ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Watching and Waiting in Mantle Cell Lymphoma

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H&O What is the current outlook in mantle cell lymphoma (MCL)?

PM I think the overall outlook is better than ever for patients with this disease. The prognosis in MCL appears to be improving. This is likely a reflection of better pathology, resulting in lead-time bias from earlier identification of more indolent cases and the inclusion of cases that might have been mistaken for curable lymphomas (eg, diffuse large B-cell lymphoma) in the past, as well as the application of modern therapeutic modalities. Therapeutic approaches include aggressive therapies with high response rates and promising progression-free survival rates, which may be applied to younger healthy patients, as well as less aggressive approaches. There are a number of new drugs that have been approved and others that are in development that are likely to change the way patients are managed and will hopefully improve survival more than any strategy we have seen in the past.

H&O What are the current treatment approaches in MCL?

PM There is no standard treatment approach for patients with MCL. The disease course can be highly variable. Some patients may have very aggressive disease, whereas others may have a much more indolent disease course, at least initially. The current World Health Organization classification subdivides MCL into variants based on morphology, but this probably does not capture the true biological diversity that exists among patients. As such, there is no singular, optimal frontline therapy. Potential strategies include chemotherapy, immunotherapy, stem cell transplantation, and novel biologic agents. Although MCL often responds well to frontline chemotherapy, the responses are not durable and often last for a relatively short period. Issues to consider when formulating a treatment plan include disease-related factors, such as biological markers and the course of the disease so far, treatment goals, and patient characteristics.

H&O In which subset of patients has a watch and wait strategy been utilized?

PM Given the burden and pace progression of disease, most patients with MCL require treatment at diagnosis, but this is not uniformly true. Over the last few years, researchers have identified groups of patients who have a more indolent disease course and extended survival. Although there are no specific diagnostic criteria available for the recognition of these patients, there is evolving evidence of clinicopathologic differences identifying this group from patients with classical MCL. Many patients with more indolent disease present with a non-nodal, leukemic picture similar to chronic lymphocytic leukemia and a low Ki-67. These patients usually have no acute symptoms. Treatment can often be delayed without markedly affecting overall outcome. In addition to Ki-67, potential biomarkers for identifying more indolent MCL patients include lack of SOX11 expression and hypermutated immunoglobulin heavy chain (IgHV), but these are unlikely to be definitive biomarkers and need to be validated in additional studies.

H&O Can you please discuss your research on using the watch and wait approach in patients with MCL?

PM My colleagues and I at Weill Cornell Medical Center questioned whether immediate therapy is necessary in all MCL patients. In our study, which was published in 2009 in the *Journal of Clinical Oncology*, 31 out of 97 patients with newly diagnosed MCL were observed for at least 3 months before initial systemic therapy (median time to treatment, 12 months; range, 4-128 months). The median follow-up for the initial observation group was 55 months, and 54% of patients were considered intermediate or high risk by the Mantle Cell International Prognostic Index (MIPI) score. In multivariate analysis, time to treatment was not predictive for overall survival, although the initially observed group had superior survival to those treated immediately (median OS, not reached vs 64 months, respectively; *P*=.004).

H&O Have other studies reported similar results with this approach?

PM Eve and associates also reported on separate cohorts of patients who did not receive upfront chemotherapy at the time of diagnosis, but were instead managed with a watch and wait approach. This study, which was published in 2009 in the *Journal of Clinical Oncology*, also found that watching and waiting did not have adverse effects on survival outcomes. The authors concluded that if such patients can be reliably identified, chemotherapy for this group, with its attendant morbidity, could reasonably be deferred.

H&O What are the potential advantages and disadvantages of the watch and wait strategy that patients should consider?

PM One benefit of the watch and wait approach is that it allows patients to come to terms with their disease. Patients may decide to seek a second, third, or even fourth opinion without having to worry about certain details, including cost of therapy, how their day-to-day life will be affected by the treatment process, and other emotional and logistic factors. Another important benefit of watch and wait is that patients are not exposed to treatment before they need to be. Their quality of life will not be negatively impacted by having to travel to a hospital for treatment and they will not have any treatment side effects.

However, some patients may find it very hard to cope with a deferred initial treatment strategy. They may experience anxiety from the idea of having to live with a disease and wait for it to get worse before any action is taken, and that can inhibit their ability to go on with everyday life.

H&O What are the biggest challenges for the future?

PM There is an important need to greatly improve outcomes for MCL patients. Although a number of treatment regimens have been evaluated for frontline therapy, it has been hard to identify broadly applicable therapies with the potential to significantly improve survival. Durable responses can be achieved in many patients with the use of intensive therapeutic approaches, often including high-dose chemotherapy with stem cell rescue. However, progression still occurs in most patients, and significant and profound morbidity are areas of concern. A nearly inescapable risk of relapse is often associated with chemoresistance, creating a large unmet need in this field.

Novel agents targeting specific pathways within MCL represent one of the most exciting possibilities for improving patient outcomes. Combining novel and targeted agents with chemotherapeutic backbones, or exploring alternative dosing/maintenance schedules may be beneficial in the short term but will not likely result in major breakthroughs in the long term. Future research should focus on understanding the variability that exists between patients and the biological changes that evolve over time. Novel agents are likely to be effective for specific patient subsets rather than all patients, and learning about resistance to these drugs will help provide rationale for better combinations.

Lastly, improving the ability to identify patients with an indolent course of MCL is crucial. Research goals should include identification of better diagnostic and prognostic tools, as well as predictive biomarkers.

Suggested Readings

Eve HE, Furtado MV, Hamon MD, Rule SAJ. Time to treatment does not influence overall survival in newly diagnosed mantle cell lymphoma. *J Clin Oncol*. 2009;27(32):e189–e190.

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Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.