

ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

Update in the Management of Mantle Cell Lymphoma



Andre Goy, MD, MS
Chairman, Executive Director
John Theurer Cancer Center
Hackensack University Medical Center
Hackensack, New Jersey

H&O Can you please provide an overview of mantle cell lymphoma (MCL)?

AG Mantle cell lymphoma (MCL) was officially recognized as a separate entity in 1994 by the World Health Organization (WHO). MCL is a relatively rare subtype of non-Hodgkin lymphoma (NHL), representing only about 6% of NHL. MCL typically responds to chemotherapy initially, but often relapses and becomes chemo-resistant over time. A small subset of patients can have a rather indolent course and may be monitored initially. A number of novel therapies are helping change the field in MCL, especially in the relapsed/refractory setting.

H&O How is MCL typically treated?

AG Over the last 2 decades, the survival of MCL patients has clearly improved, essentially due to the use of dose-intensive strategies with or without autologous stem cell transplantation (ASCT) in the frontline setting. The selection of treatment relies on the age of the patient (median age at diagnosis, mid to late 60s) and/or the presence of comorbid conditions at presentation. Patients who are eligible for intensive strategies can receive either cyclophosphamide, vincristine, doxorubicin, and dexamethasone (classic hyper-CVAD) plus rituximab (Rituxan, Genentech/Biogen Idec) alternating with cytarabine and methotrexate or induction therapy followed by ASCT. This approach has resulted in a dramatic improvement of median progression-free survival (PFS) in excess of 5 years versus 18–24 months with the use of standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP).

For older patients or those who have other comorbid conditions, R-CHOP alone is often used as a default (though the median PFS remains short and is not very different than that of CHOP alone).

An alternative to R-CHOP is bendamustine plus rituximab (BR), as shown in the StiL (Study Group Indolent Lymphomas) trial. In that study, BR was compared to R-CHOP as frontline therapy in indolent lymphoma, including MCL. The results showed a dramatic improvement in PFS in favor of BR, particularly in the follicular lymphoma subset (PFS more than doubled). There was no difference in overall survival (OS), but significantly less toxicity, again in favor of the BR combination. In the MCL subset of the StiL trial (90 patients), results also showed better PFS in BR over R-CHOP. Similar results in favor of BR in MCL patients were reported at the 2012 American Society of Hematology (ASH) meeting, as part of BRIGHT (Bendamustine Rituximab Investigational Non-Hodgkin's Trial). The favorable toxicity profile of BR also makes it an appealing option for MCL patients. BR has consequently become an interesting backbone to combine with other treatments, including biologics, for the management of MCL.

H&O How is maintenance therapy evolving in MCL?

AG Given the pattern of relapse seen in MCL, it appears logical to develop maintenance strategies after induction chemotherapy. A study by Kluin-Nelemans and associates, which compared R-CHOP versus fludarabine, cyclophosphamide, and rituximab (FCR) as induction therapy for older MCL patients (median age, 70 years), was recently published in the *New England Journal of Medicine*. Responding patients were randomized to receive maintenance therapy with rituximab or interferon. The primary endpoint of this study was time to treatment failure (TTF). Results showed better outcome with R-CHOP and more progression on FCR. Rituximab maintenance was superior to interferon, as expected,

and showed a dramatic improvement in both PFS and OS after R-CHOP induction, but not after FCR. These remarkable results established a new potential standard with R-CHOP followed by rituximab maintenance in elderly MCL patients. Ongoing studies are looking at the integration of other biologicals as part of maintenance strategies. Lenalidomide (Revlimid, Celgene) is one of several novel emerging agents that provide an obvious opportunity to help prevent recurrence in MCL patients after induction.

H&O Despite these advances, what obstacles remain?

AG Although the results for frontline therapy have improved greatly, most patients with MCL still relapse and, over time, often become resistant to chemotherapy. There is no proven curative therapy, and no established standard of care in that setting. There is clear evidence that achieving a deep and early complete remission in MCL translates into clinical benefit and superior OS in some studies, as shown by the large randomized trial from the MCL European Union (EU) consortium, which was recently updated and presented at the 2012 ASH meeting. This study looked at a high-dose cytarabine-containing regimen versus R-CHOP-containing induction, both followed by high-dose therapy and ASCT (no maintenance therapy). Results showed that the high-dose cytarabine arm obtained a higher CR and molecular CR compared to the R-CHOP arm, which translated into a better OS. Achieving a molecular CR will likely become an important endpoint in MCL moving forward and is already part of some new ongoing trials in Europe.

H&O Are there any approved treatments for patients with relapsed MCL?

AG The only drug that has been approved in MCL in the relapse setting is bortezomib (Velcade, Millennium), which was approved in 2006. Bortezomib is the first of its class of proteasome inhibitors and showed promising activity in several phase II trials as early as 2003. Approval of bortezomib was based on a confirmatory pivotal study (PINNACLE), which I led. PINNACLE was a prospective, multicenter, single-arm, open-label study of patients with MCL whose disease progressed following at least 1 prior therapy. Results showed an OS rate of 31%, and a complete response (CR)/CR unconfirmed (CRu) rate of 8%. The median duration of response was 9.3 months, and up to 27 months in patients who achieved a CR/CRu. Ongoing combination studies are looking at the best way to integrate bortezomib as part of the other chemoimmunotherapy regimens used in MCL.

H&O What was the design of the EMERGE trial?

AG The EMERGE (A Study to Determine the Efficacy and Safety of Lenalidomide in Patients With Mantle Cell NHL Who Have Relapsed or Progressed After Treatment With Bortezomib or Are Refractory to Bortezomib) trial, also known as MCL-001, was a study to confirm the activity of lenalidomide (previously reported in a single-institution, smaller, phase II study) in a defined relapsed/refractory MCL population. In this trial, which was presented at ASH 2012, we looked at single-agent lenalidomide in relapsed/refractory MCL patients who had failed 4 of the classic therapies used in MCL, including anthracycline- or mitoxantrone-based therapy, cyclophosphamide, rituximab, and bortezomib. A total of 134 MCL patients received lenalidomide 25 mg/day for 21 out of every 28 days until disease progression or unacceptable toxicities. This was a heavily pretreated population, with a median of 4 prior therapies (range, 2–10). Two-thirds of patients were refractory to bortezomib, more than half had a high tumor burden, one-third of the patients had bulky disease, and one-third had received ASCT.

H&O What were the main findings?

AG This trial, which by design included a central review, showed an OS of 28% and a CR/CRu of 8%, with an additional 29% of patients showing stable disease. The median time to response was 2.2 months, and the median time to CR/CRu was 3.7 months. At a median follow-up of 9.9 months, patients had a median PFS of 4 months and a median OS of 19 months. The median duration of response (part of the primary endpoint) was more than 16 months, with the longest response being more than 29 months at the time of data cutoff in July 2012. Of notice, responses were seen in all patients, regardless of number of prior therapies, prior high-dose therapy, bulky disease, or if they were refractory to last therapy or to bortezomib.

Overall, lenalidomide was well tolerated and demonstrated an expected toxicity profile. The most common grade 3/4 adverse events were neutropenia (43%), thrombocytopenia (27%), anemia (11%), pneumonia (8%), fatigue (7%), leukopenia (7%), and febrile neutropenia (7%). Other adverse events included tumor flare reaction (10%), deep vein thrombosis (4%), pulmonary embolism (2%), and invasive second primary malignancies (2%). Only a very small number of patients required dose reductions or discontinued treatment.

H&O What are the implications of this study?

AG Based on its mechanisms of action and the activity seen in very heavily pretreated MCL patients, it is logical to develop strategies to integrate lenalidomide into regimens used for

the management of MCL. This will include lenalidomide in combination with induction therapy and, more specifically, lenalidomide as part of maintenance strategies, particularly in elderly MCL patients. In addition, lenalidomide plus rituximab has shown dramatic activity in relapsed/refractory MCL and is currently being tested in the frontline setting. The SPRINT (A Study to Determine the Efficacy of Lenalidomide Versus Investigator's Choice in Patients With Relapsed or Refractory Mantle Cell Lymphoma) trial in Europe is looking at lenalidomide versus investigator treatment of choice in relapsed/refractory MCL as well.

H&O What other novel agents are showing promise in MCL?

AG A number of novel agents are emerging in relapsed/refractory MCL. The mTOR inhibitors (temsirolimus [Torisel, Wyeth Pharms] and everolimus [Afinitor, Novartis]) target the PI3K/mTOR pathway, with an OS of about 30% and median response duration of approximately 6 months. They are currently being tested as part of combination therapy. Among the most exciting agents is ibrutinib, a BTK inhibitor that targets the B-cell receptor (BCR) signaling pathway. Ibrutinib has shown response rates of 60–70% in patients with relapsed/refractory MCL, with a CR rate of 20%, which appears to increase over time. Ibrutinib is well-tolerated, so it will be an important part of the treatment landscape in MCL. Idelalisib also targets the BCR signaling pathway, and has demonstrated strong activity in relapsed/refractory MCL as well. Other emerging agents include cell cycle inhibitors, histone deacetylase (HDAC) inhibitors (mostly preclinical data), new monoclonal antibodies, and more recently, ABT199 (Bcl-2 inhibitor/BH3 mimetic), which showed very promising results in phase I trials already.

H&O What are the most important areas of focus for the future?

AG Despite a clear improvement of outcome in MCL over the last 2 decades, the prognosis of MCL patients

in the relapsed/refractory setting is still poor, illustrating the need to develop novel options for these patients. A subset of patients can enjoy long-term disease-free survival after allogeneic stem cell transplantation (non-myeloablative), though the incidence of chronic graft-versus-host disease exceeds 50%. A number of novel agents will help develop strategies, either as combination with induction therapy or sequentially (as maintenance), as well as nonchemotherapy options in elderly or “indolent” MCL cases.

The impressive progress in understanding MCL biology will likely enable us to better stratify patients for optimal treatment strategies in the future. It is becoming even more critical for physicians to encourage patients to participate in clinical trials in order to continue improving outcomes in MCL.

Suggested Readings

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