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Chronic lymphocytic leukemia - Section 3

Towards control of chronic lymphocytic leukemia using chemotherapy-free combinations

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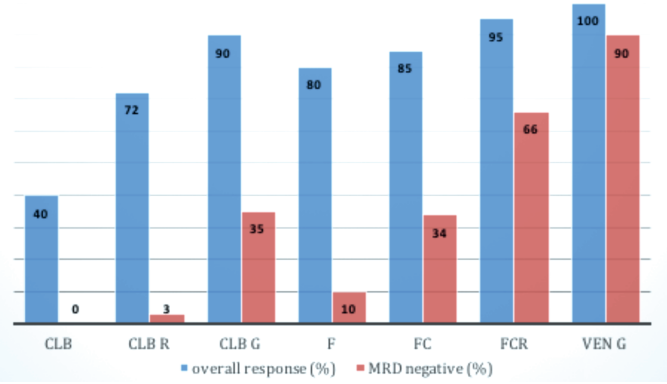
Take Home Messages

- The last two decades have witnessed an unprecedented progress in the management of CLL.
- Combinations of novel, targeted agents yield very high rates of overall responses and of minimal residual disease (MRD)-negative remissions.
- To translate this progress into clinical reality for future generations, CLL patients should be treated today within clinical trials whenever possible.

Tremendous progress has been achieved in our understanding of the pathogenesis of CLL. The use of whole exome sequencing and large, clinical CLL databases has allowed describing the genomic landscape in CLL.[1] In addition, stimulation of the B-cell receptor and the interaction of CLL cells with their microenvironment, in particular macrophages, is essential for CLL pathogenesis.[2,3] Conventional therapies with alkylators and monoclonal antibodies[4] or with kinase inhibitors (KI) may act in part through microenvironmental cells.[5]

Inspired by this progress, new therapeutic options have become available. As a consequence, the management of patients with CLL is currently undergoing profound changes. During the last decade the outcome of first-line therapies has markedly improved. We have learned that the choice of initial therapy (e.g. by adding CD20 antibodies to chemotherapy) creates a survival benefit for CLL patients.[6,7] More recently, the advent of targeted agents such as ibrutinib,[8] idelalisib,[9] or venetoclax,[10,11] has increased our therapeutic armamentarium even further. Finally, CAR-T cells are also effective therapies for some CLL patients[12] but their definitive place remains to be determined. The comparison of the overall response rates and minimal residual disease (MRD) negative remissions obtained with various treatment options illustrates this quite impressive progress (Figure 1).

Using these novel agents, we now need to optimize the combinations and sequencing of these novel agents to create long-lasting remissions or even to achieve cure for CLL patients. The so called "real-world" observations suggest that ibrutinib appears superior to idelalisib when used as first KI.[13] In the setting of KI failure, alternate KI or venetoclax therapy appear superior to chemoimmunotherapy.[13] Together, these data lend further support for clinical studies that optimize the sequencing strategy. Future trials should also incorporate a comprehensive assessment of prognostic parameters, or use prognostic scores such as the CLL-IPI[14] for treatment selection. One of these trial concepts uses sequential, targeted therapies to eradicate residual disease.[15,16] Moreover, we are actively investigating combinations of all available drugs, as well as novel strategies to prevent clonal evolution of CLL[17,18] in order to achieve long-lasting remissions or even cure for CLL patients. So far, results obtained by these combination therapies appear very promising, in particular when combining anti-CD20 antibodies with targeted agents.[19-21] For example, the CLL2-BAG protocol (using bendamustine,



CLB = Chlorambucil, R = Rituximab, G = Obinutuzumab (GA101), F = Fludarabin, C = Cyclophosphamid, Ven = Venetoclax. MRD negative (%) = rate of patients achieving a response with less than 1 CLL cells in 10.000 leukocytes (10e-4) in the peripheral blood.

Figure 1. Overall response and MRD negative remissions achieved by different first line therapies in CLL in trials of the GCLLSG. The results illustrate the improved therapeutic efficacy observed over the last decades.

venetoclax and obinutuzumab) yielded excellent overall response and MRD-neg response rates around 90% both in treatment naïve and pre-treated patients.[22] Similarly, the Murano trial yielded MRD-neg response rates of 83.5% using venetoclax plus rituximab in relapsed CLL patients.[23]

Finally, kinase inhibitors may enhance the function of T cells.[24] It was shown that >/=5 cycles of ibrutinib therapy improved the expansion of CD19-directed CAR T cells (CTL019), in association with a decreased expression of the immunosuppressive molecule programmed cell death 1 on T cells and of CD200 on B-CLL cells.[25]

Taken together, it is obvious that the current clinical research disposes of a plethora of novel drugs that offer the potential for a long-term control or even cure of CLL. It is our responsibility to make this a reality by conducting carefully planned, academic, prospective protocols and by convincing our patients to participate in these trials.

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