Therapies (2020) 75, 221—224

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

DRUGS AND ORPHAN DISEASES

Patients' organizations in rare diseases and involvement in drug information: Illustrations with LMC France, the French Association of Chronic Myeloid leukemia☆

Mina Daban[a], Clémence Lacroix[b], Joëlle Micallef[b,*]

[a] LMC France, 13010 Marseille, France
[b] Inserm, service de pharmacologie clinique et pharmacovigilance, Inst Neurosci Syst, Aix-Marseille université, AP—HM, 13005 Marseille, France

Received 16 September 2019; accepted 15 November 2019
Available online 13 February 2020

KEYWORDS
Patients' advocacy;
Rare disease;
Chronic myeloid leukemia;
Pharmacology;
Drug information;
Orphan drugs

Summary There are few areas in medicine in which patient-parent advocacy groups play such a central and prominent role as in the field of rare diseases. As illustrated by the French Association of Chronic Myeloid Leukemia (LMC France), its contribution is not only focused on its role as participants or key informant related to clinical studies but also on drug information and drug safety. The discovery of tyrosine kinase inhibitors against the BCR-ABL1 oncogenic fusion protein has revolutionized the management of CML, becoming a chronic illness rather than a life-threatening disease. Because ensuring ongoing well-being requires some knowledge, LMC France has built, in synergy with healthcare professionals from its scientific council, a CML-specific, patient-friendly knowledge base including resources and knowledge related to drug information (drug development, generics, pharmacovigilance) and drug safety using several educational tools such as videos, CML support, and CML drug sheets. To disseminate more largely, an e-university learning for regional key informants from LMC France and also CML patients and their caregivers was launched, including a large resources related to drug information and drug safety in synergy with hematologists and clinical pharmacologists.

☆ LMC France, 13010 Marseille, France.

* Corresponding author. Service de pharmacologie clinique, 254, rue Saint-Pierre, 13005 Marseille, France.
E-mail addresses: contact@lmc-france.fr (M. Daban), joelle.micallef@ap-hm.fr (J. Micallef).

https://doi.org/10.1016/j.therap.2020.02.014

Abbreviations

CML chronic myeloid leukemia
EURORDIS European Organization for rare diseases
TKIs tyrosine kinase inhibitors

Introduction

There are well-established patients' organizations active at local or regional while others are involved at national, European or international levels. Some are coalitions or organizations working across diseases, channeling the voice of the whole patient community on cross-cutting issues, while some are condition-specific, meaning that they deal with a single disease (Charcot-Marie Tooth, Rett syndrome...) or disease area (rare diseases...) [1,2]. As outlined by Wastfelt et al, there are few areas in medicine in which patient-parent advocacy groups play such a central and prominent role as in the field of rare diseases [3]. The main activities of patient organizations are set out in four different areas (policy, capacity-building ad education, peer support and research & development (see for review the European Patients Forum 2017 work programme) [2]. More precisely many types of patients organizations have a role at all levels from research funding to regulatory aspect of the orphan-drug market, including production and promotion of educational information and the design of public policy and study projects [1,4]. This activity is particular relevant because translating research into therapies for patients was the most urgent priority for the decade outlined by EURORDIS, the European Organization for rare diseases [5]. In the present paper, we illustrate the activities of the French Association of Chronic Myeloid Leukemia (LMC France) on drug information and drug safety, in synergy with hematologists and clinical pharmacologists.

Chronic myeloid leukemia (CML): update on diagnosis, therapy and monitoring

CML is a rare myeloproliferative neoplasm with an incidence of 1-2 cases per 100,000 adults. It accounts for approximately 8000 and 10,000 CML cases in France and around 800 new cases diagnosed each year. In USA, it is estimated about 9000 new CML cases [6]. CML is often asymptomatic and diagnosed during a route physical examination or blood tests. Sometimes, during the chronic phase of CML, patients can exhibit common signs and symptoms like fatigue, weight loss, malaise, easy satiety and pain. CML is a chronic blood and bone marrow disease that results from a transformation of a stem cell. In CML cells, a part of the chromosome 9 is exchanged with a part the chromosome 22 leading to the formation of the Philadelphia chromosome. As a consequence, ABL1 gene normally found on chromosome 9 moves and joins BCR gene normally found on chromosome 22. This BCR-ABL1 fusion then produces an abnormal gene called the oncogene BCR-ABL1 with an increased and uncontrolled tyrosine kinase activity. The diagnosis consists in documenting an unexplained leukocytosis with the presence of the Philadelphia chromosome abnormability. Until 2000, drug therapy for CML was limited to nonspecific agents such as busulfan, hydroxyurea or interferon-alpha. Then, the apparition of oral and targeted therapies with the commercialization of tyrosine kinase inhibitors (TKIs) revolutionized the treatment of CML. These small molecules were able to interfere with the interaction between the BCR-ABL1 oncoprotein and adenosine triphosphate, thus blocking cellular proliferation of the malignant clone. This new therapeutic improves the 10-year surviving rate from 20% to around 83% [7]. Imatinib was the first TKI synthetized and approved in 2001. Imatinib represents the 1st generation of TKI and it is generally used as a first line treatment. Nevertheless, some patients can be resistant or intolerant to this TKI. Further structural and chemical changes led to new generations of TKI: nilotinib, dasatinib and bosutinib representing the 2nd generation, and ponatinib for the 3rd generation. Ponatinib can be specifically used in case of a particular genetic mutation called T315I. Generic medications of imatinib and dasatinib are available in France since 2016 and 2019 respectively. The continuous daily treatment over many years is burdened by the occurrence of adverse events [8]. For example imatinib therapy can be associated with some adverse events both haematologic and non-hematologic, which are easy to manage, but sometimes they have a negative impact on health-related quality of life [9]. Pulmonary arterial hypertension has also been reported with the use of dasatinib, patients have to stop the treatment to recover [8]. Indeed, several cases were reported by the French pharmacovigilance network, leading to an information by French medical regulatory authorities in April 2011 intended for clinicians [10]. Furthermore, all TKIs can affect the cardiovascular system but the frequency of cardiac adverse events is depending on which molecule is used. Reduction or interruption of TKI treatment must only be done if the management of the adverse event cannot be accomplished otherwise, and monitoring is needed to detect resolution of the adverse event as soon as possible. Therapeutic drug monitoring could also assist in investigation of the observance, the absence of response, and the drug-drug interactions [11]. Nevertheless, each TKI has a different toxicity profile and clinicians should select the best for each patient.

The French Association of Chronic Myeloid Leukemia: LMC France

LMC France was founded in 2010 by Mina Daban, diagnosed CML in 2003, treated by ITK and in remission today. The association is characterized by a strong partnership of patients, families, friends and health care professionals (hematologists, pharmacologists, biologists, pharmacists, physicians...) has more than 2 000 registered members and aim to support patients and their family, to support clinical research, and to promote information and education [12].

The Association has a scientific council that guarantees the quality of the data available via its different educational supports. Its organization is decentralized through 10 key-informants in French regions. LMC France has received national and international recognition for its achievements. LMC France is member of the CML advocate network [13]. During is general assembly in February 26, 2011, LMC France

proposed the idea of creating a world-wide awareness day on September 22. On day 9/22 (representing also the genetic change of chromosomes 9 and 22 that is cause the CML), international CML Awareness day was celebrated across the world [14]. LMC France has published a whitebook in 2013 leading to 16 propositions for optimizing care, quality of life, and new strategies for patients [15]. Three years after in 2016, its whitebook was updated leading to identify current and future challenges that need to be addressed appropriately [16]. More precisely, the whitebook has reported a study among CML patients showing that 91% are interested by a formation on CML, its diagnosis and its treatments. Based on this result and because CML patients are geographically dispersed, LMC France launched the first e-university learning for CML patients and their caregivers including several videos on drug information and safety (see below) [17].

Its actions related to drug information and drug safety

Facilitating access to information and providing educational material and scientific information in a patient-friendly language to patient is one of the main objectives of LMC France [18].

CML drug information

LMC France provide an area on its internet site where CML drug sheets are ready for download to patients [19]. These drug sheets included a summarized information on name (brand name and generic form if available), indication (first line or/and second line), date of approval, mechanisms of action, the main adverse effects, the drug-drug interactions and also the drug interaction with herbal products. The use of alternative medicine is particularly common in patients with cancer. Recent surveys have reported that approximately one third to one half of these patients use some type of alternative medicine, such as vitamins and herbal products. Because patients may not consider these alternative products to be drugs, they frequently do not report their use of such agents to their physician or pharmacist whereas this herbal product (such as St John's Wort) affect significantly the pharmacokinetic of imatinib and may compromise therapeutic outcome [20]. Awareness of these potential interactions between herbal products anticancer agents through these educating supports is also helpful.

The introduction of generic forms

The introduction of generic imatinib in many countries can often leave patients confused. Patients often have many questions about generics and about switching from the brand form to a generic form. To explain and promote generic use, several educational materials have been realized including a generic sheet. During the world CML day in September 2016, a conference by Pr Joëlle Micallef, clinical pharmacologist, on drug development and post marketing surveillance including a specific topic on generic has been done [21]. Through the e-university, a video devoted specifically to the generics is available through answers to the following questions: (i) What are generics and do they differentiate from the brand name form? (ii) Which generics of CML TKI exist? (iii) What do we know about efficacy and safety? (iv) Are generics monitored as brand name? [22].

The pharmacovigilance system

The involvement of patients in pharmacovigilance has been increasing since the last decade and particularly in Europe due to European regulation encouraging patients to report adverse drug reactions to local or national drug safety authorities [23]. LMC France encourage patients to report their adverse events to the French network of pharmacovigilance using the site of drug agency or other means of communication (phone, letter...). Besides CML patients report frequent questions related to the French pharmacovigilance system such as what is the pharmacovigilance, what is its scope, what is the role of the French Drug Agency, what is the role of the European drug agency, what is an adverse effect, what means benefits/risk ratio, is the report of adverse events anonymous.... In order to answer more accurately an interview between Mina Daban from LMC France and Joëlle Micallef from the French pharmacovigilance network has been recorded (available via LMC France site and the e-university site).

Adherence in CML: research and tools

Non-adherence to treatment in chronic diseases is a well-known problem. The dramatic evolution in CML treatment in the last decade, resulting from the introduction of imatinib and followed by second generation TKIs, has turned CML into a kind of chronic disease where patients need to take their medication on daily basis.

In 2012, the CML advocates network (including LMC France) decided to conduct large, scientifically sound international study on adherence [24]. It enrolled patients from 9 from September 2012 to January 2013 based on a comprehensive questionnaire in 12 languages. The aim of this study was to investigate motivations and behavioral patterns of adherence in CML and subsequently support hematologists and patients to improve adherence and develop suitable adherence tools. Overall 2151 patients treated with TKIs from 63 countries were enrolled after filling a questionnaire about their treatment adherence. Results show more than 32% of highly adherent participants and about 21% of low adherence participants. Demographic factors seem to be involved in a better adherence in treatment such as a higher age (median age in highly participants: 55 years old) and male sex. The main factors partially influencing were the quality of the doctor-patient relationship, the management of side effects and the number of doses per day. Patients who feel well informed about their disease are significantly more adherent. It highlights the importance of the information in the field of rare diseases. Improving adherence is a team work involving patients, doctors, relatives, nurses and pharmacists but also patients' organizations, expert groups and researchers. Because stimulating awareness and education regarding their specific treatment has been shown to positively influence medical compliance, LMC France has launched also a mobile app in promoting medication adherence and education called CML coach [25].

Conclusion

Patients' organizations in rare disease are among the most empowered group in the area of health. As illustrated by LMC France, its contribution is not only focused on its role as participants or key informant related to clinical studies but also on drug information and drug safety. The discovery of TKIs against the BCR-ABL1 oncogenic fusion protein has revolutionized the management of CML, becoming a chronic illness rather than a life-threatening disease. Because ensuring ongoing wellbeing requires some knowledge, LMC France has built a CML-specific, patient-friendly knowledge base including resources and knowledge related to drug information and drug safety (via several educational tools such as videos, CML support, CML drug sheets). To disseminate more largely, an e-university learning for patients and their caregivers was launched, including a large of resources related to drug information and safety.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Aymé S, Kole A, Groft S. Empowerment of patients: lessons from the rare diseases community. Lancet 2008;371(9629):2048—51.

[2] European patients Forum. The added value of patients' organizations; 2017. https://www.eu-patient.eu/globalassets/library/publications/epf_added_value_report_final.pdf. [Accessed January 20, 2020 (36 pp.)].

[3] Wästfelt M, Fadeel B, Henter JI. A journey of hope: lessons learned from studies on rare diseases and orphan drugs. J Intern Med 2006;260(1):1—10.

[4] Micallef J, Boutouyrie P, Blin O. Pharmacology and drug development in rare diseases: the attractiveness and expertise of the French medical pharmacology. Fundam Clin Pharmacol 2017;31(6):685—94.

[5] Eurordis. Patients'priorities and needs for rare disease research 2014—2020; 2011. http://download2.eurordis.org/documents/pdf/what_how%20_are_disease_research.pdf. [Accessed January 20, 2020 (23 pp.)].

[6] Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2018 update on diagnosis, therapy and monitoring. Am J Hematol 2018;93(3):442—59.

[7] Mughal TI, Radich JP, Deininger MW, Apperley JF, Hughes TP, Harrison CJ, et al. Chronic myeloid Leukemia: reminiscences and dreams. Haematologica 2016;101(5):541—58.

[8] Steegmann JL, Baccarani M, Breccia M, Casado LF, García-Gutiérrez V, Hochhaus A, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia 2016;30(8):1648—71.

[9] Eşkazan AE. Tyrosine kinase inhibitors (TKIs) used in the management of chronic myeloid leukaemia are associated with haematologic toxicities — Which TKI is the safest? Br J Clin Pharmacol 2019;85(10):2241—3.

[10] ANSM. Lettre aux professionnels de santé. In: Risque d'hypertension artérielle pulmonaire chez les patients traités par Sprycel® (dasatinib); 2011. https://ansm.sante.fr/S-informer/Informations-de-securite-Lettres-aux-professionnels-de-sante/Sprycel-R-dasatinib-risque-d-hypertension-arterielle-pulmonaire-Lettre-aux-professionnels-de-sante/(language)/fre-FR. [Accessed January 20, 2020].

[11] Bouchet S, Royer B, Le Guellec C, Titier K, groupe Suivi Thérapeutique Pharmacologique de la Société Française de Pharmacologie et de Thérapeutique. Therapeutic drug monitoring of tyrosine-kinase inhibitors in the treatment of chronic myelogenous leukaemia: interests and limits. Therapie 2010;65(3):213—8.

[12] Association LMC France; 2019. https://www.lmc-france.fr/ [Accessed January 20, 2020].

[13] CML Advocates Network For Chronic Myeloid Leukemia Patient Group Advocates; 2019. https://www.cmladvocates.net/ [Accessed January 20, 2020).

[14] World CML Day; 2019. https://www.cmladvocates.net/world-cml-day-9-22. [Accessed January 20, 2020].

[15] LMC-France. Livre blanc des 1ers états généraux de la leucémie myéloïde chronique; 2013. https://www.lmc-france.fr/télécharger-le-livre-blanc-de-la-lmc/. [Accessed January 20, 2020].

[16] LMC-France. Livre blanc des 2èmes états généraux de la leucémie myéloïde chronique; 2016. https://www.lmc-france.fr/telechargement/télécharger-le-2nd-livre-blanc-de-la-lmc/. [Accessed January 20, 2020].

[17] LMC-France. La e-université LMC France; 2019. https://www.lmc-france.fr/au-service-du-patient/la-e-université-lmc-france/. [Accessed January 20, 2020].

[18] LMC France. Journée d'informations et d'échanges ANSM- avec les associations de patients; 2013. https://ansm.sante.fr/var/ansm_site/storage/original/application/a753eee83ee53d92ccfab2bd036090c0.pdf. [Accessed January 20, 2020 (24 pp.)].

[19] LMC France. Les fiches LMC France; 2019. https://www.lmc-france.fr/au-service-du-patient/les-outils-patients/les-fiches-lmc-france/. [Accessed January 20, 2020].

[20] Bulletin de pharmacovigilance Marseille et Nice 2018. https://www.rfcrpv.fr/wp-content/uploads/2018/02/pharmacovigilance-26-interactif.pdf [Accessed January 20, 2020 (12 pp.)].

[21] Micallef J. Essais cliniques et médicaments dans la vraie vie. Journée mondiale de la LMC; 2016. https://www.youtube.com/watch?v=pmQuJHoAQWs. [Accessed January 20, 2020].

[22] Micallef J. Les médicaments génériques; 2019. https://www.lmc-france.fr/vid%C3%A9os/les-vid%C3%A9os-%C3%A9ducationnelles/. [Accessed January 20, 2020].

[23] Margraff F, Bertram D. Adverse drug reaction reporting by patients: an overview of fifty countries. Drug Saf 2014;37(6):409—19.

[24] Geissler J, Sharf G, Bombaci F, Daban M, De Jong J, Gavin T, et al. Factors influencing adherence in CML and ways to improvement: results of a patient-driven survey of 2546 patients in 63 countries. J Cancer Res Clin Oncol 2017;143(7):1167—76.

[25] LMC. LMC coach; 2019. https://www.lmc-france.fr/au-service-du-patient/les-outils-patients/lmcoach-le-service-mobile-lmc-france/. [Accessed January 20, 2020].