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Precision medicine in chronic lymphatic leukemia: Cost-effectiveness analysis of the new targeted therapies

Medicina de precisión en leucemia linfática crónica: Análisis de coste-efectividad de nuevas combinaciones dirigidas

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Chronic lymphatic leukemia (CLL) is the most frequent kind of chronic leukemia in the Western World, with a prevalence of 5 cases per 100,000 inhabitants[1]. CLL is a neoplasm that is diagnosed mostly in the elderly (70% of patients are over 65 at the time of diagnosis and median patient age is 70 years). The condition is characterized by a widely heterogeneous clinical presentation, whereby some patients are without symptoms and may not require treatment for decades while others experience a rapid progression of the disease, which may on occasion exhibit an aggressive clinical behavior.

CLL is one of the hematologic neoplasms that has benefited the most from therapies targeted at molecules selectively expressed in tumor cells (precision medicine). A series of novel drugs have been developed in the last few years that have changed the prognosis of the disease in terms of response and survival. These include Burton's tyrosine kinase (BTK) inhibitors such as ibrutinib, bcl-2 inhibitors like venetoclax, and several monoclonal antibodies targeted at the CD20 molecule (rituximab, ofatumumab, and obinotuzumab)[2]. Moreover, following the publication of biological studies that brought to light a series of cytogenetic and molecular alterations associated with poor prognosis, several groups have recently undertaken clinical trials in an attempt to improve the prognosis of patients with CLL and chromosome 17p deletion or p53 gene mutations. These alterations significantly affect the choice of first-line treatment. The advent of the new drugs has resulted in immune-chemotherapy being increasingly administered only to patients with a satisfactory functional status whose CLL is not accompanied by p53 gene alterations and who exhibit mutated immunoglobulin heavy chain variable region (IgVH) genes.

Until very recently, first-line treatment in patients under 70 years of age or in those unfit to receive immune therapy consisted in the use of BTK inhibitors (ibrutinib) or a combination of anti-CD20 therapy plus chlorambucil in patients where BTK inhibitors were contraindicated. The recommended treatment for all other patients was a BTK inhibitor, except for fit patients with mutated IgVH genes, who could be amenable to immune-chemotherapy (e.g., FCR). BTK inhibitors have been regarded as a mainstay in the treatment of CLL. A series of long-term first-line studies have shown that ibrutinib, administered until progression or toxicity, achieves a significant increase in progression-free survival (PFS) in all risk groups[3]. Contrary to what happens in patients who receive the drug at an advanced stage of the disease (second or third line of treatment), first-line patients usually exhibit greater tolerance, with over 70% of those responding to the treatment receiving ibrutinib for more than four years. Although some preliminary analyses have shown that a selected group of these patients could maintain their response once the drug has been suspended[4], discontinuation of ibrutinib in patients with a satisfactory response has not been well established in clinical practice, the treatment being typically maintained until progression or toxicity. Median duration of treatment in patients who receive the drug as first-line therapy is usually five years, which entails a high economic cost for the health system[5].

The introduction of new drugs has made it possible to increase the therapeutic options available to first-line patients. Venetoclax is a selective oral BCL-2 inhibitor capable of achieving high response rates in CLL patients who are in remission, including those testing negative for minimal residual disease (MRD)[6]. These findings have generated an interest in analyzing the effect of the drug on first-line CLL patients. The combination of venetoclax and obinutuzumab (O) showed superior results in terms of complete response and PFS as compared with the O-chlorambucil combination[7]. In addition, the venetoclax-O combination resulted in a high rate of responses with negative MRD, which is associated with higher PFS. These findings have positioned the venetoclax-O combination as an alternative first-line treatment for patients with CLL, on a par with ibrutinib[8].

Given the current situation of first-line CLL treatment, where the indication of immune-chemotherapy (e.g., FCR) is becoming increasingly limited, it is essential to conduct pharmacoeconomic and cost-efficiency analyses of new combinations of targeted therapies.

The study by Moreno *et al.*[9] included in this issue is extremely timely as it performs a cost-efficiency analysis of the main combinations studied in different clinical trials with CLL patients. The study concludes that the venetoclax-O combination is associated with a lower cost than other drugs, particularly ibrutinib. This finding is of great relevance for therapy selection, as both options are currently available as first-line treatment. Although no studies have so far compared venetoclax-O vs. ibrutinib, the findings of the CLL-14 (first-line) study and of the MURANO study (in patients in remission)[10] demonstrate the high effectiveness of the venetoclax-O combination, including a complete response (with negative MRD). Undoubtedly, one of the reasons behind the lower cost associated with the venetoclax-O combination has to do with its fixed dosing regimen (12 or 24 months), which contrasts with the indefinite administration required by ibrutinib. Some of the drawbacks of the venetoclax-O combination, which must be duly considered, are the intravenous administration required for obinutuzumab, the need to admit patients at high risk of tumor lysis and, very importantly, the potential negative impact that an anti-CD20 antibody may have for the development of COVID-19. In any event, future clinical trials should look into therapeutic regimens that contemplate the administration of drugs for a fixed period or, alternatively, or analyze the possibility of discontinuing the drug in patients achieving a sustained complete response, as this would enable the introduction of more cost-effective therapeutic regimens.

Lastly, mention must be made of the potential role of treatments using genetically engineered T-cells equipped with chimeric antigen receptors (CAR-Ts). Recent studies with CART19 cells in CLL patients in remission further to multiple treatments (100% ibrutinib and 60% venetoclax) produced a high response rate, with 45% complete responses[11]. Given that CART19 therapies are often administered at earlier stages in patients with aggressive B lymphomas (currently under evaluation for second-line treatment), it cannot be ruled out that CAR-T therapy may in the near future be contemplated for early-stage CLL patients. Efficacy and toxicity studies will contribute to establishing the therapeutic positioning of CAR-T therapy in the context of CLL, although the fact CART-T can be administered in one single dose is already a significant advantage.

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