blood® commentary

CLINICAL TRIALS AND OBSERVATIONS

Comment on Le Gouill et al, page 877

Building on BTK inhibition in MCL

Kami Maddocks | The Ohio State University

Bruton tyrosine kinase inhibitors (BTKi) have changed the treatment paradigm for mantle cell lymphoma (MCL). In this issue of *Blood*, Le Gouill et al[1] report results of a phase 1/2 trial in patients with relapsed or previously untreated MCL receiving therapy with the BTKi ibrutinib in combination with obinutuzumab and venetoclax.

Survival outcomes in MCL have improved with current treatment approaches, including chemoimmunotherapy induction, consolidation with autologous stem cell transplant in select patients, and rituximab maintenance strategies for initial therapy followed by novel targeted therapies at relapse. Despite this progress, MCL remains incurable, and patients will ultimately relapse with shortened remission durations with each successive therapy. Many challenges remain in treating patients with MCL, including the inability of many patients to tolerate aggressive frontline approaches due to associated toxicities, poor outcomes in high-risk populations regardless of treatment approach, and low rate of deep remissions despite high rates of overall responses with single-agent targeted therapies. LeGouill et al report results of their phase 1/2 trial of the nonchemotherapeutic triplet of ibrutinib, obinutuzumab, and venetoclax showing the combination to be well tolerated and highly active as treatment in both patients with relapsed and previously untreated MCL. Furthermore, they demonstrate the triplet combination induces high rates of molecular complete responses (CRs), including in patients with high-risk disease that have inferior outcomes with standard therapies.

Ibrutinib was the first of 3 oral BTKi approved for the treatment of relapsed MCL based on an unprecedented single-agent overall response rate (ORR) of 68% in a phase 2 study of patients with relapsed/refractory MCL.[2] Despite the high ORR seen, a mere 21% achieved a CR to treatment with a median progression-free survival (PFS) of 13.9 months. A pooled analysis of 370 patients treated with single-agent ibrutinib over 3 different clinical trials reported similar results[3]; however, when analyzed by prior lines of treatment, those patients who received ibrutinib as second-line therapy achieved deeper remissions (CR 37%) and had better outcomes, with more than double the median PFS (25.4 vs 12.1 months).[4] The median duration of response (DOR) was twice as long (35.6 months) in those patients having received only 1 prior therapy compared with those with >1 prior therapy and significantly longer in those patients who achieved a CR, regardless of prior lines of therapy. These results suggested BTKi should be prioritized as second-line treatment, and this approach has largely been adapted in practice. However, most patients will develop resistance to ibrutinib at which time prognosis is often poor.[5]

In this article, LeGouill et al report results of their phase 1/2 study in 9 relapsed patients treated with obinutuzumab + ibrutinib (ARM A); in 24 relapsed patients treated with obinutuzumab, ibrutinib, and venetoclax (ARM B); and in 15 treatment-naive patients treated with the triplet (ARM C). In ARM A, 7/9 (78%) achieved a CR; 1- and 2-year PFS and OS were 89%, and median DOR was not reached. In ARM B, 16/24 (67%) achieved a CR; 1-year PFS and OS were 74.5% and 87.5%, and median DOR was not reached. In ARM C, 14/15 (90%) achieved CR and 1-year PFS and OS were 93.3% and 100%. Among 32 patients evaluable for minimal residual disease (MRD), 26 were MRD negative (81%) by allele-specific oligonucleotide (ASO)-quantitative polymerase chain reaction in the peripheral blood after cycle 3 (including 11 patients with TP53 alterations) with 4/6 (66%) MRD negative in cohort A, 10/14 (71.4%) MRD negative in cohort B, and 12/12 (100%) MRD negative in cohort C.

Clinical trials exploring rational combination strategies to improve upon single-agent BTKi depth of response and duration of remission have been a high priority. Single-agent venetoclax responses are similar to those with BTKi[6] with evidence for synergistic activity.[7] The phase 2 AIM study of venetoclax in combination with ibrutinib reported a 71% ORR with 62% positron emission tomography–CR at week 16 and 38% of patients MRD negative by ASO–polymerase chain reaction.[8] The estimated 12-month and 18-month PFS were 75% and 57%, respectively. An ongoing randomized phase 3 trial is evaluating ibrutinib vs ibrutinib + venetoclax in relapsed/refractory MCL (#NCT03112174). LeGouill et al report the triplet combination of obinutuzumab, ibrutinib, and venetoclax produces a high rate of clinical and molecular remissions with a promising 2-year PFS of 69.5% in previously treated patients, which compares favorably to single-agent BTKi. Clinical and molecular remissions were seen in high-risk patient populations with historically poor outcomes, including those with TP53 mutated disease and blastoid histology who have short remissions with ibrutinib therapy.[4] Although the numbers are small, the triplet appears to induce higher rates of early MRD-negative

remissions than seen in the AIM study, and longer follow-up will show if this translates into prolonged remission durations and at what toxicity cost. Recognizing the trial was not designed to compare treatment arms, it is striking that the outcomes in ARM A were similarly favorable to ARM B, with less associated toxicity and challenges the role of triplet therapy over the ideal doublet. There is a paucity of data with obinutuzumab in MCL, but this compares favorably to the remissions seen in combination with rituximab[9] and supports further trials utilizing obinutuzumab as the preferred anti-CD20 antibody. Nonchemotherapeutic frontline regimens are likely the future in MCL with the potential to be highly active and reasonably well tolerated. The rate of clinical and molecular remissions in these 14 treatment-naive patients, along with the improved toxicity profile compared with the relapsed cohort, warrant this triplet to be prioritized for further study, particularly in those with high-risk disease features. Whether ibrutinib will be the preferred BTKi in combination remains to be seen. Fixed duration therapy in combinations that induce high rates of molecular remission provide the ability to spare ongoing toxicity, including the financial toxicity seen with these agents. The role of retreatment at relapse in such scenarios remains unclear.

Conflict-of-interest disclosure: The author has received research funding from Bristol-Myers Squibb, Novartis, and Pharmacyclics and has consulted for ADC Therapeutics, Astra Zeneca, Beigene, Bristol-Myers Squibb, Celgene, KITE, Morphosys, and Seattle Genetics. ■

REFERENCES

1. Le Gouill S, Morschhauser F, Chiron D, et al. Ibrutinib, obinutuzumab, and venetoclax in relapsed and untreated patients with mantle cell lymphoma: a phase 1/2 trial. *Blood*. 2021; 137(7):877-887.
2. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2013;369(6):507-516.
3. Rule S, Dreyling M, Goy A, et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. *Br J Haematol*. 2017;179(3): 430-438.
4. Rule S, Dreyling M, Goy A, et al. Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis. *Haematologica*. 2019;104(5): e211-e214.
5. Martin P, Maddocks K, Leonard JP, et al. Postibrutinib outcomes in patients with mantle cell lymphoma. *Blood*. 2016;127(12):1559-1563.
6. Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol*. 2017;35(8): 826-833.
7. Portell CA, Axelrod M, Brett L, et al. Synergistic cytotoxicity of ibrutinib and the BCL2 antagonist, ABT-199(GDC-0199) in mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL): molecular analysis reveals mechanisms of target interactions. [abstract] *Blood*. 2014;124(21). Abstract 509.
8. Tam CS, Anderson MA, Pott C, et al. Ibrutinib plus venetoclax for the treatment of mantle-cell lymphoma. *N Engl J Med*. 2018;378(13): 1211-1223.
9. Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. *Lancet Oncol*. 2016; 17(1):48-56.

DOI 10.1182/blood.2020009781

CLINICAL TRIALS AND OBSERVATIONS

Comment on Curtis et al, page 896

New is forgotten old: IMiDs against chronic GVHD

Aleksandr Lazaryan | Moffitt Cancer Center

In this issue of *Blood*, Curtis et al present the results of a randomized phase 2 trial demonstrating activity and safety of pomalidomide for advanced chronic graft-versus-host disease (cGVHD) with fibrotic manifestations involving joint, fascia, and skin. This article is of a broad interest to hematologists and hematopoietic cell transplantation (HCT) providers, since it addresses an unmet medical need for patients with glucocorticoid-refractory cGVHD with advanced fibrotic manifestations.[1]

The high potency of pomalidomide is paired with more favorable toxicity profile compared with its structurally related immunomodulatory drugs (IMiDs). While thalidomide demonstrated variable efficacy in multiple trials of cGVHD,[2] it currently has a very limited use in advanced cGVHD, as its potentially effective dose of ≥200 mg/day is often associated with excessive neurologic, gastrointestinal, and hematologic toxicities. A broader use of lenalidomide in GVHD was halted by the risks of myelosuppression and GVHD propagation. Notably, lenalidomide maintenance after allogeneic HCT in patients with multiple myeloma increased incidence of acute GVHD in pivotal HOVON 76 and 07-REV trials.[3,4] The multicenter study by Curtis et al extends findings from the prior early-phase trial of pomalidomide in a smaller group of allograft recipients with glucocorticoid-refractory moderate-to-severe cGVHD.[5] Despite promising early efficacy, pomalidomide was poorly tolerated at the dose of 3 mg/day in that trial.[5] The phase 2 trial by Curtis et al has determined oral pomalidomide 0.5 mg/day as the optimal therapeutic dose for future use in sclerotic cGVHD (see figure).

Patients with extensive sclerotic cGVHD are often refractory to available therapies and have poor overall survival.[6] Curtis et al demonstrate that pomalidomide benefits fibrotic phenotypes of cGVHD. Imatinib and rituximab were compared in a randomized phase 2 trial of cGVHD patients with cutaneous sclerosis, but both led to suboptimal significant clinical responses at 6 months (26% and 27%, respectively).[7] In this study by Curtis et al, the overall response rate to pomalidomide was 47% in an intent-to-treat analysis and 67% among all evaluable patients at 6 months. Significant improvements in joint/fascia National Institutes of Health scores and skin involvement were achieved in patients with a median of 5 prior lines of therapy and 5 organs affected by cGVHD. Such heavily pretreated patients include a representative real-world sample of the cGVHD population impacted by substantial disability, morbidity, and impaired quality of life.

Failure-free survival has emerged as an important composite study end point of treatment change, nonrelapse mortality, and recurrent malignancy, used across