

# ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

## High-Dose Cytarabine in Mantle Cell Lymphoma



Peter Martin, MD  
Assistant Professor of Medicine  
Department of Hematology  
Weill Cornell Medical College  
Cornell University  
New York, New York

**H&O** What are the current high-intensity regimens for mantle cell lymphoma (MCL)?

**PM** There are 2 commonly used high-intensity therapies for young, fit patients with MCL. One is a regimen that alternates rituximab (Rituxan, Genentech/Biogen Idec), cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP), as described in the MCL Younger Trial of the European Mantle Cell Lymphoma Network, published by Hermine and colleagues. In this study, patients received R-CHOP alternating with R-DHAP for a total of 6 cycles. The other regimen is called the Nordic regimen, and uses rituximab with alternating cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (Maxi-CHOP) and high-dose cytarabine. Both of those induction regimens are followed by autologous stem cell transplantation (ASCT).

**H&O** Can these therapies be used in all patients?

**PM** No; most prospective studies using high-dose cytarabine have restricted the age to patients younger than 65 years. Some of them limit the age to 60 or 70 years, but 65 years seems to be the most common cutoff. That is not to say that people younger than 65 years must receive cytarabine or that people older than 65 years cannot receive cytarabine, but this is where the evidence exists. If we are practicing evidence-based medicine, then it is better to follow the existing data.

**H&O** Based on these age cutoffs, how many patients would be eligible to receive the high-intensity regimens?

**PM** A minority of patients are eligible. The average age of diagnosis of MCL is approximately 68 years, and it continues to increase as the population gets older. Therefore, the vast majority of patients in a real-world setting are not candidates for ASCT or high-intensity regimens that might include high-dose cytarabine. Realistically, less than 25% of patients with a new diagnosis of MCL would be candidates for high-intensity regimens that include high-dose cytarabine. There are intermediate-dose cytarabine-containing regimens that might be reasonable considerations for older patients, but a younger and more rare patient population is eligible for high-dose cytarabine.

**H&O** How much does high-dose cytarabine improve patient outcome?

**PM** I do not think that has been very well defined. Not all of these data have sufficient long-term follow-up to comment on overall survival outcomes. Historically, patients were given R-CHOP followed by ASCT. The MCL-2 trial, published by Geisler and colleagues, added high-dose cytarabine and rituximab, and found that the outcomes were far superior in terms of progression-free survival and overall survival. However, these outcomes may not be solely due to high-dose cytarabine. Other explanations include the addition of rituximab, other changes in supportive care,

and better pathology. Cytarabine may be part of that story, but it may not be the whole story.

The better trial to evaluate the potential role of cytarabine is the MCL Younger Trial that I mentioned earlier, which is a phase 3 trial published by Hermine and colleagues that compared 6 cycles of R-CHOP vs the R-CHOP/R-DHAP regimen. In this trial, the addition of R-DHAP seemed to reduce the risk of disease progression by approximately 30%. The study also found that the R-CHOP/R-DHAP regimen prepared people for ASCT better than R-CHOP alone.

### **H&O** Have any trials examined a high-dose cytarabine-containing regimen alone?

**PM** Yes, after the success of their MCL-2 trial, the Nordic Lymphoma Group started a series of follow-up studies, including the MCL-5 trial, in which they tested exclusively high-dose cytarabine plus rituximab induction. This trial, published by Laurell and colleagues, is interesting but does not receive a lot of attention, partially because only 5 patients total were enrolled. The rationale was that, even in patients receiving the Maxi-CHOP/high-dose cytarabine regimen, some high-risk patients did not have good outcomes. Therefore, receiving more high-dose cytarabine earlier on, as opposed to alternating with other therapies, might have a beneficial effect, in particular for those high-risk patients.

This was a noble goal and the rationale was sound, but four of the first 5 patients treated had poor outcomes. Because of this, the researchers decided not to pursue that regimen any further. It is a bit unclear why the study was a failure. One potential explanation is that the study used rituximab and high-dose cytarabine, not R-DHAP, which is the regimen used in the MCL Younger Trial. So perhaps a high-dose cytarabine-based regimen must include dexamethasone or a platinum-based drug. The other possibility is that they were unlucky and happened to enroll 4 very treatment-resistant patients at the beginning. Nonetheless, it would be difficult ethically to continue pursuing this regimen.

The R-DHAP regimen, which includes high-dose cytarabine and rituximab with added corticosteroids and platinum, also has been studied by itself. The results were reported at the 2015 International Conference on Malignant Lymphoma by Le Gouill and colleagues. In this study, patients received 4 doses of R-DHAP, underwent ASCT, and were randomly assigned to rituximab maintenance. The induction therapy contains fewer cycles than previous studies but uses more cytarabine overall. Patients who did not have a good response to the 4 cycles of R-DHAP were given additional doses of R-CHOP, but interestingly, R-CHOP treatment did not further improve outcomes in those patients who were resistant to

R-DHAP. This study suggests that the R-DHAP regimen, without an anthracycline-based regimen like R-CHOP or Maxi-R-CHOP, might be sufficient by itself.

### **H&O** Have any other studies examined the utility of high-dose cytarabine in MCL?

**PM** The Nordic Lymphoma Group performed an observational study, published by Abrahamsson and colleagues, that took place over a decade and included almost 1400 patients with MCL in Sweden and Denmark. This study is relevant because of its size and because it represents a real-world patient population, as opposed to the highly selected patient population of clinical trials.

The first interesting finding of this study was the actual percentage of patients who received a high-intensity regimen including cytarabine in this real-world setting. The study found that less than 25% of patients received an MCL-2-type regimen, meaning that even in a region that is highly organized and where guidelines exist and are followed, only a minority of patients are eligible to receive a high-dose cytarabine- and ASCT-based regimen. In the United States, the percentage is likely even less, closer to 15%.

Despite the low percentage of patients who received a high-dose cytarabine regimen, the study found that these patients had better outcomes. However, these data are hard to interpret because they come from an observational trial, and many unmeasured biases could work their way into the analysis. This study looked at ASCT—which can be a surrogate for use of high-dose cytarabine—and outcomes, adjusted for rituximab use and risk using the Mantle Cell Lymphoma International Prognostic Index (MIPI). Even when adjusting for those factors, ASCT was associated with superior outcomes.

It is important to note that the observation groups were not identical. The average age of the transplant group was younger than 60 years, whereas the average of the nontransplant group was older than 70 years. Therefore, there are other reasons why patients receiving high-dose cytarabine and ASCT in that setting might have done better. But overall, the patients who were treated with an MCL-2-type regimen and ASCT did well by most standards, suggesting that in a real-world patient population, this is a feasible regimen for a minority of patients, and the outcomes are generally good.

### **H&O** Are there any other clinical trials of importance that you would like to discuss?

**PM** Another regimen worth mentioning is cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (hyper-CVAD). This includes a slightly lower dose of cytarabine than R-DHAP, but still contains a relatively high dose of cytarabine.

This regimen has been studied thoroughly by a group from MD Anderson, with well over a decade of follow-up. In this single-center phase 2 trial published by Romaguera and colleagues, a hyper-CVAD and rituximab regimen performed well. A multicenter prospective clinical trial published by Bernstein and colleagues found that outcomes after hyper-CVAD treatment were good, but not as good as they were in the single-center trial. However, in another phase 2 trial presented at the 2015 International Conference on Malignant Lymphoma by Chen and colleagues, hyper-CVAD was compared with rituximab plus bendamustine (Treanda, Teva). This trial was closed early owing to challenges with the hyper-CVAD regimen and stem cell collection. I think these studies show that some centers may be able to deliver hyper-CVAD to a very select patient population. But in a real-world setting, hyper-CVAD is probably not a good choice as an intensive strategy for most patients with MCL.

#### **H&O** Are any clinical trials currently in development?

**PM** There also are studies examining ways to deliver cytarabine to a less-fit patient population, but those regimens tend not to include higher doses of cytarabine. One such regimen consists of rituximab, bendamustine, and cytarabine (R-BAC). At least preliminarily, this regimen looks promising.

#### **H&O** What impact do these findings have on the treatment of MCL?

**PM** This is hard to answer for a few reasons, but we can make one statement fairly conclusively: in most centers that consider transplant of younger patients to be standard of care, most patients will receive a high-dose cytarabine regimen prior to transplant. If the physician feels that a patient should receive an intensive strategy, then cytarabine likely will be part of that regimen, whereas in the past, that may not have been true.

It is hard to know, however, whether these studies will change the number of patients who actually receive high-intensity regimens. I think that in the United States, different centers have a bias towards different treatments. Some centers consider intensive strategies to be standard of care, and will pursue them in the vast majority of their patients, even older ones. By contrast, some centers are not yet convinced that intensive strategies are beneficial and may not pursue high-dose cytarabine and ASCT, even in patients who might be candidates. This may be because there is a low-risk population that does well independent of high-dose cytarabine and ASCT, and a high-risk population that does poorly regardless of whether they receive

high-dose cytarabine and ASCT. The toxicity that comes from these regimens is considerable, so selecting that niche patient population that has the most to benefit and the least to lose is a challenge.

The other major change that is happening in the United States and all around the world is the evolution of other therapies. For example, bendamustine has really taken hold, and rituximab maintenance is considered standard of care in some settings and seems to improve overall survival in some cases. There also are treatments for patients with relapsed or refractory MCL that have good response rates and good response durations, so it may not be as important to get a very long first remission at the expense of considerable toxicity.

#### **H&O** What are the side effects and toxicities?

**PM** High-dose cytarabine is relatively well tolerated; its primary side effect is myelosuppression. Most people receiving a high-dose cytarabine-based regimen will have significant neutropenia and significant thrombocytopenia, and some may need transfusions. Combining high-dose cytarabine with high-dose methotrexate increases myelosuppression significantly, and that is likely why the hyper-CVAD regimen is poorly tolerated by many patients. Cytarabine also is commonly associated with gastrointestinal upset, nausea, vomiting, and diarrhea. Rash occurs frequently, but is not a major complication. Cerebellar toxicity and neurotoxicity are major concerns, particularly in older patients, and that is why regimens that are used in patients older than 65 years have a reduction in the dose of cytarabine. Neurotoxicity is avoidable by selecting the patient population appropriately, but it is a devastating side effect if it occurs. There also can be ocular toxicity, so patients will receive corticosteroid eye drops to reduce that side effect.

#### **H&O** In what setting are these regimens typically used?

**PM** All of these regimens are used in the frontline setting. That is not to say that they would not work in the relapsed setting, but if a patient already has received very intensive therapy, it does not make sense to continue with more intensive strategies afterward. Some younger patients who receive minimally intensive therapy might benefit from subsequent intensive therapy, but that is uncommon.

#### **H&O** What do you think is the future of high-dose cytarabine in MCL?

**PM** I think that in patients receiving high-intensity therapy with ASCT, there is a good chance that high-dose cytarabine should be part of the induction regimen. But, whether high-dose cytarabine has a role in younger patients

who are not being treated with ASCT remains unclear. Researchers also are still investigating how to use cytarabine in older patients who may not be headed toward ASCT.

I think that treatment strategies for MCL are evolving. It is great that new options are available for real-world patients with MCL who probably are not candidates for the most aggressive treatments. As those therapies evolve, there may be less of a role for high-intensity regimens. Researchers also may determine the patient population that is most likely to benefit from the high-intensity regimens, and be able to spare other patients from that toxicity. However, with the constantly evolving treatments, it becomes challenging to study MCL. Phase 3 and large phase 2 trials in the United States tend to accrue patients slowly, and often we run the risk of having results that are irrelevant by the time the study is completed. Although it is good that treatments are evolving so quickly, it is sometimes hard for the clinical trials to keep up.

## Suggested Readings

- Abrahamsson A, Albertsson-Lindblad A, Brown PN, et al. Real world data on primary treatment for mantle cell lymphoma: a Nordic Lymphoma Group observational study. *Blood*. 2014;124(8):1288-1295.
- Bernstein SH, Epner E, Unger JM, et al. A phase II multicenter trial of hyper-CVAD MTX/Ara-C and rituximab in patients with previously untreated mantle cell lymphoma; SWOG 0213. *Ann Oncol*. 2013;24(6):1587-1593.
- Chen R, Li H, Bernstein SH, et al. Results of a randomized phase II trial of R-HCVAD versus R-bendamustine followed by autologous stem cell transplants for patients with mantle cell lymphoma: US Intergroup S1106. Paper presented at: 13th International Conference on Malignant Lymphoma; June 17-20, 2015; Lugano, Switzerland. Abstract 62.
- Delarue R, Haioun C, Ribrag V, et al; Groupe d'Etude des Lymphomes de l'Adulte (GELA). CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. *Blood*. 2013;121(1):48-53.
- Geisler CH, Kolstad A, Laurell A, et al; Nordic Lymphoma Group. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood*. 2008;112(7):2687-2693.
- Hermine O, Hoster E, Walewski J, et al. Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) increases overall survival when compared to 6 courses of CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: final analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net) [ASH abstract 151]. *Blood*. 2012;120(21)(suppl).
- Kluin-Nelemans HC, Hoster E, Hermine O, et al. Treatment of older patients with mantle-cell lymphoma. *N Engl J Med*. 2012;367(6):520-531.
- Laurell A, Kolstad A, Jerkeman M, Rätty R, Geisler CH. High dose cytarabine with rituximab is not enough in first-line treatment of mantle cell lymphoma with high proliferation: early closure of the Nordic Lymphoma Group Mantle Cell Lymphoma 5 trial. *Leuk Lymphoma*. 2014;55(5):1206-1208.
- Le Gouill S, Cartron G, Tournilhac O, et al. Rituximab maintenance versus WW after R-DHAP plus ASCT in untreated patients with MCL: interim analysis of the LYMA trial, a LYSA study. Paper presented at: 13th International Conference on Malignant Lymphoma; June 17-20, 2015; Lugano, Switzerland. Abstract 61.
- Romaguera JE, Fayad LE, Feng L, et al. Ten-year follow-up after intense chemoimmunotherapy with Rituximab-HyperCVAD alternating with Rituximab-high dose methotrexate/cytarabine (R-MA) and without stem cell transplantation in patients with untreated aggressive mantle cell lymphoma. *Br J Haematol*. 2010;150(2):200-208.
- Visco C, Chiappella A, Franceschetti S, et al. Rituximab, bendamustine, and cytarabine (RBAC500) as induction therapy in elderly patients with mantle cell lymphoma: a phase 2 study from the Fondazione Italiana Linfomi. Paper presented at: 13th International Conference on Malignant Lymphoma; June 17-20, 2015; Lugano, Switzerland. Abstract 59.
- 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.