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PERSPECTIVE

How could patient reported outcomes improve patient management in chronic myeloid leukemia?

Federico De Marchi, Marta Medeot, Renato Fanin and Mario Tiribelli

Division of Hematology and BMT, Department of Experimental and Clinical Medical Sciences, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy

ABSTRACT

Introduction: Patients reported outcome (PRO) are still under-used in patients with chronic myeloid leukemia (CML) treated with tyrosine kinase inhibitors (TKIs), though data on the correlation between quality of life (QoL) and therapeutic efficacy are increasingly known. Chronic low-grade toxicities can reduce patient's QoL and negatively impact on adherence.

Areas covered: This review will focus on the role of QoL questionnaires in patients with CML, receiving imatinib or newer TKIs (dasatinib, nilotinib, bosutinib, ponatinib). Physicians tend to underestimate the impact of TKI-related symptoms, in particular fatigue, that negatively affect QoL and can be a reason of poor adherence to therapy, with detrimental effect on long-term response. Few studies pointed out the role of PRO in CML, and there is paucity of questionnaires specifically designed for CML patients.

Expert commentary: We recommend a wider use of PRO to join the pursuit of a rapid and deep responses with an optimization of QoL.

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Chronic myeloid leukemia; quality of life; patient reported outcome; tyrosine kinase inhibitors; prognosis

1. Introduction

Chronic myeloid leukemia (CML) is a clonal disorder of hematopoietic stem cell characterized by the presence of Philadelphia chromosome (Ph+), resulting in the fusion gene BCR-ABL [1].

Treatment and prognosis of CML has radically changed with the introduction of tyrosine-kinase inhibitors (TKIs), the first example of highly effective target therapy in onco-hematology [2]. TKIs have significantly increased life-expectancy in CML, and patients treated with imatinib, the TKI with longest follow-up, have a survival close, if note equal, to that of general population [3]. The TKI success has therefore made CML therapy similar to that of other chronic diseases, in which the most important aspect is the continuative, daily, drug taking, with serial monitoring of BCR/ABL transcript, a specific and reliable marker of response to treatment [4]. Adherence to therapy is emerging as one of the pivotal aspects in CML treatment, as even a slight reduction in taken TKI seems to negatively impact on response [5]. It is important to underline as each different TKI has a peculiar safety profile with characteristic side effect, both in the short and long term, that can impact on adherence to therapy and quality of life (QoL) [6]. Imatinib's most common toxicities are peripheral edema, nausea, muscle cramps, and muscle-skeletal pain [7], while long-term toxicities of second- and third-generation TKIs are still to be accurately defined, with some notable exception such as peripheral arterial obstructive disease (PAOD) for nilotinib and pleural effusion for dasatinib [8,9]. However, though TKIs have improved QoL compared with previous CML therapy, such as interferon or chemotherapy [10], TKI treatment is associated with a worsening in QoL and symptoms reported by patients are often more serious than how they are perceived by physicians [11]. Generally, QoL is evaluated with specific questionnaires that are filled by the patients during the course of treatment. The importance and relevance of these questionnaires is highlighted by a large, population-based study involving about half a million people included in the UK population biobank project, showing that self-reported health was the strongest predictor of survival among all the analyzed factors [12]. Self-reported QoL has been proved to impact on overall survival (OS) in various clinical conditions spanning from neoplastic diseases [13], arthritis [14], obstructive pulmonary diseases [15], hemodialysis [16], HIV infection [17] and in more than 2,000 elderly patients from a large integrated-delivery network in the USA [18]. Patient-reported outcomes (PRO) are defined as the measurement of every aspect of patient's health, including disease-related symptoms, autonomy, disease and therapy perception, toxicities or adverse events, physical, psychological, and social aspects, all as reported from the patient him/herself without any second-party interpretation. PRO can be used to identify and quantify various aspects of patient's status, ranging from pain intensity to overall health quality [19]. The questionnaires consist of dozens (usually more than thirty) of questions, aimed to evaluate different aspects of individual well-being [20,21].

As PRO have demonstrated in different settings a prognostic value in terms of survival, it would be of great interest to evaluate if specific interventions aimed to improve related outcomes could impact on life expectancy. PRO seems to

CONTACT Mario Tiribelli mario.tiribelli@uniud.it Division of Hematology and BMT, Department of Experimental and Clinical Medical Sciences, Azienda Sanitaria Universitaria Integrata di Udine, P.le S. M. Misericordia, 15, 33100 Udine, Italy

influence the chance of a patient-physician communication on symptoms during outpatient visits, resulting in a better control of the same symptoms and consequently an improved patient's satisfaction [22,23].

2. PRO in hematological malignancies

QoL questionnaires are gaining importance in hematologic disorders and, in few cases, were already included in consensus conferences and guidelines. A Canadian study on 445 patients with high-risk myelodysplastic syndromes (MDS) demonstrated that patient-reported fatigue, quantified by a validated questionnaire (EORTC QLQ-C30) [24], independently predicts OS and was superior as predictors compared to widely used scores (IPSS or IPSS-R) based on objective parameters such as number of cytopenias, blast count or cytogenetics [25]. In MDS, it would be of interest to verify if QoL is associated with risk of evolution to AML or what is the impact of QoL questionnaires in low-risk MDS patients. In this latter setting, it has been found that low-intermediate risk 5q- patients benefit from lenalidomide therapy due to a reduction in red-cell transfusion frequency and increased hemoglobin levels, resulting in a better reported QoL; this subjective benefit persists over time, justifying long-term treatment [26].

In multiple myeloma (MM), the same EORTC QLC-C30 questionnaire was included in a randomized trial (NMSG 4/90) comparing melphalan/prednisone versus melphalan/prednisone plus alpha-2b interferon alph-2b in newly diagnosed patients [27]. Physical and cognitive functioning, pain, fatigue and reported QoL were associated, in univariate analysis, with survival; in multivariate analysis, physical functioning and WHO-defined performance status emerged as independent prognostic factors, and the best risk stratification was obtained by combining physical functioning score with an objective, measurable data (i.e. beta-2 microglobulin). An impact of QoL questionnaires on the outcome of myeloma patients has been confirmed in another study (SUMMIT) evaluating 202 patients with resistant/refractory MM treated with proteasome inhibitor bortezomib. Patients enrolled received four questionnaires (EORTC, QLQ C30, QLQ MY24 e FACT GOG Ntx [24,28–31]) at different time points. QoL scores obtained were not only associated with survival, but also with response to treatment, while reported QoL progressively declined in patients with progressive disease [32]. PRO thus helped in interpreting response to treatment.

QoL questionnaires permitted also to extrapolate various evidences that could impact on treatment and clinical practice of hematological neoplasms. In acute myeloid leukemia (AML) patients, physical exercise during hospitalization for induction chemotherapy has a positive impact on QoL by reducing symptoms and fatigue [33]. In patients with low-intermediate risk acute promyelocytic leukemia (APL), induction therapy with all-trans retinoic acid (ATRA) plus arsenic trioxide (ATO) is equally effective than ATRA plus chemotherapy but is superior in terms of QoL, thus emerging as standard induction therapy [34]. In myelofibrosis patients, a ≥ 50% improvement from baseline in symptom score during treatment with ruxolitinib had a key role in US FDA full approval to the drug [35]. In a British study on 431 chronic lymphocytic leukemia (CLL) patients, a reduction in PRO scores has been associated with disease-related symptoms, recommending to start treatment in patients experiencing symptomatic disease, to improve QoL [36,37].

The use of the specific Medical Outcomes Study Short Form 36 questionnaire [38] prior to in 336 patients predicts overall mortality after transplant independently and as well as other commonly used non-PRO indexes [39]. In the same study, a reduction in the score early after HSCT was associated with an increased overall mortality and treatment-related mortality. Moreover, PRO gave also nonclinical information, underlining for example that, in the USA, patients receiving HSCT experience a reduction in QoL due to transplant-generated economical restraints, reported by specific questionnaires [40].

In summary, inclusion of PRO during treatment can result in incorporation of patient's point of view in a comprehensive evaluation, with improvement in the clinical management. QoL questionnaires may give independent prognostic information, beside traditional clinical parameters. PRO could impact also on survival, as they allow an earlier recognition of disease-related symptoms, or when used to implement further therapies aimed at QoL improvement and to adequate therapies to perceived side effects.

3. PRO in CML

Few studies have focused on QoL in patients with CML receiving TKIs (Table 1), though five different drugs (imatinib, nilotinib, dasatinib, bosutinib, and ponatinib) have been approved for first- or second-line therapy [41] and though these drugs are designed for life-time use, at least until treatment-free remission studies would give definitive results for drug discontinuation in selected cases [42]. TKIs guarantee a survival not significantly inferior compared to normal people's, and no differences in progression-free survival (PFS) and OS at 5 years have been reported for patients receiving imatinib, dasatinib, or nilotinib, even if safety profiles of the three drugs differ [43,44]. It is therefore evident the importance of a tool able precisely report on patient's QoL, symptoms, side effects and drug tolerability of long-lasting, daily treatments.

3.1. Imatinib

PRO have been used to evaluate QoL in CML patients treated with imatinib; the pivotal IRIS study, that led to approval of front-line use of imatinib, showed that TKI was superior to interferon alfa plus low-dose cytarabine, also in terms of QoL [10]. However, the multicenter Imatinib Long-Term (side) Effects (ILTE) study, analyzing more than 800 patients treated with imatinib for a median of almost 6 years, found out that about half of the patients experienced side effects interfering with daily activities [3]. Efficace et al. compared QoL profiles of general population and of 448 patients receiving imatinib with favorable response. After a median of 5 years of therapy, the commonest reported symptom was fatigue (82%), while at least a third of patients complained of fluid retention and pain; the biggest QoL differences were found in younger (18–39 years) and female patients [45]. Interestingly,

Table 1. Summary of studies focusing on QoL in patients with CML receiving TKIs.

First author	Patient selection	Treatment	Number of patients	Main results
Hahn	CP-CML frontline	IMA 400 vs. IFN-LDAC	1049	Physical function and well-being superior with IMA (even after cross-over)
Efficace	CP-CML frontline in CCyR	IMA 400 (78%) IMA ≠ 400 (22%)	448	Worst QoL impairment in young pts and females; fatigue most reported
Efficace	CP-CML frontline in CCyR	IMA 400 (78%) IMA ≠ 400 (22%)	442	Fatigue is the symptom most often underestimated by physicians
Guérin	CP-CML frontline	IMA 400 vs. NILO 600–800	593	AEs similar or lower for NILO than IMA
Labeit	CP-CML frontline	IMA 400 vs. DASA 100	812	No differences between DASA and IMA in QoL
Trask	CP-CML after IMA failure	BOSU 500	271	Little improvement or no changes during BOSU tx

CP-CML: chronic-phase chronic myeloid leukemia; CCyR: complete cytogenetic response; IFN-LDAC: interferon plus low-dose cytarabine; IMA: imatinib; NILO: nilotinib; DASA: dasatinib; BOSU: bosutinib; QoL: quality of life; pts: patients; AEs: adverse events; tx: therapy.

symptoms reported by patients are more intense than what is perceived by the treating physician.

An analysis on 442 dyads of questionnaires on health status and symptom severity completed by CML patients on imatinib therapy and by their physicians showed an agreement on symptoms ranging from 34% (muscle cramps) to 66% (nausea) [11]. Patients reported higher severity on all the evaluated symptoms, and fatigue was the most frequently underestimated by physicians (51%), that overestimated general health status in two-third of patients. This study suggest that the use of PRO could enhance the management of CML patients, as the main cause of non-adherence to treatment, a critical factor on achievement of optimal response to imatinib [46], is the attempt to avoid side effects [47–49].

3.2. Second-generation TKIs

Data on second-generation TKIs are scantier and uneven [50], derived mainly from studies utilizing various PRO and different end points. From the ENESTnd study, comparing nilotinib and imatinib as frontline treatment, incidence rate of low-grade adverse events was lower in nilotinib arm, but nonetheless impacting on QoL in terms of psychiatric and so called 'general' disorders [51]. In the UK SPIRIT2 trial, comparing first-line dasatinib and imatinib, no significant differences emerged in terms of reported QoL, but data's limited details do not allow for definitive conclusions [52]. Regarding bosutinib, Trask et al. reported an improvement in physical and emotional well-being in imatinib-resistant or -intolerant CML patients at 24 and 48 months after bosutinib start [53].

Few studies focused on a real-life setting, however confirming a reduction of perceived QoL during TKI therapy, an association between QoL and treatment satisfaction, and a possible increase of QoL with prolongation of therapy [54–56].

3.3. Value of different QoL questionnaires

As a general consideration, PRO used in most studies have not been designed specifically for CML patients. In the past years, some leukemia-specific QoL instruments have been developed. The Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) [57] combines a general QoL scale (FACT-G) with a specific subscale designed for acute and chronic leukemia, comprising both physical, emotional and social items. Though quite extensive (44 items) the FACT-Leu has proven to be a reliable tool to assess patients' perceived health and useful in both clinical research and every-day practice [58]. The MD Anderson Symptom Inventory (MDASI)-CML [59] is the evolution of the MDASI, an instrument designed to evaluate how common symptoms of cancer and its treatment infer with daily activities [60]. Compared to its general counterpart, the CML-specific questionnaire is composed of 7 items derived from interview of 35 CML patients and subsequently validated in 152 patients longitudinally followed at MD Anderson Cancer Center. The main strengths of this item are its briefness and the numeric scale of symptom grading, that can be easily understood, translated into other languages and administered by telephone or electronically. In 2014, the European Organization for Research and Treatment of Cancer designed a disease-specific QoL questionnaire for CML patients, the EORTC QLQ-CML24 [61]. It is the result of a three-step process of generation of health-related QoL issues relevant for CML by literature review and interviews with health-care professionals and patients, construction of 30-items provisional questionnaire, and test of the questionnaire in a large cohort of patients form 10 countries (USA, Europe and Asia). The final result is a module of 24 items covering symptom burden, impact on daily life and on mood, perception of body image, satisfaction with care and with social life. EORTC QLQ-CML24 is a patient-centered approach that may bypass the under-estimation of symptom's intensity by treating physicians.

Systematic and standardized implementation of this specific tool could help the physician in correctly interpreting patient-reported symptoms, resulting in a possible improvement of therapy and patient's satisfaction [62].

4. Expert commentary

Despite having been introduced since more than 10 years in neoplastic and chronic diseases, QoL PRO are less used in hematological malignancies. In CML, in particular, the successes of target therapy may have in some way shifted the focus from the patient to the diseases. Hundreds of studies have reported the efficacy of imatinib first-, and then of second- and third-generation TKIs, in terms of cytogenetic and molecular responses, long-term survival and even treatment-free remission, while only a handful of papers focused on patient-reported physical and psychological symptoms, fears, and expectations. Far from neglecting the capital importance

of objective and measurable responses, we just want to point out that the patient's perspective might have been underevaluated. As demonstrated by the work of Efficace et al. [11], physicians perceived a lower severity for all symptoms than their CML patients, while overestimating patients' health status in two-third of the cases. This misperception can be really detrimental, as the excellent results of TKI therapy are linked to a regular assumption of these oral drugs. The underestimation of treatment side effect, even mild (the so-called grade 0–I toxicities) but affecting patient QoL, such as fatigue and pain, may generate in patients a sensation of not being properly listened to, that can cause lack of adherence. The search for quick and deep responses, prerequisites for favorable progression-free and overall survival, should be ideally gathered with an optimization of QoL, as the latter is impacting on the former when long-term oral therapy is involved. In this scenario, physicians must rely on PRO, as no one can better describe his/her symptoms and feeling as the patient.

5. Five-year view

PRO implementation in CML patients could provide information useful for the management of TKI therapy and generate data potentially impacting on disease course. To date, QoL questionnaires consist of numerous questions that demand a significant amount of time to be answered, and this is hardly compatible with the time generally allowed for a follow-up visit. Thus, we expect that, in the next years, easier questionnaires will be designed, so that patients can complete them at home and return them at the following visit. To increase response rate and patients' compliance, it is of paramount importance for the physician to explain in detail to patients how important are careful and sincere answers to QoL questionnaires. To extrapolate from PRO data useful information in a reasonable time, patient's answers should be summed up in synthetic classes, expression of the total of single scores, with the aim to give clinician a global picture of patient's well-being.

Once the methodic is standardized and routinely used in the out-patient practice, the use of CML-specific PRO at various time-points of therapy (i.e. baseline, after 3, 6, and 12 months and yearly thereafter) will define if QoL during continuous TKI treatment is inferior to general population, in which symptoms and amount. This could also help to identify candidates to drug discontinuation, not only according to a deep and sustained molecular response but also considering the burden of treatment on QoL.

A better definition of QoL will allow us to more efficiently follow CML patients over time, with a prompt detection of symptoms and, consequently, a rapid intervention, resulting in an increased compliance and patient's satisfaction. As noncompliance of oral medications seems to be mostly aimed to avoid side effects, a rapid detection of patient reported symptoms could positively impact on adherence to TKI therapy, a prerequisite for optimal response. Along with a favorable impact on long-term survival, 'PRO-induced' adherence may have also a positive economic repercussion, as more patients could achieve a sustained deep molecular response, thus becoming candidate for treatment discontinuation. More, PRO might be used to define which TKI has a better tolerability profile in specific CML subset (younger or elderly patients, patients with comorbidities, etc.). This data, in association with the well-standardized response parameters, may help us in finding an answer to the still open question 'What is the best TKI for this particular patient given the excellent therapies available?' [63].

Beside large-scale implementation, it will be necessary to design drug-specific questionnaires, as different TKIs have different safety profiles, so questions aimed at detecting early symptoms related to a certain inhibitor could give treating physician a supplement information. As a matter of fact, with such effective therapies the QoL of CML patients is impacted more by side effects of TKIs than by disease itself [64].

Finally, it would be of great interest to analyze potential correlations between perceived health and objective parameters, such as molecular response. Is it possible that a given PRO is associated with a specific therapeutic response? If the case, QoL questionnaires could be combined with response criteria in a dynamic prognostic score, to identify patients that should continue the therapy in use, those who should change dosage or TKI, or even the candidates to treatment discontinuation.

Key issues

- Five different tyrosine kinase inhibitors (TKIs) targeting BCR-ABL oncoprotein are approved for the treatment of patients with chronic myeloid leukemia (CML).
- TKIs are effective and, generally, well tolerated, though long-term data are still scanty for second- (dasatinib, nilotinib, bosutinib) and third- (ponatinib) generation TKIs.
- Chronic low-grade toxicities during TKI therapy can reduce patient quality of life (QoL) and thus negatively impact on adherence.
- Physician often tend to underestimate symptoms, such as fatigue and pain.
- Lack of recognition and poor treatment of therapy-related symptoms may cause reduced adherence to treatment, with negative consequences on response.
- Patient reported outcomes (PRO) are associated with improved symptom control, increased patient satisfaction and, in most cancer clinical trials, longer overall survival (OS).
- The use of QoL PRO in CML patients is still limited, and generally derived from studies of imatinib; even less is known on PRO in patients treated with second- and third-generation TKIs.
- The development and dissemination of questionnaires specifically designed for CML patients (such as MDASI-CML and EORTC QLQ-CML24) is warranted to define the benefits of TKIs and optimize treatment.

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