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Consensus Statement

Cardiovascular management of patients with chronic myeloid leukemia from a multidisciplinary perspective, and proposing action protocol by consensus meeting☆

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ABSTRACT

Introduction and objectives: The second generation tyrosine kinase inhibitors (TKI, dasatinib and nilotinib) used in chronic myeloid leukemia (CML) treatment have shown a benefit compared to imatinib in responses achieved and disease progression. However, both have been related to some cardiovascular toxicity, being more frequent in patients with cardiovascular risk factors (CVRFs). Nowadays, due to the lack of recommendations for CML patients, CVRF management is carried out heterogeneously. The aim of this work is to develop recommendations on the prevention and monitoring of cardiovascular events (CVD) in patients with CML treated with TKIs.
Material and methods: Experts from the Spanish Group of Chronic Myeloid Leukemia together with experts in cardiovascular risk have elaborated, after a consensus meeting, recommendations for the prevention and follow-up of CVE in patients with CML treated with TKI.
Results: Recommendations regarding the necessary information to be collected on clinical history, treatment decisions, as well as treatment and monitoring of CVRFs are shown in this document.
Conclusions: TKI treatment requires comprehensive patient management from a multidisciplinary approach, in which both the prevention and management of CVRFs are essential.

Gestión cardiovascular de los pacientes con leucemia mieloide crónica desde una perspectiva multidisciplinar, y propuesta de protocolo de actuación por reunión de consenso

Palabras clave:
Leucemia mieloide crónica
Tratamiento integral
Factores de riesgo cardiovascular
Conferencia de consenso

RESUMEN

Introducción y objetivos: Los inhibidores de la tirosina cinasa (ITC) denominados de segunda generación (dasatinib y nilotinib) empleados en el tratamiento de la leucemia mieloide crónica (LMC) han demostrado un beneficio frente a imatinib en respuestas alcanzadas y progresiones de la enfermedad. No obstante, estos inhibidores se han relacionado con alguna forma de toxicidad cardiovascular, ocurriendo en su mayor parte en pacientes con factores de riesgo cardiovasculares (FRCV). El control de los FRCV se debe

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considerar por tanto imprescindible para un tratamiento adecuado de la LMC. En la actualidad, debido a la falta de recomendaciones en pacientes con LMC, el tratamiento de los FRCV se realiza de forma muy heterogénea. El objetivo de este trabajo es elaborar recomendaciones sobre la prevención y el seguimiento de episodios cardiovasculares (ECV) en pacientes con LMC tratados con ITC.
Material y métodos: Expertos del Grupo Español de Leucemia Mieloide Crónica, junto con expertos en riesgo cardiovascular, hemos elaborado, con base en una reunión de consenso, recomendaciones de prevención y seguimiento de ECV en pacientes con LMC tratados con ITC.
Resultados: En este documento se muestran las recomendaciones de consenso con respecto a la información necesaria a recoger en la historia clínica, la toma de decisiones terapéuticas, así como el tratamiento y el seguimiento de los FRCV.
Conclusiones: El tratamiento con ITC requiere un manejo integral del paciente que deberá realizarse desde un abordaje multidisciplinar, en el que tanto la prevención como el tratamiento de los FRCV es fundamental.

Chronic myeloid leukemia (CML) is a chronic myeloproliferative neoplasm characterised in cytogenetic by the presence of the Philadelphia chromosome (Ph), resulting from t(9;22) (q34;q11). The result of this translocation is the formation for the BCR-ABL gene fusion and the BCR-ABL chimeric protein, which has an increased tyrosine kinase activity and plays a key role in the development of the disease.[1]

CML is the first condition in which the genetic alteration responsible was identified, and as a result was also the first condition in which medications directed against tyrosine kinase activity of the BCR-ABL1 protein were developed.[1]

The arrival of inhibitors called tyrosine kinase (TKI) has dramatically changed the prognosis of CML, as they induce deep responses, measured at the molecular level. This means that the disease has gone from a life expectancy of 3–4 years in patients who do not receive haematopoietic stem cell transplantation, to currently having one similar to that of the general population. Despite the excellent results obtained with TKI, when it is suspended the disease reappears, and today CML is considered an incurable ailment without haematopoietic stem cell transplantation (strategy reserved only for patients that do not respond to TKI because of its high morbidity and mortality), so that the expert recommendation is to maintain treatment for life. In this new scenario where we can assume that the disease becomes chronic, we begin to see how a number of CML patients will die from causes beyond their leukemia.[2]

Currently, the leading cause of death in the western population are cardiovascular events (CVE)[3] which is why prevention through active treatment of cardiovascular risk factors (CVRF) is recommended for the general population. In many cases this includes a multidisciplinary follow-up by different specialists.[4]

In recent years it has been noted that cancer patients who have long-term survival rates may have a higher incidence of CVE, often favoured by the treatment they have received.[5]

In this sense, secondary effects of TKI treatments called “off-target” have been identified. One of the side effects that has caused most concern has been the increase of CVE. Thus, treatment with second generation TKI, nilotinib or dasatinib, has been linked to an increased incidence of CVE when compared with imatinib.[6–8]

Nilotinib appears to increase the incidence of peripheral arterial obstructive disease (PAOD) and dasatinib has been linked to an increased incidence of pulmonary hypertension (PHT). It also appears that the percentage of cardiac ischaemic events increases with use of nilotinib or dasatinib compared with imatinib. With a follow-up period of 5 years, the DASISION study reported an incidence of cardiac ischaemic events of 4% compared with 2% with dasatinib compared with 2% with imatinib, and the ENESTnd study obtained 3.9% with nilotinib (doses of 300 mg/12 h) compared with 1.8% with imatinib. Regarding PAOD, its incidence at 5 years in the ENESTnd and DASISION study was 2.5% for nilotinib (dose of 300 mg/12 h) of 0% for dasatinib and 1% for imatinib.[7,8] Finally, the incidence of pulmonary hypertension in patients treated with dasatinib seems to have figures that are lower than 1%.[6] Most CVE observed in patients treated with TKI occurred in those that had high cardiovascular risk. The mechanism which enhances CVE occurrence is still unknown. However, it has been observed that nilotinib produces an increase of cholesterol and glucose that we can assume favours the onset of a cardiovascular risk factor; it is postulated that proper patient selection and strict control of CVRF reduce the occurrence of such episodes.[6] In contrast, the mechanisms by which dasatinib is associated with HTP are unknown. Given that second generation TKIs are more effective than first-line imatinib (increased depth of the molecular response and fewer progressions at advanced stages) and are able to save 50% of patients after imatinib failure. Knowing that cardiovascular risk exists and treating it actively would be essential to ensure that therapeutic efficacy is not restricted by vascular comorbidity.[2]

For these reasons, the Spanish Group of Chronic Myeloid Leukemia (GELMC) of the Spanish Society of Haematology and Haemotherapy drew up recommendations based on a comprehensive perspective of the patient, focusing on the management of cardiovascular risk, with the purpose of establishing a set of easy-to-use guidelines aimed at the necessary diagnostic tests and therapeutic options for the management of cardiovascular risk.

Thus, when establishing guidelines for multidisciplinary work in clinical practice, we should know what the haematologist can usually control and treat and what should be controlled by a specialist.

This document will summarise the results of the consensus meeting held between the members of GELMC and a group of specialists from different cardiovascular risk areas as well as the subsequent consensus of all members of the GELMC to establish recommendations for the prevention and monitoring of CVE in patients with CML treated with TKI, from the perspectives of clinical practice and haematologist consultation.

The consensus meeting presented two key objectives: first, to review the literature and scientific evidence available in order to evaluate GELMC’s existing recommendations regarding the comprehensive treatment of patients with CML, and second, to discuss the opinion of expert haematologists on how to properly prevent and treat CVRF in patients with CML treated with TKI, establishing simple diagnostic and therapeutic protocols for haematologist