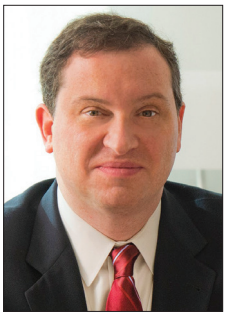
My Ongoing Debate



Some would argue that the first tenet of chronic lymphocytic leukemia (CLL) is to "watch and wait" until patients have an indication for treatment. This tenet is based on clinical trials from the late 1970s and early 1980s, in which patients who did not require therapy were randomized to either chlorambucil plus prednisone or observation until they demonstrated disease progression. Overall survival was equal or better in those patients who deferred therapy vs those who immediately initiated therapy.

There are multiple problems, in my opinion, with applying the watch-and-wait paradigm to CLL in 2023. First, the trials were conducted with two agents that are largely ineffective for the treatment of CLL. Second, the use of chlorambucil can lead to mild cytopenia and myelosuppression, caused by cumulative damage to DNA over time. Third, the field of CLL has undergone a revolutionary change over the past ten years with the introduction of targeted agents. These agents provide great efficacy along with excellent safety and tolerability, which alters the risk/benefit ratio of intervention. Finally, and perhaps most importantly, these trials enrolled all patients. Current prognostic markers can identify which patients are likely to demonstrate early progression and therefore are more likely to benefit from early intervention.

Let me provide a clinical scenario that illustrates my concerns. A 59-year-old man is diagnosed with asymptomatic Rai stage I CLL based upon small axillary lymphadenopathy and an absolute lymphocyte count of 9000 lymphocytes per microliter. As is the standard of care, he is told that he should remain on observation until he has an indication for treatment. But what if the next-generation sequencing panel finds a *NOTCH1* frameshift mutation? This mutation is associated with an approximate 35% risk of developing a Richter transformation (RT) in 5 years (Rossi D et al. *Br J Haematol*. 2012;158[3]:426-429). Furthermore, 48% of patients who develop an RT do so before treatment is indicated for their CLL, and the median survival of patients with RT is 2.1 years (Parikh SA et al. *Br J Haematol*. 2013;162[6]:774-782).

The question now is whether proceeding with "watch and wait" is the best strategy for this patient, knowing that he has such a high risk of dying of an RT. I view the development of RT as our greatest obstacle as CLL physicians. RT has been the only cause of CLL-related mortality in my practice for years. Why not treat this patient for CLL at diagnosis, reduce the tumor load, halt proliferation and possibly clonal evolution, and perhaps avoid the development of an RT?

I admit that I do not know whether anything I do will be able to affect this patient's risk of transforming. But given the efficacy, safety, and tolerability of our novel agents, isn't it worth trying? In thinking about this problem, I am struck by data suggesting that the events leading to transformation and to mutations that cause Bruton tyrosine kinase inhibitor (BTKi) resistance develop during the watch-and-wait period (Burger JA et al. *Nat Commun*. 2016;7:11589; Woyach JA et al. *J Clin Oncol*. 2017;35[13]:1437-1443). One could take these data to suggest that proliferation during the watch-and-wait period in genomically unstable CLL leads to mutational changes that result in BTKi resistance and RT. With BTKi's ability to suppress proliferation and reduce tumor burden, might this decrease the risk of mutations leading to BTKi resistance and the occurrence of RT?

With the above in mind, perhaps starting treatment at diagnosis in a patient with a *NOTCH1* mutation might prevent the development of an RT. Because patients with *NOTCH1* mutations demonstrate more aggressive disease and earlier time to treatment, the short time off therapy that is lost could be inconsequential to preventing an RT. We do have patients who remain on BTKi therapy for longer than ten years, without any apparent harm. The most problematic aspect of this debate is the absence of clinical data supporting a benefit. But, as I sit across from my patients with *NOTCH1* mutations and ponder their prognosis, knowing we will never have adequate data to address this question, I find myself more fearful of RT than of any consequences of earlier initiation of therapy. I also run this scenario for those who have not only *NOTCH1* mutations, but complex karyotypes, deletion 17p, *TP53* mutations, and subset 8 stereotyped *IGHV* genes, all of which are associated with similar or higher rates for the development of RT and BTKi resistance. I also remind myself that the only reason I have lost a patient to a cause related to CLL is RT. I then have a very frank discussion with my patients. What do you do?

Sincerely,

Richard R. Furman, MD