bristol-Myers Squibb and Pfizer.

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