Chronic myeloid leukemia: room for improvement?

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Following the introduction of imatinib and several other tyrosine kinase inhibitors (TKIs), the clinical scenario of Philadelphia chromosome-positive (Ph+) and BCR-ABL1-positive (BCR-ABL1+) chronic myeloid leukemia (CML) has changed almost completely.[1] Although the number of studies is limited, and the follow up is short and sometimes defective, survival data are substantial; around 90% at 5 years, 89% at 6 years, 86% at 8 years, and 83-84% at 10 years[2-10] (Table 1). Only 50% of deaths are due to the progression of leukemia, while 50% occur in remission and are due to other causes which occasionally include treatment-related toxicity and related complications. Relative survival analyses have concluded that the life expectancy of a patient with chronic phase (CP) CML, under proper TKI treatment, is now very close or almost identical to the life expectancy of non-leukemic, age-matched individuals.[11,12] New drugs, both TKIs and non-TKIs, are emerging. New, more sophisticated molecular technologies are available. So, which problems remain to be solved? Is there still room for improvement, and where?

There is still room for improvement for patients with newly diagnosed accelerated phase (AP) and blastic phase (BP) CML, and to some extent also for patients with high-risk CP CML. The former account for 4% to 5% of all newly diagnosed patients.[13] They respond to the TKI treatment, but the extent of response is inferior, and their ultimate outcome is still unclear.[1] High-risk patients account for 10% to 25% of newly diagnosed CP CML patients, depending on which risk score is used, but even using Sokal, which is less selective and includes many more patients than Euro, European Treatment Outcome Study (EUTOS), and the new EUTOS long-term survival score,[14] the outcome of these patients is inferior, with a reported survival of 83%-89% at 5-6 years and of 68% at 10 years[7,10] (Table 1). In addition, the presence of clonal chromosome abnormalities in Ph+ cells (CCA/Ph+) at baseline, which occurs in 3% to 4% of patients, is a marker of an inferior outcome.[1] It is believed that all these patients (AP, BP,

Table 1. A summary of the outcome of treatment with TKIs of newly diagnosed CP CML patients. Only the studies reporting on more than 200 patients, with a median follow-up observation of longer than 5 years, are listed. Notice the important differences in age and in the proportion of high-risk patients. MD Anderson, German CML IV and GIMEMA are academic studies. The Swedish data are taken from a population-based registry. IRIS, ENESTnd and DASISION are company-sponsored, registrative studies

Study	IRIS[2,10]	MDA[6]	German CML IV[4,7]	GIMEMA[5]	ENESTnd[8]	DASISION[9]	ENESTnd[8]	DASISION[9]	SWEDEN[3]
First-line treatment	Ima(A)	(B)	Ima (C)	Ima (D)	Ima 400 OD	Ima 400 OD	Nil 300 OD	Das 100 OD	(E)
No. pts	553	483	1536	559	282	260	282	259	717
Follow up, median	10.9 y	8.3 y	7.1 y	6.3 y	5.5 y	5.5 y	5.5 y	5.5 y	5.1 y
Follow up, missing %	20.1	NR	0.1	4.1	NR	NR	NR	NR	17.8
Age, median	50 y	(F)	53 y	52 y	46 y	49 y	47 y	46 y	60 y
High-risk %	18 Sokal	7 Sokal	12 EUTOS	22 Sokal	28 Sokal	19 EURO	28 Sokal	19 EURO	32 Sokal
Progressions %	6.5	NR	6.7	5.7	7.4	7.3	3.5	4.6	NR
Deaths, total %	16.1	11.0	12.0	11.6	7.8	10.0	6.4	10.0	NR
Deaths, leukemia %	9.0	NR	NR	5.7	5.7	6.5	2.1	3.5	NR
Deaths, other causes %	7.0	NR	NR	5.9	2.1	3.5	4.2	6.6	NR
OS 5 years %	89	93	90	NR	92	90	94	91	83
OS 6 years %	88	NR	NR	89	NR	NR	NR	NR	NA
OS 8 years %	NR	NR	86	NA	NA	NA	NA	NA	NA
OS 10 years %	83	83	84	NA	NA	NA	NA	NA	NA
OS low-risk % (at)	90 (10y)	NR	NR	94 (6y)	100 (5y)	NR	97 (5y)	NR	95 (5y)
OS high-risk % (at)	69 (10y)	NR	NR	83 (6y)	84 (5y)	NR	89 (5y)	NR	78 (5y)

(A) 400 mg once daily (OD). (B) Imatinib 400 mg OD (14% of patients), imatinib 400 mg twice daily (TD) (9%), imatinib 400 mg OD + pegylated interferon-α (33%), nilotinib (dose not specified) 21%, dasatinib (dose not specified) 22%. (C) imatinib 400 mg OD (26.4% of patients), imatinib 400 mg OD + interferon-α (28.2%), imatinib 400 mg OD + low dose cytarabine (10.3%), imatinib 400 mg OD after interferon-α (8.3%), imatinib 400 mg TD (27.3%). (D) imatinib 400 mg OD (76% of patients), imatinib 400 mg TD (24%). (E) No details, but TKIs for most patients. "A small and decreasing proportion of elderly patients received first-line treatment with the intention of palliation (i.e., not including TKIs or upfront HSCT)".[3] (F) 40.8% of patients were less than 45 years old, 46.0% were 45 to 64 years old, 13.2% were ≥ 65 years old, no patient was ≥ 80 years old. NR: not reported; NA: not available; No.: number; pts: patients; OS: overall survival.

high-risk CP, CCA/Ph+) can benefit more from second- or third-generation TKIs, and that some of them, in particular those of younger age, are candidates for allogeneic stem cell transplantation. However, much needed prospective, specifically addressed trials are lacking.

But is there still room for improvement for the 80% to 90% of patients who become optimal responders and have a normal life expectancy? TKIs cannot prolong life, but their proper use can help to improve the quality of life without precluding the achievement of a remission that remains stable even after treatment discontinuation (treatment-free remission, TFR). Concerning the quality of life, many studies report that the side effects or toxic effects of TKIs were "manageable", could be tolerated, and did not impel a change of TKI. Typically, such studies were designed to limit the switch from one TKI to another, and were analyzed more to define the tolerability profile of a specific TKI than to assess the quality of life of the patients. We suggest that in the case of so-called "manageable" side effects, mild or recurrent, that impair the daily life of a patient, more consideration should be given to a change of the drug and also to a change of the dose, provided that an optimal response is maintained. At times a patient-adapted policy, that is a policy adapted to side effects and to response, can be more convenient. For that purpose, trials may not be necessary, but a careful long-term observation will be important to control overall how patients adapt to side effects and to pick up on the so-called unexpected adverse events.

TFR is an acronym that fully expresses the success of therapy, combining the perception of cure, a normal life expectancy, no treatment-related side effects and complications, independence from drugs, in addition to a proper use of the financial resources of health systems that are more and more challenged by the introduction of new and effective, but also expensive drugs.[15-17] It is expected that a more widespread use of second-generation TKIs in first-line treatment would result in increased TFR. However, evidence is still missing as there are no studies reporting on the benefit (the TFR rate) and the cost (toxicity) of a policy of imatinib use *vs.* a policy of the use of second-generation TKIs, either in early or late first- or second-line therapy.[17] Such studies require time, patience and resources, but are necessary in order to move from expectation to evidence. Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) and the Haemato Oncology Foundation for Adults in the Netherlands (HOVON) are currently running a trial of first-line nilotinib *vs*. first-line imatinib therapy with a switch to nilotinib in the event of less than optimal response, with the TFR rate at 5 years being the primary endpoint.[18] More than five years will be required to obtain answers from this study. Furthermore, the choice between continuing treatment indefinitely and no treatment at all may be challenged and alternative policies are currently being tested, either of partial, intermittent treatment,[19,20] or of graded discontinuation.[21] For the time being we must acknowledge that any recommendation concerning the policy of treatment regarding TFR is not yet evidence-based. In all likelihood, the best policy does not exist, and different policies may be successful in different situations.

Notwithstanding the fact that the treatment and the modalities of treatment for TFR are still an issue for research, it should not be overlooked that treatment discontinuation and TFR are already a reality in practice, and are the goal of more and more patients. There are solid data showing that treatment discontinuation after five or more years of TKIs, and after one or more years of deep molecular response (MR), such as MR 4.0 (BCR-ABL1 ≤ 0.01% on the international scale), and particularly MR 4.5 (BCR-ABL1 ≤ 0.0032%, on the international scale) results in a rate of TFR of 50% or more, and that in the event of molecular relapse the resumption of treatment brings all patients back to molecular remission.[15,16,22,23]

In summary, once a deep MR is achieved, and provided that careful molecular monitoring is assured, no patient will die of leukemia because of treatment discontinuation, and 50% will enjoy a treatment-free life. Therefore, we suggest that both the possibilities and the problems of treatment discontinuation should be discussed not only with all the patients who fit the current, provisional eligibility criteria for discontinuation, but also with newly diagnosed patients.

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Minimal residual disease in mantle cell lymphoma: are we ready for a personalized treatment approach?

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Mantle cell lymphoma (MCL) is nowadays recognized as a spectrum of diseases, characterized by significantly different treatment responses and outcomes. Some predictors of clinical and biological outcome have been established and validated over recent years, and these are either assessable at baseline (mainly MCL international prognostic indexes, Ki-67 proliferative index and genomic aberrations) or during treatment (functional imaging and minimal residual disease, MRD). MRD is defined as the minimal traceable persistence of lymphoma cells after a successful treatment. Many methods to monitor MRD have been published; however, the most sensitive and the most commonly used and best standardized approach in MCL is represented by the allele-specific oligonucleotide (ASO) quantitative polymerase chain reaction (qPCR) method.[1] The most relevant prospective trials investigating the impact of MRD on MCL patient outcome are listed in Table 1A.

The clinical role of MRD analysis in MCL is reflected according to four major aspects (Figure 1).

MRD provides early feedback on the efficacy of the clearance of different induction regimens. The dynamics and stability of tumor shrinkage after treatment can currently be precisely tracked by MRD kinetics; these data might be useful as an early *in vivo* predictor of the anti-lymphoma effect of a new compound.[6,9,10] Moreover, MRD can be used as a surrogate end point for progression-free survival (PFS) comparing the efficacy of different treatments in randomized trials, thus accelerating the development, and eventually the approval, of new drugs. For example, the superior outcome of the cytarabine-containing experimental arm of the "MCL Younger" phase III trial of the European MCL Network was heralded by a higher rate of MRD clearance many years before publication of the final results.[5,15]

MRD can provide an early prediction of disease recurrence. Even in the context of an incurable disease like MCL, the deepness of treatment response measured by MRD widely reflects patient outcome in large, prospective trials.[3-5] The predictive role of MRD analysis in MCL was confirmed in different patient subsets (both younger and elderly), treatment strategies (autologous transplantation and conventional immuno-chemotherapy), tissues (bone marrow and peripheral blood) and time points (end of induction and during maintenance treatment).[4]

MRD allows for risk stratification of patients after treatment. MRD describes the efficacy of therapy and presence of even minimal, resistant tumor clones; thus, this approach identifies patients at higher risk of recurrence after an apparently successful treatment. Actually, persistence of MRD positivity or recurrence after a transient MRD negativity precedes clinical relapse, with a median time lag of 18 months.[16]

MRD might drive pre-emptive treatment. As MRD positivity predicts upcoming clinical relapse, this approach can guide treatment tailoring, with the aim of preventing or delaying overt disease progression. In a number of prospective reports, a pre-emptive rituximab treatment of MRD positive patients was able to reconvert them to MRD negativity, with the possibility of also prolonging their PFS.[8,17]

Nevertheless, some limitations still hamper the widespread use of MRD analysis in clinical routine. The two major obstacles as far as methodology is concerned are the need for patient-specific primers and standardization issues. At present, the ASO-qPCR strategy relies upon either the clonal rearrangement of the IGH gene or the BCL-1/IGH rearrangement, derived from the t(11;14); both of these DNA sequences are unique for each B-cell clone, so individual primers are required for each patient to guarantee a reliable sensitivity. Thus a "one-fits-all" easy-to-use *in vitro* diagnostic medical device (IVD-kit) is not conceivable in MRD diagnostics so far, and access to an experienced and dedicated laboratory is mandatory. In addition, a rigorous standardization of the methods is essential in order to provide comparable results among different centers. Only selected laboratories across Europe