Mantle cell lymphoma - Section 3

Management of mantle cell lymphoma in the era of targeted drugs

Tadeusz Robak

Medical University of Lodz, Poland

MCL is a heterogeneous lymphoma, with indolent course not requiring treatment at diagnosis in some patients, to aggressive disease that needs immediate therapy in others. Fit patients, usually younger than 65 years, should be treated with high-dose cytarabine containing regimen before autologous stem cell transplantation (ASCT).[1] At present, 3 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and 3 cycles of R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin) followed by ASCT is the most widely used first-line therapy in younger fit patients.[2] In patients not suitable for ASCT, R-CHOP alone is a commonly used treatment.[3] In addition, bendamustine plus rituximab (BR) induced significantly longer progression free survival (PFS) (69.5 months *vs* 31.2 months; P<0.0001) and was better tolerated than R-CHOP in large, randomized study.[4] The replacement of vincristine with bortezomib in R-CHOP (VR-CAP) is even more promising in frontline therapy in MCL patients who are not ineligible or not considered for ASCT. In the randomized phase 3 LYM-3002 study, the VR-CAP regimen significantly prolonged PFS and improved CR rate when compared to R-CHOP.[5] Bortezomib is the first proteasome inhibitor approved by the FDA for first line treatment, both in the US and the EU. Lenalidomide is also of value in frontline treatment of MCL.[7] Four targeted drugs, bortezomib, lenalidomide, ibrutinib and temsirolimus have showed activity in relapsed or refractory MCL (Table 1).[5-16] In particular, ibrutinib has shown impressive single-agent responses with excellent tolerability and a modest side-effect profile in refractory/relapsed MCL.[13] This agent can be probably incorporated into frontline therapy combinations and maintenance strategies in the near future. They have been approved in EU and/or US for treatment of patients with previously treated MCL. Finally, maintenance with rituximab, bortezomib or radioimmunotherapy is also promising in MCL.[3,6,17]

Table 1. Larger recent clinical trials with targeted drugs in mantle cell lymphoma.

Study	Treatment	N	Study phase	OR	CR	PFS	OS
Newly diagnosed patients							
Robak *et al.* 2015[5]	VR-CAP *vs* R-CHOP	243 *vs* 244	II	92% *vs* 89%	53% *vs* 42%	24.7 mo *vs* 14.4 mo (P<0.001)	Median not reached *vs* 56.3 mo (P=0.17)
Till *et al.* 2016[6]	R-CHOP + bortezomib induction + bortezomib maintenance	65	II	83%	57%	2-year PFS - 62% 5- year PFS - 28%	2-year OS - 85% 5- year OS - 66%
Ruan *et al.* 2006[7]	Lenalidomide plus rituximab	38	II	92%	64%	2-year PFS 85%	2-year OS 97%
Relapsed / refractory patients							
Goy *et al.* 2007 MCL-001 (EMERGE)[10]	Lenalidomide alone	134	II	28%	7.5%	4 mo	19 mo
Wang *et al.* 2012[11]	Lenalidomide plus rituximab	52	I/II	57%	36%	11.1 mo	24.3 mo
Trneny *et al.* 2015 (SPRINT)[12]	Lenalidomide *vs* best investigator's choice	170 *vs* 84	II	40% *vs* 11% (P<0.001)	5% *vs* 0% (0.043)	8.7 mo *vs* 5.2 mo (P=0.004)	27.9 mo *vs* 21.2 mo (P=0.52)
Wang *et al.* 2015[13]	Ibrutinib alone	111	II	67%	23%	24-mo PFS 31%	24-mo OS 47%
Wang *et al.* 2015[14]	Ibrutinib + rituximab	50	II	88%	44%	Not reached	Not reached
Hess *et al.* 2009[15]	Temsirolimus 175/75-mg *vs* temsirolimus 175/25-mg *vs* investigator's choice		III	22% *vs* 6% *vs*2% (P=0.0019)	1% *vs* 0% *vs* 1%	4.8 mo *vs* 3.7 mo *vs* 1.8 mo (P=0.0009)	11.1m *vs* 8.8 mo *vs* 9.5 mo (P=0.3519)
Dreyling *et al.* 2015[16]	Ibrutinib *vs* temsirolimus	139 *vs* 141	III	72% *vs* 40% (P<0.0001)	19% *vs* 1%	14.6 mo *vs* 6.2 mo (P<0.0001)	Median not reached *vs* 21.3 mo (P=0.1324)

ASCT: autologous stem cell transplantation; CR: complete response; mo: months; OR: overall response; OS: overall survival; PFS: progression free survival; VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

Mantle cell lymphoma - Section 3

References

1. Dreyling M, Geisler C, Hermine O, Kluin-Nelemans HC, Le Gouill S, Rule S, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl 3):iii83-92.
2. Hermine O, Hoster E, Walewski J, Ribrag V, Brousse N, Thieblemont C, et al. Alternating courses of 3x CHOPand 3x DHAP plus rituximab followed by a high-dose ARA -C containingmyeloablative 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). Blood. Available from: https://ash.confex.com/ash/2012/webprogram/Paper54717.html
3. Kluin-Nelemans HC, Hoster E, Hermine O, Walewski J, Trneny M, Geisler CH, et al. Treatment of older patients with mantle-cell lymphoma. N Engl J Med. 2012;367(6):520-31.

*4. Rummel MJ, Niederle N, Maschmeyer G, Banat GA, von Grünhagen U, Losem C. 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):1203-10.

Results of the large randomized phase III study study on bendamustin combined with rituximab in first line treatment of MCL.

*5. Robak T, Huang H, Jin J, Liu T, Samoilova O, Pylypenko H, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med 2015;372(10):944-53.

The first randomized phase 3 study incorporating bortezomib into frontline treatment for newly diagnosed MCL patients not considered for intensive therapy and bone marrow transplantation.

6. Till BG, Li H, Bernstein SH, Fisher RI, Burack WR, Rimsza LM, et al. Phase II trial of R-CHOP plus bortezomib induction therapy followed by bortezomib maintenance for newly diagnosed mantle cell lymphoma: SWOG S0601. Br J Haematol. 2016;172(2):208-18.
7. Ruan J, Martin P, Shah B, Schuster SJ, Smith SM, Furman RR, et al. Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma. N Engl J Med. 2015;373(19):1835-44.
8. Fisher RI, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006; 24(30):4867-74.
9. Rule S. Velcade combinations in mantle cell lymphoma: are we learning anything? Leuk Lymphoma. 2011;52(4):545-7.

*10. Goy A, Sinha R, Williams ME, Kalayoglu Besisik S, Drach J, Ramchandren R, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol. 2013;31(29):3688-95.

Seminal paper demonstrating the clinical activity and safety of lenalidomide in patients with mantle-cell lymphoma refractory to bortezomib.

11. Wang M, Fayad L, Wagner-Bartak N, Zhang L, Hagemeister F, Neelapu SS, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. Lancet Oncol. 2012;13(7):716-23.
12. Trneny M, Lamy T, Walewski J, Jurczak W, Belada D, Mayer J, et al. Phase II randomized, multicenter study of lenalidomide vs best investigator's choice in relapsed/refractory mantle cell lymphoma: Results of the MCL-002 (SPRINT) study. Blood. Available from: https://ash.confex.com/ash/2014/webprogram/Paper69212.html

*13. Wang ML, Blum KA, Martin P, Goy A, Auer R, Kahl BS, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood. 2015;126(6):739-45.

The pivotal study evaluating activity and safety of Bruton tyrosine kinase inhibitor ibrutinib in relapsed/refractory MCL.

14. Wang ML, Lee H, Chuang H, Wagner-Bartak N, Hagemeister F, Westin J, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. Lancet Oncol. 2016;17(1):48-56.

*15. Hess G, Herbrecht R, Romaguera J, Verhoef G, Crump M, Gisselbrecht C, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol. 2009;27(23):3822-9.

The first randomized phase 3 study evaluating temsirolimus in relapsed or refractory mantle cell lymphoma.

16. Dreyling M, Jurczak W, Jerkeman M, Silva RS, Rusconi C, Trneny M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. Lancet. 2016;387(10020):770-8.
17. Gouill SL, Thieblemont C, Oberic L, Bouabdallah K, Gyan E, Damaj G, et al. Rituximab maintenance versus wait and watch after four courses of R-DHAP followed by autologous stem cell transplantation in previously untreated young patients with mantle cell lymphoma: first interim analysis of the phase III prospective Lyma trial, a Lysa Study. Blood. Available from: https://ash.confex.com/ash/2014/webprogram/Paper69738.html