NEW AND EMERGING THERAPIES FOR MCL

Mantle cell lymphoma (MCL) is an incurable rare sub-type of B-cell non-Hodgkin lymphoma (NHL) with historically poor outcomes. Patients normally experience repeated remissions, relapses, and resistance to therapy.[1,2] Unlike the case for other lymphomas, chemoimmunotherapy (CIT) remains the standard option for front-line MCL therapy. Despite good responses to upfront therapy, patients eventually relapse.[2] However, with recent progress in the understanding of the biology of this disease, the treatment landscape for MCL is evolving rapidly, with many promising new and emergent agents being evaluated in clinical trials.[1,2]

NEW AND EMERGING ROLES FOR BTK INHIBITORS IN MCL

Bruton's tyrosine kinase inhibitors (BTKis) have become the primary treatment choice for relapsed/refractory (R/R) MCL, as they have shown promising survival outcomes especially in patients in the early stages of the disease.[2] The addition of BTKis to front-line CIT, before CIT, and as a replacement for CIT (chemotherapy-free regimens) in the front-line setting is being tested in a number of clinical trials with promising results.[3]

Ibrutinib

The combination of ibrutinib with various CIT regimens is being tested for front-line MCL with promising results:

- Ibrutinib plus bendamustine and rituximab (BR) significantly prolonged progression-free survival (PFS; 80.6 vs 52.9 months) in the SHINE study (NCT01776840)[4]
- 2-year ibrutinib maintenance following R-CHOP/R-DHAP with or without autologous stem cell transplant (ASCT) is being tested in the Triangle study[5]
- In the WINDOW-1 (NCT02427620) trial, which is evaluating the combination of ibrutinib plus rituximab (IR) followed by R-hyper-CVAD, with 22 months of follow-up, the complete response rate is 88% without CIT and 94% with CIT[6]
- Similarly, in WINDOW-2, which tested IR and venetoclax (IRV) followed by risk-stratified observation or short course R-hyper-CVAD/MTX, the mean 2-year PFS was 92% and overall survival (OS) was 90%[7]

WINDOW-1 and WINDOW-2 start to show how BTKis can be used in chemotherapy-free regimens for front-line MCL. Other ibrutinib studies that explore this include two non-randomized IR phase II studies, which also had positive results.[8,9]

Acalabrutinib

Trials with acalabrutinib* in these settings are also ongoing:

- NCT02972840 and NCT04115631 are testing the addition of acalabrutinib to BR with and without cytarabine[10,11]
- NCT04765111 is testing CIT-free acalabrutinib plus rituximab in the front-line setting[12]

*An immediate-release film-coated tablet formulation of acalabrutinib maleate was recently approved;[13] the clinical effect is expected to be comparable with that of acalabrutinib capsules at approved dosing.

Zanubrutinib

A phase III study (NCT04002297) of zanubrutinib plus rituximab (ZR) for transplant-ineligible patients is also ongoing.[14]

PROMISING NOVEL AGENTS FOR BTKI-RESISTANT MCL

Ibrutinib, acalabrutinib, and zanubrutinib are all approved for R/R MCL.[2] A combination of ibrutinib and venetoclax is being evaluated in the SYMPATICO study (NCT03112174). With a median follow-up of 31 months, the median PFS was 35 months.[14] However, despite the great results from BTKi therapy in the R/R setting, as with CIT, eventually patients do develop resistance and progress. The outcomes for patients who progress following BTKi therapy are extremely poor, with a median OS of only 6 to 10 months.[1,2] The approved options for these patients are CAR T-cell therapy and CIT, but there is no established preferred combination and sequencing of therapies.[1,2] Therefore, there is a great need for new options.

Pirtobrutinib

Contrary to the other BTKis presented above, pirtobrutinib is a non-covalent (reversible) BTKi. Importantly, pirtobrutinib inhibits BTK even when the C481 binding site is mutated, making it a promising option for BTKi-resistant MCL.[16] The efficacy and safety of pirtobrutinib is being evaluated in various trials.

- The phase I/II BRUIN trial (NCT03740529) of pirtobrutinib in R/R B-cell malignancies showed promising results in the MCL cohort with an overall response rate (ORR) of 51% in patients previously treated with another BTKi, 82% for BTK-naïve patients, 64% for previous stem cell transplant, and 50% for previous CAR-T therapy.[17,18] These results make pirtobrutinib a promising option for patients with BTKi-resistant MCL.
- Additionally, the phase III BRUIN-MCL-321 (NCT04662255) is comparing pirtobrutinib to the available BTKis in the R/R MCL setting.[19]

Zilovertamab vedotin

Zilovertamab (ZV) is an antibody-drug conjugate (ADC). The antibody of ZV binds specifically to the receptor tyrosine kinase-like orphan receptor 1 (ROR1), which is pathologically expressed in various cancers including MCL. ZV had and ORR of 47% in patients with R/R MCL with previous BTKi exposure in a phase I trial and will be studied further.[1]

Bispecific antibodies

Bispecific antibodies including glofitamab, odronextamab, mosunetuzumab, and epcoritamab are in rapid development. While most of the focus has been in other cancers, results in small MCL cohorts are promising and further clinical development is likely to occur.[1]

CONCLUSIONS

The treatment landscape and paradigm for MCL have evolved rapidly in the past few years. This trend is likely to continue as new agents are being evaluated in clinical trials. BTKis are likely to continue to play an important role in management of this disease.

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