Editorial Commentary

Slaying the real giants in the war on chronic lymphocytic leukemia

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"*Progress might have been alright once, but it has gone on too long*"—Ogden Nash

Over the past few decades, the treatment of chronic lymphocytic leukemia (CLL) has undergone a seismic revolution. Nonetheless, this history has been characterized by Don Quixote-like battles with windmills along the way. In the 1950's, alkylating agents such as cyclophosphamide and chlorambucil (CLB) were the best that was available with debates as to which was preferred, with or without other drugs such as prednisone or vincristine. Then, in the early 1990's, a major new era began with the introduction of the purine analogs, fludarabine, 2'-deoxycoformycin (pentostatin), and chlorodeoxyadenosine (cladribine). The result was basically a therapeutic beauty pageant that lasted for years from which fludarabine emerged with the crown (1). Fludarabine when pitted against CLB in untreated patients failed to benefit the elderly (2). The combination with cyclophosphamide (FC) was superior to the single agent fludarabine, albeit with greater toxicity (3). From Jena in the German Democratic Republic came the bifunctional alkylating agent bendamustine which, not surprisingly, bested CLB (4), then challenged fludarabine. The first major step forward did not involve pitting alkylating agents or chemotherapy drugs against each other, with minimal progress. It was a biological therapy, the anti-CD20 rituximab, the first antibody approved for human use improved on the efficacy of FC in untreated patients (5). The battle raged between fludarabine and bendamustine, both in combination with rituximab (6). The winner of the battle was a bit subject to interpretation; fludarabine cyclophosphamide and rituximab (FCR) may be preferred in the younger patients, but bendamustine plus rituximab (BR) was the clear winner in older patients, mostly related to differences in toxicity. Nonetheless, both of these regimens were myelosuppressive and immunosuppressive and involved multiple intravenous infusions. Despite thousands of patients on clinical trials, overall progress over these decades was modest.

And then a better understanding of B-cell biology changed CLL therapy forever, relegating chemoimmunotherapy to a dusty rear-view mirror. A number of pathways downstream from the B-cell receptor play a critical role in the survival of the malignant B cells. The first agent to receive regulatory approval by the US Food and Drug Administration was the PI3K inhibitor idelalisib (7,8), the use of which has been limited by its unfavorable toxicity profile, especially in combination with other agents. It was the Bruton tyrosine kinase inhibitor (BTKi) class of drugs that has provided some of the most meaningful benefit to patients, with the high response rates achieved with ibrutinib and acalabrutinib, which are quite durable (9,10), and have replaced chemoimmunotherapy in patients with CLL (11,12). Yet, given the toxicities of ibrutinib, second generation BTKi have emerged into clinical practice and are supplanting it. Acalabrutinib has demonstrated at least comparable efficacy with less toxicity than ibrutinib based on the ELEVATE-RR study, a proper head to head comparison (13). However, when it came to front-line use, the ELEVATE-TN study once again bested CLB-obinutuzumab, a pathetic comparator, a mere windmill (14).

With the ongoing search to improve on the efficacy and safety profile of a BTKi comes zanubrutinib. This agent has demonstrated activity in a number of B-cell malignancies, including CLL (15,16), mantle cell lymphoma (17,18), and, in the MAGNOLIA trial, marginal zone lymphoma (19).

Zanubrutinib slew the true ibrutinib giant in the phase III ASPEN study in Waldenström macroglobulinemia in in which it showed both improved efficacy and safety (20).

We are now finally rewarded for our wait for the results of the SEQUIOA study (21). In this randomized phase III trial, 590 patients aged 64 year or greater, or younger with comorbidities, with previously untreated CLL without chromosome 17p deletion (17p–) were allocated to either zanubrutinib at 160 mg twice daily until progression or intolerability, or bendamustine-rituximab; patients with 17p– were appropriately treated on a separate cohort with zanubrutinib alone. The patients in the two comparative arms were well matched. At a median follow-up of 26.2 months, the median progression free survival (PFS), which was the primary endpoint, was not yet met in either group. However, the estimated PFS at 24 months was 85.5% (95% CI: 80.1% to 89.6%) with zanubrutinib compared with 69.5% (62.4% to 75.5%) for BR. This benefit was sustained regardless of age, sex, or other risk features including stage, immunoglobulin heavy chain gene (IGHV) mutational status, presence of 11q;23. Overall response rates were also higher with zanubrutinib (94.6% *vs.* 85.3%). Regarding safety, more patients remained on zanubrutinib than were able to complete the 6 cycles of BR. Neutropenia was more common with BR, requiring growth factor support in a higher proportion of patients. Although infection rates were similar between the arms, there was a greater incidence of COVID-19 with zanubrutinib, reflecting its continuous administration. Bleeding events were more common with zanubrutinib, but were rarely serious. Surprisingly, the likelihood of atrial fibrillation was comparable between the randomized arms. This study once again demonstrates the obsolescence of myelosuppressive and immunosuppressive chemotherapy.

But why do we continue to tilt at windmills, pretending they are giants? We went through the alkylating period, then purine analogues. Enough beating up on sick puppies just to get a drug on the market. Regulatory agencies should reject control arms that include chemoimmunotherapy such as CLB-obinutuzumab or BR, or monotherapy with drugs such as the inferior and rarely mentioned, even less used, ofatumumab (22). Such comparators should be banned, if for no other reason than we are knowingly subjecting patients to inferior treatment.

There are clearly more compelling questions to be asked. It is clear that, among the BTKi, ibrutinib has the poorest risk/benefit ratio. But how do we decide between acalabrutinib, with its new formulation allowing gastric acid reducing drugs, and zanubrutinib once approved by regulatory agencies? To its credit, zanubrutinib will be priced lower than the competition. Yet all of these drugs share similar mechanisms of resistance. However, on the horizon is pirtobrutinib, which, unlike the other available BTKi, is non-covalent. Preliminary data suggest impressive activity with a favorable tolerability profile, even in patients resistant to other BTKis (23). This drug has the potential to be a total game-changer. But, what is its optimal role in the treatment paradigm? Clinical trials exploring this question are ongoing.

How do we decide whether to incorporate an anti-CD20 antibody? Although randomized trials fail to show benefit adding rituximab to ibrutinib (11), there is a suggestion of benefit from adding obinutuzumab to acalabrutinib (14). How do we determine which patients are more likely to benefit from BTKi therapy or a time limited approach such as venetoclax-obinutuzumab (24)? There is a suggestion that BTKi may be preferred in patients with 17p–/TP53 mutations and unmutated IGHV; however, whether that reflects greater activity or longer duration of treatment is not clear. Given the impressive efficacy with both BTKi and the BCL-2 inhibitor venetoclax, empiric combinations have been developed. Tam and coworkers recently reported the fixed duration cohort of the CAPTIVATE regimen combining ibrutinib with venetoclax (25). The 24-month PFS and overall survival (OS) rates of 95% and 98%, respectively are impressive with 60% of patients being undetectable for minimal residual disease in the bone marrow. Nevertheless, whether combinations or sequences are more beneficial remains unknown (26), but is the subject of ongoing clinical trials such as the GAIA/German CLL Study Group CLL-13 [fludarabine, cyclophosphamide plus rituximab for patients ≤65 years or bendamustine plus rituximab for patients >65 years *vs.* 12 cycles of venetoclax plus rituximab (RVe), plus obinutuzumab (GVe) or plus ibrutinib and obinutuzumab (GIVe)] and CLL-17 (ibrutinib *vs.* venetoclax-obinutuzumab *vs.* ibrutinib-venetoclax) studies. These studies should define the current standard for comparison in future phase III trials.

Yet, we must also reconsider how we use the highly active but B-cell depleting menu of drugs (27). A recent decision by the US Food and Drug Administration virtually obliterated the entire class of PI3Ki in lymphoma and CLL (28), leaving a vacuum beyond BTKi and BCL-2 inhibition. Based on the demise of the U2 regimen (umbralisib-ublituximab) (29), a highly effective, but indefinite treatment brought about by deaths from COVID-19,

and even the increase in COVID-19 related events in the present study, new time limited strategies need to be developed with retreatment upon progression. Intermittent dosing schedules should be considered. The risk-benefit ratio of adding multiple cycles of anti-CD20 antibodies also needs to be taken into account.

Nonetheless, the current manuscript clearly demonstrates the efficacy of zanubrutinib a new BTKi, in previously untreated CLL. This drug is at least as effective as, and is better tolerated than ibrutinib, suffers from fewer drug interactions than acalabrutinib, and will likely be less expensive (at least in the U.S.) than its current competitors. These features clearly represent progress. But the path forward should avoid repeatedly poking our lances at windmills and, instead, focus our efforts on the real giants standing in the way of improving the outcome of patients with CLL.

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