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Consensus statement

Update of the Grupo Español de Leucemia Linfocítica Crónica clinical guidelines of the management of chronic lymphocytic leukemia☆

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ABSTRACT

Background and objective: The broad therapeutic arsenal and the biological heterogeneity of patients with chronic lymphocytic leukemia (CLL) makes it difficult to standardize treatment for CLL patients with specific clinical settings in routine clinical practice. These considerations prompted us to elaborate the present consensus document, which constitutes an update of the previous version published in 2013, mainly focusing on novel treatment strategies that have been developed over last 5 years, namely B-cell receptor inhibitors (ibrutinib and idelalisib), anti-CD20 monoclonal antibodies (ofatumumab and obinutuzumab), and Bcl-2 inhibitors (venetoclax).
Material and methods: A group of experts from the Spanish Chronic Lymphocytic Leukemia Group reviewed all published literature from January 2010 to January 2016, in order to provide recommendations based on clinical evidence. For those areas without strong scientific evidence, the panel of experts established consensus criteria based on their clinical experience.
Results: The project has resulted in several practical recommendations that will facilitate the diagnosis, treatment, and follow-up of patients with CLL.
Conclusions: There are many controversial issues in the management of CLL with no appropriate studies for making consensus recommendations.

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Actualización de las guías nacionales de consenso del Grupo Español de Leucemia Linfocítica Crónica para el tratamiento y seguimiento de la leucemia linfocítica crónica

Palabras clave:
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RESUMEN

Antecedentes y objetivo: El amplio arsenal terapéutico junto con la heterogeneidad biológica de los pacientes hace que sea difícil estandarizar el tratamiento de la leucemia linfocítica crónica (LLC) en la práctica clínica. Estas consideraciones han motivado la preparación del presente documento de consenso, que se trata de una actualización de la versión publicada en 2013, prestando especial atención a las estrategias de tratamiento que han aparecido en los últimos 5 años, como los inhibidores del receptor de células B (ibrutinib e idelalisib), los nuevos anticuerpos monoclonales anti-CD20 (ofatumumab y obinutuzumab) y los inhibidores de Bcl-2 (venetoclax).

Material y métodos: Un grupo de expertos del Grupo Español de Leucemia Linfocítica Crónica ha revisado la bibliografía publicada entre 2010 y 2016 para poder establecer una serie de recomendaciones basadas en la evidencia clínica. En aquellas áreas donde no se encontró una evidencia científica, el grupo de expertos estableció recomendaciones por consenso con base en sus experiencias clínicas.

Resultados: Como resultado del proyecto se ha establecido un conjunto de recomendaciones de carácter práctico que facilitarán el diagnóstico, el tratamiento y el seguimiento de los pacientes con LLC.

Conclusiones: Existen muchos aspectos del tratamiento de la LLC que resultan ser temas controvertidos sobre los que no hay estudios apropiados para generar recomendaciones de forma consensuada.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common hematological neoplasm in Western countries (5/100,000 population-year). The incidence increases with age up to 30 cases per 100,000 population-year in people aged over 70. The mean age at diagnosis is 68–70. It is more common in men than in women (2:1) and 30% of patients are below 64 years old.[1] CLL is a disease with a very heterogeneous clinical course. Thus, half of the patients will never report progression of their disease, with a life expectancy similar to that of the normal general population. On the contrary, the other half of the patients will need treatment throughout the course of their disease and their life expectancy will drop as a result of CLL. Current therapies have shown high response rates. However, CLL remains incurable and many patients relapse throughout the course of the disease. The treatment of CLL has undergone many changes in recent years. For over 3 decades the standard treatment was chlorambucil (Clb). In the 1990s, purine analogs were included, alone or in combination with alkylating agents. In the last decade, the inclusion of anti-CD20 monoclonal antibodies (rituximab, ofatumumab, and obinutuzumab), bendamustine, B-cell receptor inhibitors (BCR), such as ibrutinib and idelalisib, and Bcl-2 antagonists (venetoclax) have changed the CLL treatment paradigm. The broad therapeutic arsenal, coupled with the biological heterogeneity of patients, makes it difficult to standardize CLL treatment in clinical practice. All these considerations have led us to draft this consensus document.

Methodology

To obtain a consensus document with the most up-to-date information, we reviewed the studies published in the MEDLINE and EMBASE databases and the abstracts reported at the annual meeting of the American Society of Hematology (2015). The keywords used in the bibliographic search were: *chronic lymphocytic leukemia*, *treatment* and *relapse*. It was limited to studies conducted in humans from 2010 to 2016 (January). A total of 310 references were obtained: 76 on first-line therapy, 139 on second-line therapy and 95 on other therapies. The bibliographic references were classified in accordance with the level of evidence (Table 1), following the criteria provided by the U.S. Agency for Health Research and Quality.[2] They were also assigned by therapy groups: first line, relapse/refractoriness and supportive therapy. A group of experts from the Spanish Society of Hematology and Hemotherapy and the Spanish Group of Chronic Lymphocytic Leukemia (GELLC) evaluated all the information collected and provided a series of recommendations and therapeutic algorithms based on proven clinical evidence. Recommendations were classified in accordance with the criteria of the U.S. National Comprehensive Cancer Network (Table 1).[3] In those areas where no scientific evidence was reported, the group of experts provided consensus recommendations based on their clinical experiences. This document is an update of the guidelines published in 2013.[4]

Table 1
Levels of evidence and degrees of recommendation.

	Levels of evidence
Level 1a	Meta-analysis of well-designed, randomized, controlled clinical trials
Level 2b	At least one randomized controlled trial
Level 2a	At least one well-designed randomized controlled trial
Level 2b	At least one non-fully experimental, well-designed study, such as cohort studies
Level 3	Well-designed non-experimental descriptive studies such as comparative studies, correlation studies or case-control studies
Level 4	Documents or opinions of expert committees or clinical experiences from prestigious authorities or case series studies
	Degrees of recommendation
Category 1	Available evidence is high quality evidence and there is consensus among experts
Category 2A	Available evidence is moderate quality evidence and there is consensus among experts
Category 2B	Available evidence is moderate quality evidence and there is no unanimous consensus among experts
Category 3	Available evidence is of any degree and there is no consensus among experts