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The 21st century revolution in CLL: Why this matters to patients

Brian Koffman [a, *], Andrew Schorr [b]

[a] CLL Society Inc., PO Box 1390, Claremont, CA 91711, USA
[b] Carlsbad, CA, USA

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A B S T R A C T

The 21st century has seen rapid, positive changes in the management of chronic lymphocytic leukaemia from the patient's perspective. New prognostic and predictive markers have ushered in the start of more precise and individualized therapy. For the first time, combined therapy [fludarabine, cyclophosphamide and rituximab] has been shown to prolong life significantly. Clinical trials have become more adaptive, faster and more patient friendly. Perhaps the greatest change of all is the development of novel oral agents (ibrutinib and idelalisib) and powerful monoclonal antibodies that offer robust and durable disease control. Finally, access to and understanding of these changes through an empowered and educated patient population has grown through live education forums and the Internet.

Introduction

From the patient's perspective, the 21st century has brought many rapid and clinically significant improvements in the management of chronic lymphocytic leukaemia (CLL). These include deeper understanding of the underlying biology, better diagnostics, helpful new prognostic and predictive markers, improved early disease management, introduction of the first treatments shown to prolong life, newly designed and more patient-friendly clinical trials, and – perhaps the greatest change of all –

* Corresponding author.
E-mail address: Bkoffman@CLLSociety.org (B. Koffman).

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the development of novel oral agents and powerful monoclonal antibodies that offer robust and durable disease control.

These changes have been adopted rapidly by a patient population that is increasingly engaged, empowered and educated in live forums, particularly through the Internet.

In trying to summarize the patient's perspective, the Editors of this issue sought two writers with long and very different personal experiences of CLL as patients, educators and advocates. This chapter is the result of the work of both authors. The tone of this review reflects the distinct views of two of the thousands of possible patients with CLL. No attempt was made to blend the efforts. This chapter is not a dispassionate overview of the subject, but aims to provide the reader with an understanding of the issues that matter to patients.

Diagnostics and prognostics

When a patient is diagnosed with CLL, judgement regarding when to commence treatment is based on the lymphocyte count, signs and symptoms (e.g. night sweats, enlarged lymph nodes and spleen). A patient and his/her physician watch the rate of increase of lymphocytes ('doubling time'), and may look at beta2 microglobulin (beta2) levels and mutational status as prognostic factors. Previously, treatment often depended upon the age of the patient, as older patients received chlorambucil and younger patients received fludarabine, sometimes in combination with cyclophosphamide, given that a transplant might be a second-line treatment for younger, fitter patients if drug therapy did not work or the effectiveness subsided.

It would be a relief to a patient to find out that their CLL was 'mutated' (ZAP-70 mutational status) and the beta2 levels were low, as these are markers of good prognosis. Some patients also decide to seek a second opinion from a CLL expert in order to verify the opinion of their community oncologist.

Time is the biggest determining factor. Will CLL progress or not? If so, how fast? Approximately 15% of patients with 'smouldering' CLL never need treatment, so watching and waiting could be the best option for patients with good prognostic markers.

Nowadays, so much has changed and more changes lie ahead. This relates directly to a genetic understanding of CLL. Patients with some mutations are thought to have a more aggressive type of CLL, and may need treatment sooner with the expectation that standard therapy will be less effective or that more targeted oral therapy should be used 'up front'.

From the patient's point of view, the possibility for the clinical team to gain a more precise picture of their cancer is welcomed, and a personalized care plan makes perfect sense. The side effects of such treatments are worth it to target the specific type of CLL in a particular patient.

As patients and their physicians have been learning about oncogenes related to CLL, it has become clear that the genetic picture can change over time. Serial testing can be important when remission ends. The question then becomes, what new treatment is best for CLL that has further evolved? Again, from the patient's point of view, the more timely and precise the knowledge, the better. As patients learn about personalized medicine, they should expect to have genetic analysis of their CLL so they can be well informed and matched to available approved treatments or promising clinical trials of targeted therapies.

Chemo-immunotherapy

Despite the advent of novel oral therapies, intravenous (IV) therapies continue to have a place as effective standard combinations continue to show benefit and are typically less costly. These include fludarabine/cyclophosphomide/rituximab (FCR) and bendamustine/rituximab (BR). As an example, some patients are diagnosed through a routine blood test and have a watch-and-wait period without treatment. Subsequently, they may decide to participate in clinical trials, such as the FCR phase II trial for treatment-naïve patients. In this trial, patients received six cycles, and some fortunate patients required no further treatment.

Patients that participated in the FCR phase II trial study reported that treatment was not easy. The IV Benadryl (diphenhydramine) administered with the FCR 'whacked them out'. One patient on the initial administration actually fainted while urinating in a clinic bathroom. The first cycle, with a start-and-