

# Clinical pathway for patients with Chronic Myeloid Leukaemia: The Euriclea Project

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**Abstract.** *Background and aims:* The use of Tyrosine Kinase Inhibitors (TKIs) for the treatment of Chronic Myeloid Leukemia (CML) has definitely represented a turning point in the treatment of the onco-hematological diseases. Over the years, the interest of physicians, nurses, patients and caregivers has increasingly focused on the aspects of the humanization of care, the management of side effects and on the full and constant therapeutic adherence. The aim of the project was to define patient-oriented care processes, based on a proactive approach that can fully respond to the new health needs of CML patients. *Methods:* A nursing expert Working Group (WG) was established. WG reviewed literature about CML patients assistance and then it was conducted a survey on organizational models for the treatment of CML patients, adopted by Italian haematologic and transplant centers. Finally, the main issues regarding CML patients care were identified and discussed on a multiprofessional basis. *Results:* Euriclea Project for care of CML patients with the description of a new and expanded nurse role was defined. The Nurse Case Manager or Nursing Clinical Experts were identified as key people for the management of the side effects of treatment, the promotion of the therapeutic adherence and the evaluation of efficacy and effectiveness of the process through the identification of specific indicators for structure, process and outcome. *Discussion:* The focal areas of the care process were identified so as to define a different approach to the CML patient, through a holistic view of care and the multidisciplinary interventions.

**Key words:** clinical pathways, chronic myeloid leukaemia, tyrosine kinase inhibitors, nursing, proactive care, adherence, patient empowerment, side effects, adverse events

## Background

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm. This disease affects, in Europe, approximately 10-15 people per million inhabitants every year, on average between 60 and 65 years of age (1). The only predisposing factor is thought to be the exposure to ionizing radiation. The CML prevalence

is steadily increasing due to the significant extension of survival, achieved with the current targeted therapies based on tyrosine kinase inhibitors (TKIs) (2). The leukemia cells are characterized in 95% of cases by the presence in their nucleus of an abnormal chromosome called "Philadelphia Chromosome" from which derives the hybrid gene BCR-ABL, with high tyrosine kinase activity and responsible for leukemogenic

process (3). The introduction of target therapies based on tyrosine kinase inhibitors (TKIs), has modified the clinical outcomes and the natural history of CML (4). Thanks to the effectiveness of these drugs, in about 80-90% of patients, the timing of allogeneic stem cell transplantation can be deferred (5). Adherence to the TKIs assumption, the continuous and proper dosage of the therapies are essential conditions to achieve optimal treatment results (6, 7), but treatment pathways are long, with persistent and recurrent side effects. Although treatment related discomforts are often mild and easily controllable, they may affect various spheres, including social and psychological ones. For these reasons, treatment with TKIs is not always and only a “solution” to the disease (8, 9), but can connote itself as an element that induces a transition to a new patient life-style, with all adaptation problems that this entails. Some studies (10-12) showed a statistically significant correlation between the bio-psycho-social factors (age, sex, educational level, ethnicity, social role/employment, knowledge of the disease, duration of treatment, side effects, personality, social and financial support, doctor-patient relationship, living with chronic disease, educational sessions, depression) and adherence to therapy. Another aspect which has acquired increasing importance is the involvement of the patient (Patient Engagement) in the construction of care pathways (13). The 2013 annual report of the European Patients Forum (14) indicated the patient’s involvement in the decision making and in the treatment management process among the five strategic goals to provide an equitable and patient-centered health care. Therefore, the implementation of innovative forms of health care appears essential (15).

The “Project Euriclea” was born from the need to provide a proposal able to combine the professionals’ views and experiences, the scientific literature (evidence) and the patients’ desires and needs, in order to develop a “proactive model” to care for patients and to offer an “Initiative Healthcare”(15). The project’s aim is the harmonization of caring for CML patients, through the identification of key points that can be used in the Clinical Pathways (CPs) implementation for these patients. These CPs affirm the goals and basic elements of care based on scientific evidence (EBM/EBN) and the patient’s expectations, facilitating com-

munication, coordinating roles and sequencing the activities of the multidisciplinary care team, patients and their families (16).

## Materials and methods

A Working Group (WG) of nurses expert in the care and organizational management of CML patients was set up thanks to the interaction between the representatives of Italian Leukemia Association (AIL) CML Patients subgroup and the Italian Federation of Nurses (IPASVI), in collaboration with GITMO nurses group and the Italian Society of Hematology (SIE). Clinical, caring and organizational key points were identified and were, successively, discussed to find a consent within the WG. Only the items with the WG’s unanimous consent were then developed. In the initial phase, a literature review on the major international databases was conducted. Secondly, the Standard Operative Procedures (SOPs) of various Italian centers were collected and analysed. In addition, in order to explore the daily practice, an “ad hoc” structured questionnaire was drawn up, validated by a “focus group” and tested in ten pivotal hematologic centers before being distributed to ninety-eight GITMO centers. The questionnaire was based on international literature suggestions in order to obtain information about structures, type of organization, activities, the nurses perception regarding care pathways of CML patients, path management and care models, reception models, adherence, aspects of information and education, patient monitoring and nursing training.

## Results

### *Analysis of the results obtained from the questionnaire “Chronic Myeloid Leukemia (CML) patient’s Clinical Pathway: multicenter survey”*

Between June and July 2015, the survey was conducted in 25 Italian hematology centers. In almost all centers (96%) CML patients were treated mainly in Hematology (76%) or Onco-hematology (20%) Units and were followed as outpatients (16; 64%). A lower percentage of patients were followed in the general

outpatients services (2; 8%) or in other external surgery structures (6; 24%). At local level, the presence of a hematological home care network - albeit underdeveloped (10; 40%), the non-specialist domiciliary care (1; 44%), the support of general practitioners (15; 60%) and private care services (1; 4%) were evaluated. Regarding the availability of guidelines, procedures, protocols and operating instructions, only in 20 centers (60%) were documents for the clinical and therapeutic management of CML patients present. Furthermore, there is a lack of dedicated nurses, case manager nurses or specialists for the management of CML patients, with the exception of a single center (4%). The 60% of centers haven't SOPs concerning the monitoring of the TKIs side effects. Monitoring protocols are performed following non-codified practices, which marginally involve nurses (16%). Finally, in the last three years the 64% of the centers have not executed training programs for nurses regarding the CML.

### ***Euriclea WG activities***

Following the analysis of the relevant literature, the SOPs, the results of the survey, the WG identified 25 items deemed useful for the definition of appropriate care pathways. Each topic was discussed unifying the items in the relevant areas and a consensus vote procedure was put in place. Then the following were considered and identified by unanimous consent: nurses role, structural resources, the reception, patients information/education, assessment, nursing diagnosis, planning interventions, adherence, management of side effects, evaluation of the process. The group made a suggestion for each area based on expert opinion. The "Education" area was considered transversal to all the other identified areas, and it was excluded from this work because it was considered unanimously as a precondition to any type of approach.

### ***Nurse role***

*"Health care organizations should introduce Clinical Expert Nurses (CEN) or Case Manager Nurses (CMN) in the care pathways of CML patients"*

The WG suggests greater involvement of nurses proposing a proactive care model to take charge of

the CML patients, implementing the Clinical Expert Nurse or the Nurse Case Manager specialized in the CML management in the clinical pathways. The introduction of a dedicated Clinical Expert Nurses would ensure that patients can receive the information and support they need in a coordinated and targeted way. The CMN would assume the task of coordinating the various services required by the patient, facilitating drug management and basing their activities on specific job descriptions or professional profiles.

### ***Structural resources***

*"Health care organizations should implement dedicated nursing surgeries and specific pathways to facilitate communication to improve the quality of CML patients management"*

In relation to the disease, we suggested the creation of dedicated spaces where the CMN can operate in a prospective way so as to manage the nursing problems that require advanced skills, to facilitate patient communication and access. CMN should be responsible for the organization and coordination of the entire patients pathway.

### ***The reception***

*"The reception should be understood as a key-moment of the Clinical Pathway and should be performed by nurses in a structured way"*

The reception should ensure and enforce the relationship between patients and health care facility, orienting, reassuring and optimizing time, spaces and resources. From the first contact, an empathetic relationship between operator and patient should be established. The nurse, through the interview based on active listening, has to be able to collect medical history and clinical information using validated instruments, but also to provide info/education regarding disease and to manage the familiar relationship and the anxiety status of patient. Once the definitive diagnosis has been made, patients should receive clarification on the contents, the objectives and the expected outcomes.

### ***Patients Information/Education***

*“Adequate patients information/education plans regarding care peculiarities are fundamental throughout the course of treatment”*

The mode and the frequency of dialogue in accordance with the patient and in relation to his information/education needs has to be customized, because, in many cases, poor therapy adhesion is attributable to unclear information (17, 18). The presence of information/educational materials, such as booklets, videos, brochures, and concerning both structural/organizational aspects and welfare aspects, is required in all facilities, services and reference operating units.

### ***The Assessment***

*“The nursing assessment should be performed using validated tools”*

This stage, carried out mostly during the reception process, continues throughout the patient’s care pathway. Data are collected and registered in the clinical documentation, validated scales and tools should be used to detect vital signs and symptoms providing a multi-dimensional assessment. It is necessary to collect information on patient adherence to any ongoing therapies using validated tools in order to plan strategies helping the patients to a compliance with treatment. Various nursing assessment models, such as Gordon (19), are applicable during the pathway. In order to better customize the clinic assessment stage, it is necessary to evaluate the level of autonomy and the presence of care needs that may lead to nursing and/or clinical diagnosis.

### ***Nursing Diagnosis***

*“The nursing diagnosis is fundamental to plan the nurses care interventions”*

It’s recommended that nursing diagnoses are reported in the patients documentation. CML patients experience side effects due to TKIs treatment that could compromise the eleven Gordon functional mod-

el items (19). Therefore, it is necessary that the nurses are able to establish priorities for action and to document their activities.

### ***Interventions planning***

*“Planning nursing interventions a proactive model should be considered”*

To implement the integrated care pathway of which the CMN is a facilitator, it is imperative to create a collaborative network between this figure and all professionals, services and Care Givers (CGs) involved in the clinical pathway. From this point of view, the nurses are essential to identify clinical and organizational problems, such as risk factors that can compromise the patient’s state of health, signs and symptoms of disease evolution, patients’ needs, in order to allow a multidisciplinary approach that could reinforce the patient’s level of autonomy (engagement) (13) favoring health empowerment (20).

### ***Patients adherence to therapy with TKIs***

*“Adherence to therapy with TKIs should be strictly monitored during the treatment period”*

Adherence to therapy is the result of a dynamic process involving the entire care team, which includes personalized educational interventions and a careful evaluation of the “resources” of the patient and CGs. Adherence to therapy with TKIs, therefore, is a central theme of the entire patient pathway, from the diagnosis to the follow-up and should be evaluated with the use of validated tools. To which customized tools can be added, such as diaries and monitoring sheets, to meet the specific needs of patients and organizations (21, 22).

### ***Side effects management of patients treated with TKIs***

*“A multidisciplinary approach for the management of TKIs side effects should be considered”*

The side effects, although mild, when persistent can become intolerable for the patient. The nurse’s role

in the toxicities-management, related to treatment, is to prevent, identify and treat early complications. Hematological and biochemical side effects of TKIs represent possible alerts for potential organ damage and so it is important, for the patients' safety to perform a thorough follow-up, modulating it on the degree of patient tolerance, whilst undergoing therapy. For this reason, the NCM should be constantly updated on the patient's conditions to better plan targeted interventions regarding monitoring and counseling. Nurses are very involved in the management of non-hematological effects, including rash, pruritus, headache, gastrointestinal disturbances (nausea, vomiting, gastritis, diarrhea), muscle cramps, water retention, and cardiovascular disturbances (23). These mild but often disturbing side effects can be positively managed by nurses improving the patients quality of life and adherence to therapy. Co-administration of other drugs can interfere with the TKIs' drug action, by increasing or decreasing their activity because all inhibitors interact with some enzymes in the liver and intestine (CYP3A4), also responsible for the metabolism of other drugs. Among the commonly used drugs that interfere with TKIs to varying degrees include: antacids (omeprazole), antibiotics (itraconazole, ketoconazole, voriconazole, erythromycin, clarithromycin), antidiabetic preparations containing iron, drugs controlling blood pressure, anti-arrhythmic and anti-inflammatories (aspirin, ibuprofen, acetaminophen). Even certain foods can interfere with the metabolism of the inhibitors by modifying activities. It is necessary to pay special attention to certain foods including: grapefruit, nutmeg, liquorice and composite products such as herbal food supplements (24-26).

### ***Process evaluation and indicators***

*"The effectiveness and sustainability of CML care processes should be measured and evaluated through the use of specific indicators"*

Each pathway should be evaluated for effectiveness. Therefore it is necessary to have suitable instruments to assess whether the caring choices made can be effective in the patients treatment, if the care process has been carried out in the best possible manner,

and whether the process is sustainable from cost-effectiveness point of view. The Euriclea group has identified a number of pathway quality indicators that may be applicable to clinical practice and documentation. In Table 1 are shown the following indicators: Structure, Process, Outcome. Structure indicators include materials, appropriate equipment and recruitment of specialized personnel. Process indicators regard the presence and quality of specific Clinical Pathways and updating courses for professionals. Finally, the Outcome indicators investigate the evolution of the CML patient care process.

### **Discussion**

Even considering the small sample size, the survey shows an extreme lack of homogeneity in the approach and management of CML patients, in which the nurses have a very marginal role in the management of patients who are followed almost exclusively by doctors, and frequently without proper planning of interventions. Moreover, there are no dedicated surgeries in almost all of the centers and patients contact with the structures can be very complex. A field analysis in a center with a surgery dedicated to CML patients showed that the time care per patient is around 15-20 minutes. This fact highlights one of the main issues discussed by the WG: can such working conditions affect the quality of care offered to the patient? The focal areas of the care process were identified so as to define a different approach to the CML patient, through a holistic view of care and the multidisciplinary interventions. Adequate structures and dedicated nurse figure, such as Case Manager, able to approaching patients in a preventive, change-oriented, dynamic and flexible manner, would seem to be the best response to the patients problems. Non-adherence to therapy implies a cost increase for National health systems and is considered an indicator of care failure (21). The Italian Association of Medical Oncology (AIOM) and the Italian Society of Psychology Oncology (SIPO) have created the first guidelines to improve the the oncology patient's psychosocial state (27) also in order to improve therapeutic adherence. The importance of this concept and implications for

**Table 1.** Possible Indicators to quality assessment of a CML clinical pathway

Type	Possible indicators
<b>Structure</b>	Availability of specific information/education material Dedicated outpatient surgery presence Presence of dedicated phone lines Availability of advanced tests of molecular biology for the assessment of minimal residual disease (MRD) Presence of a psychological service for patients and their families Presence of a referring physician for CML patients Presence of case manager nurses (CMN) or clinical nurse specialist dedicated to CML patients Presence of voluntary associations, or support services to CML patients
<b>Process</b>	Presence of Clinical Pathway specific to CML Number of training events/year on CML for nurses Presence of specific documentation for management of CLM patients <ul style="list-style-type: none"> <li>• Presence of nursing care protocol for CML patients</li> <li>• Presence of a side-effects form for CML therapy</li> <li>• Presence toxicity-management form</li> </ul> First visit waiting time and subsequent visits waiting times % of patients receiving info-educational intervention and materials % of patients who undergo residual disease tests with advanced molecular biology technique % of nurses participating in CME courses on CML in the last two years % of patients who received at least an interview with referring nurse % of patients with referring physician % of patients who complete successfully the side effects form % of patients who properly fill the toxicity-management form % of patients who have missed or forgotten at least one dose without indication % of patients who have varied the time administration of therapy without indication % of patients who have reduced the dosage without indication
<b>Outcome</b>	% of patients evolved into acute forms % of patients with no response to TKIs % of patients who died from complications related to treatment with TKIs % of patients with difficulty in adherence % of patients with difficulty in adherence because of the side effects % of patients with difficulty in adherence related to poor information Number of cases/year of drug not collected from pharmacy by the patients % of admissions for complications % of adverse events related to treatment with TKIs % of patients assessed for toxicity Number of telephone contacts needed by the patients Number of additional information requested

clinical practice are widely described in the document by EBMT Nurses Group: "Adherence to orally anti-cancer drug therapies", published in 2013 (21). In the preliminary stages of this work, the WG Euriclea already considered the patients' comments and evaluations as fundamental to create the care pathway. All activities included in the project were defined taking into account clinical and organizational aspects, nurses

and doctors opinions and the needs and expectations of the patients. This work offers some indications regarding the elements necessary to improve the clinical pathways in hematology care units. The WG has defined a training program to provide the tools and methodology in order to form CML specialized Case Manager Nurses. The first dedicated nursing surgery adhering to this project for CML patients was opened

in 2016 in Rome, data is being collected regarding project efficacy. A rapid and widespread implementation of the project at a National level is necessary so as to collect sufficient data permitting valid evaluations of efficacy and cost effectiveness. This experience could also become a model useful in improving therapeutic adherence in other settings.

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