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Lenalidomide in chronic lymphocytic leukemia: the present and future in the era of tyrosine kinase inhibitors

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ABSTRACT

Lenalidomide is an immunomodulatory agent (IMiD) clinically active in chronic lymphocytic leukemia (CLL), both in heavily pre-treated patients and upfront. Lenalidomide has a unique mechanism of action in CLL. Its efficacy relies on a multifactorial mode-of-action (MOA), comprising a plethora of immunomodulatory actions, the disruption of mutualistic interactions inside CLL microenvironment and direct effects against leukemic cells. In the last few years, a number of new and highly effective drugs appeared in the scenario of CLL therapeutic options, i.e. tyrosine kinase inhibitors (TKIs), showing a good safety profile and impressive clinical response, also in high-risk patients. In this review, we describe the data from clinical studies about lenalidomide efficacy in CLL and we critically dissect the different mechanisms of action of this drug. We point the attention on open issues, including drug dosage and administration schedule, prediction of clinical response to lenalidomide, and combination therapeutic strategies. This overview would be useful to envision a possible role of lenalidomide in the treatment flow-chart of CLL, exploiting its peculiar MOA and also exploring the possible synergetic effect with new drugs.

1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in Western Countries. In the majority of cases, it affects elderly people with a median age at the onset of 72

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years, showing a highly heterogeneous clinical course (Hallek, 2013). It is commonly considered an indolent disease that progresses slowly and, in the majority of cases requires treatment only after years of clinical observation. However, some patients rapidly progress to a symptomatic disease and early require treatment. Although outcome has really improved by the use of fludarabine-based chemotherapy associated with anti-CD20 monoclonal antibodies (chemoimmunotherapy), CLL is a disorder still considered incurable due to high incidence of relapse. Patients who relapse frequently develop resistance to treatment, show fludarabine refractoriness and very poor outcome due to limited treatment options and the presence of acquired poor prognostic genetic characteristics (i.e. 17p13 deletion and/or P53 mutations) in relapsed leukemic clone, giving rise to the so-called clonal evolution. Moreover, although highly efficient, fludarabine-based chemoimmunotherapy induces substantial toxicity and cannot be used in elderly and unfit patients, who are by fact the majority of CLL patients.

Recently, a new class of drugs has shown the ability to control the disease never registered before, opening a new scenario that could probably change the landscape of CLL treatment. These drugs, and in particular tyrosine kinase inhibitors (TKIs), show a wide efficacy in relapsed and refractory CLL patients, irrespective of prognostic factors, and a good safety profile (Burger, 2014; Pallasch and Hallek, 2014). In particular, ibrutinib, an oral irreversible inhibitor of Bruton's tyrosine kinase (Btk), showed an overall response rate (ORR) of 71% and overall survival (OS) of 83% at 26 months in the relapsed CLL setting (Byrd et al., 2013). Noteworthy, the response was independent of the number of previous therapies or high-risk features, including 17p13 deletion. However, it has to be considered that very few complete responses are obtained with ibrutinib (2% in previously treated CLL, 13% in treatment naïve CLL) and progression is rapidly seen when treatment is interrupted. Moreover, some patients develop resistance to ibrutinib due to specific mutations in Btk gene (Woyach et al., 2014). Prolonged therapy with TKIs associated with high-risk cytogenetics may favor the development of resistant subclones. In this scenario, the role of combination therapy to improve responses, with the aim of attaining the clearance of residual disease, and to avoid the occurrence of resistant clone, is keenly debated.

Lenalidomide is immunomodulatory drug (IMiD) derivative of thalidomide, approved in US and Europe for the treatment of multiple myeloma (MM), myelodisplastic syndromes with 5q deletion (del5q MDS) and mantle cell lymphoma (MCL). Moreover, several studies illustrated the activity of this drug in different lymphoproliferative disorders, spanning from low-grade to high grade lymphoma, used in monotherapy or in association both with monoclonal antibodies and chemotherapy (Nowakowski et al., 2015; Desai et al., 2014; Fowler et al., 2014). Lenalidomide was also reported to be active in CLL, in relapsed/refractory patients as well as at the onset (Badoux et al., 2011; Chen et al., 2011; Chanan-Khan et al., 2006; Ferrajoli et al., 2008). Of interest, lenalidomide has a unique mechanism of action targeting not only cancer cells, but also leading to modulation and interruption of multiple interactions between CLL cell and microenvironment elements, which play a pivotal role in leukemia promotion and survival. Because of clinical efficacy and mechanism of action, great interest has been applied on its role in CLL and some reviews have been published regarding both biological activity and clinical results (Gonzalez-Rodriguez et al., 2013; Kater et al., 2014; Fecteau et al., 2014). Moreover, new aspects of lenalidomide mode of action have recently been demonstrated, modifying the concept of an agent directed only on the microenvironment accessory cells. Furthermore, the landscape of CLL treatment is rapidly changing, because of the powerful appearance of new and very active drugs, targeting tyrosine kinase like BTK and PI3K and inhibiting cellular signal pathways crucial in the biology of CLL.

In this review, we would analyze which could be the role of lenalidomide in CLL treatment in the era of TKIs, reporting data from clinical studies about the efficacy in CLL and critically analyzing the different ways of action of this drug, pointing the attention on the open issues. This overview would be useful to envision a possible location of lenalidomide in the treatment flow-chart of CLL, exploiting its peculiar mode-of action (MOA) and also exploring the possible synergetic effect with new drugs.

2. Lenalidomide in CLL as single agent

2.1. Efficacy

Lenalidomide is an oral drug well tolerated in MM patients and considered as a suitable option in management of chronic disorders, which usually affect elderly people. Moreover, preclinical studies as well as the experience accrued in MM and MDS patients demonstrated the notable ability of the drug to modulate immune system and tumor microenvironment. Given the role of microenvironment in CLL pathogenesis, it was suggested to investigate its clinical effect in this disease.

Results of lenalidomide efficacy and toxicity in CLL were first reported by Chanan-Khan et al. (2006) in relapsed/refractory CLL setting, in which lenalidomide demonstrated a good efficacy, with an ORR of 47% in a high risk, heavily-pretreated patients population, characterized by worse prognostic factors. Nevertheless, a significant incidence of toxicities was reported, particularly in terms of hematological toxicity and unexpected novel and peculiar toxicities represented by tumor lysis syndrome (TLS) and tumor flare reaction (TFR).

Afterwards, a number of studies have been published in which lenalidomide was used as single agent both in the relapsed/refractory setting and upfront (Badoux et al., 2011; Chen et al., 2011; Chanan-Khan et al., 2006; Ferrajoli et al., 2008) (Table 1). All these studies confirmed the efficacy of the drug in a significant but variable percentage of patients, reporting the occurrence of complete response (CR) in a small portion of cases using different drug dosage and schedule (Table 1). Even if generally, an initial response and a peripheral lymphocyte reduction could be seen precociously during treatment, after just one week of therapy in some instances, the median time to the best response was over a year of treatment. Moreover, a late improvement of response was often observed. Chen and colleagues reported an increase in ORR from 56 to 72% extending the follow up from 24 to 53 months with 5 patients being upgraded from partial to complete remission (Chen et al., 2014).

Noteworthy, lenalidomide was active even in CLL patients with adverse genetic features and clinical response was achieved by 31% of patients with high risk cytogenetics (11q and/or 17p deletions), 24% with unmutated immunoglobulin genes, and 25% in fludarabine refractory subset (Ferrajoli et al., 2008). Moreover, another study reported a complete response rate of 19% in patients with 11q and/or 17p deletions, with a median progression-free survival of 12.1 months, which is higher than demonstrated with other agents in comparable patient populations (Sher et al., 2010). On the other hand, it was recently reported a retrospective analysis of CLL patients harboring 17p deletion, treated upfront with fludarabine-based or rituximab-based regimen or lenalidomide. The higher probability of achieving at least a partial remission was observed only with fludarabine, cyclophosphamide and rituximab regimen, and none of the ten patients treated with lenalidomide achieved CR (Strati et al., 2014). Although patients harbouring 17p deletion can obtain response by lenalidomide treatment, probably due to its