Optimal First-Line Therapy for Previously Untreated Chronic Lymphocytic Leukemia: The Case for Chemotherapy


The last 10 years of clinical investigation in chronic lymphocytic leukemia (CLL) have established the efficacy of front-line chemoimmunotherapy in inducing remission; improving progression-free survival (PFS); and, with the addition of anti-CD20 antibodies, improving overall survival (OS).[1-3] For fit patients, the optimal regimen has recently been confirmed to be fludarabine, cyclophosphamide, and rituximab (FCR), which yielded improvements in complete response (CR), minimal residual disease clearance (MRD negativity), and PFS compared with bendamustine rituximab (BR) in the German CLL Study Group CLL10 trial.[4] For patients with comorbidities, the combination of obinutuzumab and chlorambucil improved response, CR, MRD negativity and PFS compared with rituximab chlorambucil.[2]

These regimens have the advantage of a defined treatment duration, usually 6 months, after which time patients can generally expect to be in remission for years, unbothered by ongoing therapy or the psychological burden of persistent disease. Particularly with FCR, CR is common, and recent long-term follow-up data from The University of Texas MD Anderson Cancer Center[5] and the German CLL Study Group[6] show that approximately 60% of low-risk patients, including those with mutated immunoglobulin heavy chain variable gene (IGHV) and without 17p or 11q deletion, remain in remission at 10-year follow-up, with few late relapses. This long-term plateau on the PFS curve suggests that a subset of patients are, in fact, cured by FCR. For those who do relapse, we know that the new kinase inhibitors work well as salvage therapy. Indeed, the emergence of the targeted kinase inhibitors, particularly ibrutinib and idelalisib, has raised the question of whether their profound activity in the setting of relapsed and/or refractory chronic lymphocytic leukemia should translate directly to using them as front-line therapy. Although very small studies have suggested high activity in a front-line setting,[7-9] the patients enrolled on these studies have been few in number and low risk, and the follow-up period remains very short, with 3 years being the longest duration of follow-up.[10] Several additional cautionary notes are warranted: Very few patients in these studies have achieved CR, meaning the kinase inhibitor must be continued, leading to years of therapy. In the setting of persistent disease, it is likely that genomic clonal evolution will occur in this period, leading to relapse and resistance. Furthermore, recently published data indicate that the outcomes of patients relapsing after ibrutinib are extremely poor. Half relapse with Richter’s transformation and die quickly, while even the half who relapse with chronic lymphocytic leukemia have only a 15-month median survival time.[11,12] Currently we have no known effective salvage therapy after treatment with ibrutinib, which raises the possibility that patients who receive first-line ibrutinib may actually sacrifice the benefit of other therapy for chronic lymphocytic leukemia, and lose responsiveness to other therapies upon relapse. If true, this scenario would be unlikely to result in improved OS compared with maximizing the benefit of most of our available active agents, by using them sequentially in an optimized order. Although data regarding sequential use of kinase inhibitors are currently limited, we do know that a handful of patients relapsing after idelalisib did respond well to ibrutinib,[10] whereas the likelihood of response to idelalisib after relapse on ibrutinib is unknown. Similarly, response to chemoimmunotherapy after prior therapy with kinase inhibitors in these patients is entirely unknown. In contrast, we do know...
from the initial phase Ib/II study of ibrutinib that patients at low cytogenetic risk who received ibrutinib as fifth-line therapy still derived excellent benefit, with a 3-year PFS rate of 89%[10]; this suggests ibrutinib is still highly effective given as a later line of therapy. Furthermore, although kinase inhibitors are often well tolerated, many patients do have chronic low-grade symptoms associated with their use. These can include fatigue, diarrhea, arthralgia, rash, and bruising.[13,14] Over many years of required continuous therapy these symptoms can take their toll. In addition, if patients are not fully compliant with taking their kinase inhibitor, resistance is very likely to develop. More serious toxicities may also limit the duration of treatment with these drugs; such toxicities include atrial fibrillation and bleeding for ibrutinib,[15] and colitis and pneumonitis for idelalisib.[16] Even with short follow-up periods of 12–15 months, most studies have estimated that 10% of patients discontinue therapy with ibrutinib due to toxicity. The rate of discontinuation may be higher for patients treated with idelalisib. Even patients who do not experience treatment toxicity often prefer a shorter defined duration of therapy. In addition, the psychological impact of having persistent disease and remaining a patient over a long period of time—in contrast to achieving deep remission with chemoimmunotherapy and returning to normal life—should not be underestimated. The question of long-term complications of chemoimmunotherapy has been raised, particularly with respect to the risk of developing secondary solid tumors and acute myelogenous leukemia (AML). Patients with chronic lymphocytic leukemia certainly have an increased risk of solid tumors,[17,18] but currently there is no convincing evidence that the choice of therapy influences this risk.[17] As to development of AML or myelodysplastic syndrome (MDS), the rates reported in patients with chronic lymphocytic leukemia after treatment with the FCR regimen range from 2.2% to 4.5%.[4,19,20]

While this risk of secondary AML and MDS is significant, it needs to be considered in light of the new data suggesting that FCR has curative potential, and in that light is not very different from rates of these secondary cancers after treatment with chemotherapy regimens that are potentially curative for other hematologic malignancies. Approaches to reducing this incidence while maintaining the benefit of chemoimmunotherapy could include shorter therapy duration, either planned or based on myelosuppression during therapy, as well as limitation of the use of FCR to once in the course of therapy, namely first-line. By combining kinase inhibitors with chemoimmunotherapy for defined treatment durations, we may even be able to increase the cure rate while reducing patients' exposure to chemotherapy.[21] The fact that FCR does likely cure some patients means it should not be abandoned too readily, particularly in the curable subgroups and when we have no long-term follow-up data establishing efficacy or safety of continuous indefinite therapy with kinase inhibitors. The current follow-up period with the kinase inhibitors is simply much too short to provide us with any clues as to the long-term impact on second cancers or AML, on risk of Richter’s or resistant CLL relapse, on the immune system, or on other target-organ toxicities. Nor do we know how we will decide on or find an effective salvage therapy for patients when they relapse—which will happen, since almost all patients have persistent disease. For the time being, therefore, we must remain circumspect and not willfully cast aside the hard-won, very substantial gains—including likely cure—of first-line chemoimmunotherapy.

Financial Disclosure: Dr. Brown has served as a consultant for Celgene, Gilead, Janssen, Pharmacyclics, ProNai, Roche/Genentech, and Sun BioPharma. She also serves on the advisory boards of Celgene, ProNai, and Roche/Genentech.

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