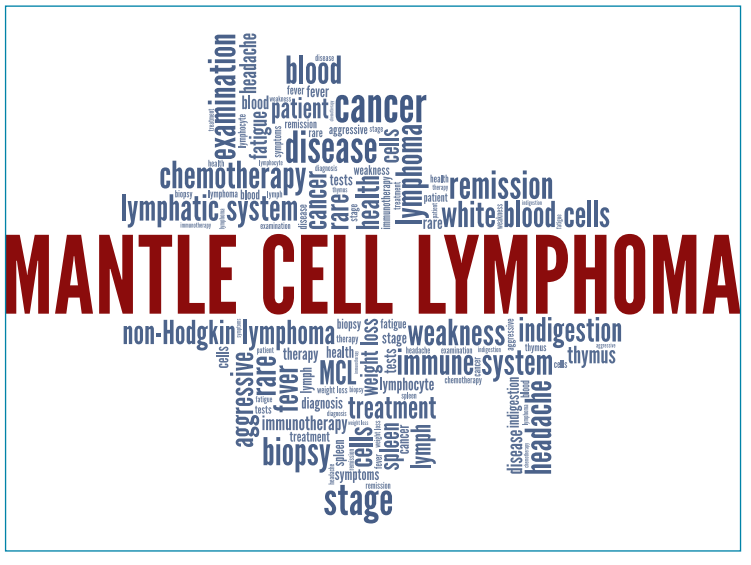
Real-World Outcomes Versus Clinical Trials for Mantle Cell Lymphoma

BY DIBASH KUMAR DAS, PHD

Mantle cell lymphoma (MCL) is an aggressive form of B-cell non-Hodgkin lymphoma. Current guidelines for the first-line treatment of patients under 65 years of age recommend an intensive chemotherapy regimen followed by autologous stem cell transplant (ASCT) and maintenance treatment with rituximab, an immunotherapy that binds to cancer cells so the immune system can attack them.

For patients over 65 years of age who cannot tolerate the intensive chemotherapy required for ASCT, recommended treatments include first-line bendamustine plus rituximab (BR) and a variety of other chemotherapy regimens, including a combination known as R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone).

In a study published in the *Journal of Clinical Oncology*, researchers have found considerable variation in the management of MCL across different clinical settings with some unanticipated strategies (2022; doi: 10.1200/JCO.21.02698). The investigators retrospectively assessed treatment patterns and outcomes in patients with MCL and evaluated the impact of ASCT in patients aged <65 years and maintenance rituximab after BR or R-CHOP. The study included data from 3,614 patients with documented first-line treatment from Flatiron Health diagnosed with MCL between 2011 and 2021. The majority of patients (87%) were from community oncology settings.



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Findings of the data from the two large, independent, real-world groups revealed several key insights. BR was the most commonly used regimen (41.5%). Among 1,265 patients aged <65 years, 30.5 percent received cytarabine-based induction and 23.5 percent received ASCT. The researchers found no significant association between ASCT and real-world time to next treatment among 962 who were transplant-eligible. The median time to next treatment was 59.9 months among 282 who received ASCT versus 48.3 months among 680 who did not receive ASCT (HR=0.84, 95% CI=0.68-1.03, P=.10). Median overall survival was 109 months in the ASCT group versus 113 months in the no-ASCT group (HR=0.86, 95% CI=0.63-1.18, P=.40).

Among a total of 1,461 patients who were considered eligible for maintenance rituximab, the maintenance rituximab after BR was associated with a longer real-world time to next treatment. The median time to next treatment was 65.3 months among 427 patients treated with BR who received maintenance rituximab versus 37.7 months among 679 who received BR alone (HR=1.96, 95% CI=1.61-2.38, P<.001); median overall survival was 89.5 months versus 78.1 months (HR=1.51, 95% CI =1.19-1.92, P<.001).

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The team confirmed the efficacy findings in the validation cohort derived from 12 academic centers in the United States and Canada (n=1,168). Median time to next treatment was 47.8 months among 160 patients receiving R-CHOP with rituximab maintenance versus 18.8 months among 195 receiving R-CHOP alone (HR=2.17, 95% CI=1.66-2.83, P<.001). Median overall survival was 99.0 months versus 81.9 months (HR=1.53, 95% CI=1.06-2.20, P=.023).

In an interview with *Oncology Times,* study authors Jonathon B. Cohen, MD, MS, and Brian T. Hill, MD, PhD, discussed the real-world findings and how future agents should be developed to ensure optimal benefit for all patients with mantle cell lymphoma. Cohen serves as Associate Professor of the Department of Hematology and Medical Oncology at Emory University School of Medicine and Co-Director of the Lymphoma Program at Emory's Winship Cancer Institute. Hill serves as Associate Professor of Medicine of the Cleveland Clinic Lerner College of Medicine, Director of the Lymphoid Malignancies Program and Staff Physician in the Cleveland Clinic Taussig Cancer Institute.

Oncology Times: *Why is it important to explore real-world differences in treatment patterns and outcomes for patients with mantle cell lymphoma across both settings?*

Cohen: "Although we have a number of very informative clinical trials to guide our treatment of patients with mantle cell lymphoma, it is always important to recognize that there is a difference between patients who participate in a study and those who are not treated on a trial, including patients who may not be eligible for trials due to comorbidities, lab abnormalities, social challenges, geographic challenges, etc. As a result, it is important to understand how those patients (which represent the majority of lymphoma patients) are treated and their outcomes. These types of projects help ensure that the data we use to inform our decisions are applicable to all patients."

Hill: "Unlike treatment for more common types of non-Hodgkin lymphoma, initial management of mantle cell lymphoma varies widely across different health care settings. There is no uniformly agreed-upon frontline induction regimen, with academic and community centers employing a range of different initial treatments. In addition, despite evidence supporting the use of consolidation autologous stem cell transplantation (ASCT) after R-CHOP treatment, most patients do not receive transplant. Furthermore, rituximab maintenance therapy is not universally applied to patients with mantle cell lymphoma, particularly in those who have received bendamustine + rituximab (BR) as their initial treatment.

"While consortia of academic sites can provide insight into the relative contribution of each of these treatments, more generalizable data can be gleaned from other sources such as the Flatiron database, which is enriched for patient-level details from community centers. Together, these tools can provide important insight into treatment patterns for a relatively uncommon disease such as mantle cell lymphoma."

Oncology Times: *ASCT was underutilized in community settings, as only about one in four eligible patients received the treatment compared with almost half of eligible patients in academic centers receiving it. What are some possible factors for the lower utilization of ASCT?*

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Cohen: "Autologous transplant has been thought for many years to be an important aspect of treatment for patients with MCL. Interestingly, this study suggests that the benefit of ASCT may not be as significant as we thought, and there are actually ongoing trials to try to answer this question.

"One challenge with uptake of ASCT is that it requires referral by a treating oncologist to a transplant center, often several hundred miles away. It requires that a patient be well enough to receive the treatment, but they must also have the resources to complete the transplant, including transportation to and from the center, social/family support, finances, etc. As a result, many patients who may be medically suitable for transplant aren't able to complete the process. Ultimately, there may also be a lack of awareness regarding who is and is not a suitable candidate for transplant. For example, we frequently can safely complete transplantation for patients in their 70s."

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to 1. Analyze data from two large, independent groups on the management of patients with mantle cell lymphoma (MCL). 2. Explain the importance of exploring real-world differences in treatment patterns and outcomes for patients with MCL in academic and community settings.

Disclosure: All authors, faculty, staff, and planners have no relevant financial relationships with any ineligible organizations regarding this educational activity.

Hill: "In addition, transplant necessitates both a prolonged hospitalization and close involvement by a dedicated patient caregiver. The toxicities can be significant and many patients may be viewed as being too old and having prohibitive medical comorbidities to safely deliver ASCT. These factors, along with other social-economic barriers, result in the minority of patients with mantle cell lymphoma receiving transplant."

Oncology Times: *Based on the study findings, what would be your recommendations to community-based practices to improve treatment regimens for this patient population?*

Cohen: "Fortunately, many of the treatments we now have are much better than what we used in the past, with new therapies commonly being developed. I think it is important that community-based oncologists have a close collaboration with their academic colleagues who see MCL on a more regular basis. Many patients can receive excellent care in their local community; but given how rare the disease is, it is important to be well-versed on the guidelines and current approaches when you do see a patient.

"I would also strongly recommend that patients be considered for and offered the opportunity to participate in clinical trials. There is still much we don't understand about this disease and trials that include a patient cohort with racial/ethnic, geographic, socioeconomic, and gender diversity helps ensure that findings are applicable to the largest group of patients."

Hill: "This large observational study from two robust contemporary datasets did not demonstrate a clear benefit to the use of ASCT in the current treatment era, with a large proportion receiving BR. In this sense, the use of transplant, particularly in older patients, may be less important than it was in the era when most patients were receiving R-CHOP.

"In addition, despite no prospective trials demonstrating an advantage to rituximab maintenance after BR, patients treated in this fashion had longer survival, both in the community datasets as well as in our academic consortium. As such, the frequently used approach of induction treatment with BR followed by rituximab maintenance rather than ASCT appears to be very safe and effective standard practice with favorable outcomes for most patients with mantle cell lymphoma."

Oncology Times: *What limitations of the current study still need to be addressed before conclusive recommendations can be made? What are some considerations these findings provide for the design of future clinical trials evaluating treatment strategies in MCL?*

Cohen: "One of the challenges of any study like this is that we are reliant upon the data generated by chart reviews. Although the data are accurate and reflect what actually happened in the real world, this type of study does not provide an awareness of what may or may not have led to a particular decision being made.

"At the end of the day, many decisions between a treatment team and the patient are based on factors beyond some of the objective data related to their case. As a result, I always counsel my colleagues to view these data with the caveat that it is not a substitute for clinical judgment when assessing an individual patient. One key point of this project, however, is that it does suggest that ASCT may not be critical and opens to the door to future studies that may include alternative approaches for young patients that may not require ASCT."

Hill: "Like any retrospective review of patient outcomes, there has been bias that could confound results. For instance, it is possible that rituximab maintenance was more commonly applied to patients who were responding favorably to induction treatment with BR, thus inflating the perceived benefit of this therapy. Because this was not a prospective randomized trial comparing observation versus maintenance rituximab, this limitation will remain a caveat that we acknowledge." OT

Dibash Kumar Das is a contributing writer.