


What Influences the Choice of Ibrutinib–Rituximab vs Classic Chemoimmunotherapy for Chronic Lymphocytic Leukemia?

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Abstract

Chronic lymphocytic leukemia (CLL), with an incidence rate between 4 and 6 cases per 100,000 persons per year, is considered the most prevalent leukemia in the western world. Chemoimmunotherapy (such as fludarabine, cyclophosphamide, and rituximab), bendamustine plus rituximab, and, more recently, novel agents such as ibrutinib (Bcr tyrosine kinase inhibitor), idelalisib (phosphatidylinositol-3-kinase δ inhibitor), and venetoclax (BCL-2 inhibitor) have changed the management of CLL. Shanafelt and colleagues compared the efficacy of ibrutinib–rituximab with that of standard chemoimmunotherapy in patients with treatment-naïve CLL. They did not, however, mention that the therapy varies on the basis of where patients live and, given that local guidelines not immediately reflect US Food and Drug Administration (FDA) updates, discrepancies in treatment occur. Important CLL goals are the availability of rapidly reproducible tests, standardization of national and international guidelines, and FDA approval-based treatment reimbursement.

Keywords

chronic lymphocytic leukemia, ibrutinib–rituximab, chemoimmunotherapy

Introduction

The 2008 World Health Organization classification described chronic lymphocytic leukemia (CLL) as a low-grade lymphoproliferative neoplasm characterized by $\geq 5 \times 10^9/l$ clonal B-cells in the peripheral circulation expressing CD5, CD19, dimCD20, and CD23¹. CLL has an incidence rate between 4 and 6 cases per 100,000 persons per year and it is considered the most prevalent leukemia in the western world^{2,3}. The clinical outcome in terms of disease progression of CLL depends on the mutational status of the variable heavy chain gene region of the B-cell receptor (BCR)⁴. A lot of efforts have been made targeting and inhibiting different components of the BCR pathway. Chemoimmunotherapy (such as fludarabine, cyclophosphamide, and rituximab [FCR]), bendamustine plus rituximab, and, more recently, novel agents such as ibrutinib (Bcr tyrosine kinase inhibitor), idelalisib (phosphatidylinositol-3-kinase δ inhibitor), and venetoclax (BCL-2 inhibitor) have changed the management of CLL^{4,5}. However, little is known about how to combine different therapies for optimal effects and which patients are most likely to benefit. There are also important discrepancies in the treatment of patients among

different countries. Shanafelt and colleagues compared the efficacy of chemo-free treatment (ibrutinib–rituximab) with that of standard chemoimmunotherapy (FCR) in patients with treatment-naïve CLL⁶. They did not, however, mention that the therapy varies on the basis of where patients live. In fact, given that local guidelines may not immediately reflect US Food and Drug Administration (FDA) updates, discrepancies in treatment occur. In Italy, FCR is the standard of care for young CLL patients, despite low tolerability and high physical/psychological impact⁴. Switching the standard of care from chemotherapy-based regimens to new chemo-free targeted treatments could improve both patient compliance and quality of life because of almost total

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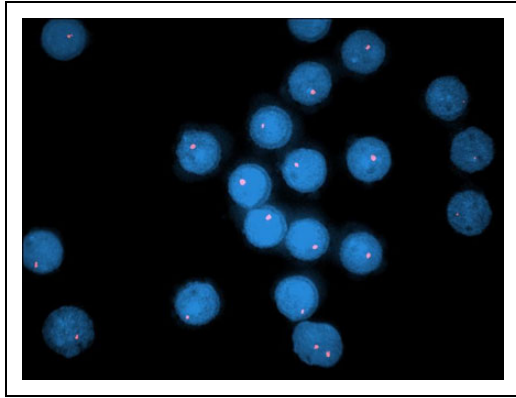


Figure 1. Fluorescence in situ hybridization analysis of CLL cells. CLL cells with del17p (100× magnification). CLL: chronic lymphocytic leukemia.

patient-centered home-based management and good treatment tolerability unburdened by gastrointestinal side-effects and alopecia.

Nowadays, ibrutinib monotherapy is limited to those with unfavorable prognosis or unamenable to chemotherapy. Patient selection on the basis of cytogenetic alterations is fundamental to define prognosis and treatment. However, some institutions with poor economic resources and specialized personnel may not be equipped to perform specific molecular tests, resulting in delays for urgent patients when samples need to be evaluated externally. Although ibrutinib may improve progression-free survival and overall survival, its long-term toxicity needs to be better studied. The issue of clonal selection, which may lead to drug resistance, also needs addressing. In our cancer center, young CLL patients with del17p undergoing frontline ibrutinib alone showed an excellent response (Fig. 1), without severe toxicity. In addition to improving survival, chemo-free combinations could also reduce overall costs because of higher tolerability and fewer hospital accesses required. Important goals in CLL are the availability of rapidly reproducible tests, standardization of national and international guidelines, and FDA approval-based treatment reimbursement. There has been substantial progress in the management of CLL patients in the past decade. With the introduction of novel agents, such as ibrutinib, the role of chemoimmunotherapy in the treatment of CLL assumes even more importance. However, the treatment depends on the center resources and to the country where the patient lives. The barriers to overcome are the

availability of reproducible tests, standardization of guidelines, and treatment reimbursement.

Author Contributions

SB, GM, and CC conceived the study and drafted the manuscript.


Declaration of Conflicting Interests

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References

1. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. World Health Organization; 2008.
2. Scarfo L, Ferreri AJ, Ghia P. Chronic lymphocytic leukaemia. *Crit Rev Oncol Hematol*. 2016;104:169–182.
3. Lenartova A, Johannesen TB, Tjønnfjord GE. National trends in incidence and survival of chronic lymphocytic leukemia in Norway for 1953-2012: a systematic analysis of population-based data. *Cancer Med*. 2016;5(12):3588–3595.
4. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164–1174.
5. Jain N, Keating M, Thompson P, et al. Ibrutinib and Venetoclax for first-line treatment of CLL. *N Engl J Med*. 2019;380(22):2095–2103.
6. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381(5):432–443.