Manejo del linfoma de células del manto en la era de las terapias diana

Management of mantle cell lymphoma in the era of targeted drugs

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Introduction

Mantle cell lymphoma (MCL) is an uncommon B-cell non Hodgkin lymphoma (NHL) accounting 3% to 6% of all new NHL cases in Western countries each year[1,2]. An annual incidence is 0.5 per 100,000 persons and an estimated prevalence of 3.5/100,000. The median age at diagnosis is 68 years, with a 3:1 male predominance[1,2].

It is a heterogeneous disease, presenting with a course that ranges from indolent and not requiring treatment at diagnosis, to an aggressive disease demanding immediate therapy. The disease is characterized by the translocation t(11;14) that leads to aberrant expression of the cell cycle regulator protein cyclin D1. The diagnosis of MCL is made on a biopsy of a lymph node, tissue, bone marrow or blood phenotype with the typical morphology of monomorphic small to medium sized lymphoid cells with irregular nuclear contours and a characteristic immunophenotype[1,2]. The Mantle Cell International Prognostic Index (MIPI) formulated by the European MCL Network is a useful tool for risk stratification. The management of MCL continues to improve, with the development of new agents and novel therapeutic strategies. Nevertheless, MCL remains an incurable disease, even in younger, fit patients. In the last 20 years, the median overall sur-

vival (OS) of the patients with MCL has improved from less than 2.5 years to more than five years, but for the overall population treated outside of clinical trials, the median OS remains below three years[3]. In recent years, significant progress in treatment outcome has been observed, mainly due to the introduction of more intensive treatment with high doses of cytotoxic drugs.

Frontline therapy for younger, fit patients

Patients who are physically fit and younger than 65 years of age should be treated with a regimen containing high-dose cytarabine (Ara-C) and rituximab with subsequent autologous stem cell transplantation (ASCT)[4,5]. At present, the most widely-used first-line therapy in such younger, fit patients comprises three cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and three cycles of R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin) followed by ASCT[6]. Delarue et al report the results of a phase II trial using a high dose of Ara-C and rituximab as an induction regimen before ASCT in previously-untreated MCL patients younger than 66 years with stage 3 or 4 MCL[6]. Sixty patients received three courses of CHOP, with rituximab in the third one, and three of R-DHAP before transplantation. The overall response (OR) rate was 95% after R-DHAP and 93% after (R)-CHOP, with complete response (CR) rate of 57% after R-DHAP. With a median follow-up of 67 months, median event-free survival (EFS) was 83 months, and median overall survival (OS) was not reached. The five-year OS was 75%.

The European Mantle Cell Lymphoma Network also investigated whether the addition of high-dose Ara-C to immunochemotherapy before ASCT improves outcome in patients aged 65 years or younger with MCL (MCL Younger trial)[7]. Previously untreated patients were randomized to receive either six courses of R-CHOP followed by myeloablative radiochemotherapy and ASCT or six cour ses of alternating R-CHOP or R-DHAP (rituximab plus dexamethasone, high-dose Ara-C, and cisplatin) followed by a high-dose cytarabine-containing conditioning regimen and ASCT. After a median follow-up of 6.1 years, time to treatment failure was significantly longer in the Ara-C group (median 9.1 years) than in the control group (3.9 years) (p=0.038). Several trials have demonstrated that patients with a high MCL MIPI score were more likely to progress and die after ASCT consolidation compared with low-intermediate risk patients. For those patients, novel therapeutic strategies based on targeted drugs are urgently needed. In addition, patients achieving minimal residual disease (MRD)-negative remissions after induction with alternating R-CHOP and R-DHAP therapy achieve significantly longer PFS and OS than patients with an MRD-positive status. For those MRD-negative patients, ASCT consolidation is probably not necessary. In addition, randomized trials have established that maintenance administration of rituximab following R-CHOP induction for two years in MCL patients is associated with increased remission duration and improved outcome[8,9].

Frontline therapy for older, less fit patients

For previously untreated older patients, R-CHOP has become the standard of care[10,11]. However, a recent randomized trial with bendamustine combined with rituximab (BR) induced significantly longer progression-free survival (PFS) than R-CHOP (69.5 months vs. 31.2 months, respectively; $p<0.0001$) [10]. Moreover, BR was also significantly better to lerated. In previously untreated patients, a promising therapeutic choice is the addition of bortezomib to induction chemotherapy[12]. The replacement of vincristine with bortezomib in R-CHOP (VR-CAP) significantly prolonged PFS and improved CR rate when compared to R-CHOP in patients who were ineligible or not considered for bone marrow transplantation were included[11]. In the large phase III LYM-3002 study, patients were randomized to receive six to eight 21-day cycles of R-CHOP or VR-CAP. The VR-CAP regimen consisted of 1.3 mg/m^2 bortezomib IV on days 1, 4, 8, and 11, plus 375 mg/m^2 rituximab, 750 mg/m^2 cyclophosphamide and 50 mg/m^2 doxorubicin, all IV, on day 1, and 100 mg/m^2 prednisone PO on days 1-5. The CR rate was higher in the VR-CAP arm than the R-CHOP arm (53% and 42%, respectively; P=0.007). The VR-CAP regimen also significantly improved PFS when compared to R-CHOP. Median PFS time was 24.7 months for VR-CAP and 14.4 months for R-CHOP (P<0.001). Patients in the VR-CAP arm also demonstrated a longer median treatment-free interval: 40.6 months compared to 20.5 months

for the R-CHOP arm (P<0.001). The median OS was not reached in the VR-CAP arm and was 56.3 months in the R-CHOP arm (P=0.17). In addition, the four-year OS rate was 10% greater in VR-CAP arm (64% for VR-CAP and 54% R-CHOP arm). However, VR-CAP was also associated with more adverse events (AEs). Grade 3 or higher AEs were reported in 93% of patients treated with VR-CAP and 85% of patients treated with R-CHOP. Serious AEs were noted in 38% of patients treated with VR-CAP and in 30% of patients treated with R-CHOP. Thrombocytopenia was also more common in the VR-CAP (72%) arm than in the R-CHOP arm (19%). In the LYM-3002 study, bortezomib dose intensity was the strongest predictor of PFS and OS in newly-diagnosed MCL treated frontline with VR-CAP[13]. The VR-CAP regimen may be an option in patients who are not eligible for transplant and do not have pre-existing peripheral neuropathy. Bortezomib is the first proteasome inhibitor to be approved for MCL in first-line treatment, both in the US and the EU. Lenalidomide is also of value in the frontline treatment of MCL[14]. Clinical trials for untreated MCL based on combinations of the immunomodulatory agent lenalidomide with other agents, including rituximab alone or rituximab and bendamustine, are ongoing (NCT01472562).

Therapy for relapsed/refractory patients

Although several potential therapies exist for relapsed/refractory patients with symptomatic MCL, the outcome is usually unsatisfactory. Promising results have been achieved with a BR regimen in patients with relapsed or refractory disease[15]. More recently, impressive OR and CR rates have been associated with Ara-C combined with BR (R-BAC)[16]. A better understanding of the pathogenesis of this disease has accelerated the development of targeted drugs and improved progress in therapy. Four targeted drugs, bortezomib, lenalidomide, ibrutinib and temsirolimus have showed promising results in relapsed or refractory MCL (**Table 1**)[17-23]. Curren -tly available data indicates that these new targeted drugs can be used alone in relapsed or refractory patients or may be considered in combination with standard immunochemotherapy. Finally, the use of maintenance regimens based on rituximab or bortezomib is also a promising approach in MCL[24,25].

Bortezomib is the first-in-class proteasome inhibitor that has revolutionized the treatment of multiple myeloma (MM) and, more recently, MCL[12]. In 2006, intravenous bortezomib was approved by the US Food and Drug Administration (FDA) for relapsed MCL after one prior therapy[12]. Approval was based on the phase II multicenter PINNACLE trial[17,18], in which the median time to progression (TTP) was found to be 6.7 months, median PFS 6.5 months, median time to next therapy (TTNT) 7.4 months, and median OS 23.5 months, with single-agent IV bortezomib. In another study, 21 patients with relapsed or refractory MCL were given a combination regimen of bortezomib, cyclophosphamide and rituximab as part of a single-arm, prospective, open-label phase II clinical trial[26]: OR was 74% and CR 42% with a median PFS of nine months and OS 36.4 months. A recent study indicates that subcutaneous bortezomib, alone or in combination, is also active and generally well-tolerated in relapsed/refractory MCL, similarly to patients with MM[27].

Lenalidomide has been found to have single-agent activity, even in patients undergoing earlier intensive treatment with advanced-stage disease who had previously received bortezomib[19]. In the phase II MCL-001 (EMERGE) study, 134 MCL patients who had relapsed or progressed after, or were refractory to bortezomib treatment were administered 25 mg lenalidomide orally on days 1 through 21 during a 28-day cycle until disease progression or intolerance[19]. The OR rate was 28% including 7.5% CR. Median PFS was 4.0 months and median OS was 19.0 months. The most common grade 3 to 4 adverse events were neutropenia (43%) and thrombocytopenia (28%). The combination of lenalidomide and rituximab has been also evaluated in relapsed or refractory patients with MCL[12]. In the MCL-002 (SPRINT) phase II randomised study, 254 patients were randomly assigned to receive lenalidomide or an investigator‘s choice of monotherapy[28]. With a median follow-up of 15.9 months, lenalidomide significantly prolonged PFS (median 8.7 months) compared with the investigator‘s choice (median 5.2 months) (p=0.004). Recently, Zaja et al reported the results of a phase II clinical trial evaluating a combination of lenalidomide with BR in second-line treatment of MCL[29]. Rituximab was given at a dose of 375 mg/m^2 on day 8 of cycle 1, and thereafter on day 1, 10 mg lenalidomide daily on days 1-14, and 70 mg/m^2 bendamustine on days 2 and 3 every

28 days. Twenty-three of 42 (55%) enrolled patients achieved a CR at the end of the consolidation phase. Median PFS was 20 months and median OS had not been reached. In February 2013 the FDA approved lenalidomide for the treatment of relapsed/progressive MCL after two prior therapies.

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

Treatment	N	Study phase	Patient characteristics	OR	CR	PFS	OS	Study
VR-CAP vs R-CHOP	243 vs 244	III	Previously untreated	92% vs 89%	53% vs 42%	24.7 m vs 14.4 m	Median not reached vs 56.3 m	Robak et al. 2015[13]
Bortezomib	155	II	Relapsed or refractory	33%	8%	6.2 m	23.5 m	Fisher et al. 2006 (PINNACLE)[17]
Lenalidomide plus rituximab	38	II	Previously untreated	92%	64%	2-year PFS 85%	2-year OS 97%	Ruan et al. 2006[14]
Lenalidomide alone	134	II	Relapsed after or refractory to bortezomib	28%	7.5%	4 m	19 m	Goy et al. 2007 MCL-001 (EMERGE)[19]
Lenalidomide plus rituximab	52	I/II	Relapsed or refractory after 1-4 previous lines of treatment	57%	36%	11.1 m	24.3 m	Wang et al. 2012[20]
Lenalidomide vs best investigator's choice	170 vs 84	II	Relapsed or refractory after median of 2 prior therapies	40% vs 11% (p<0.001)	5% vs 0% (0.043)	8.7m vs 5.2m P=0.004	27.9m vs 21.2m (p=0.52)	Trneny et al 2015 (SPRINT)[27]
Ibrutinib alone	111	II	Relapsed or refractory, 3 median prior therapies	67%	23%	24-m PFS 31%	24-m OS 47%	Wang et al. 2015[21]
Ibrutinib + rituximab	50	II	Relapsed or refractory, 3 median prior therapies	88%	44%	Not reached	Not reached	Wang et al. 2015[22]
Temsirolimus 175/75-mg vs temsirolimus 175/25-mg vs investigator's choice		III	Relapsed or refractory	22% vs 6% vs 2%	1% vs 0% vs 1%	4.8m vs 3.7m vs 1.8m	11.1m vs 8.8m vs 9.5m	Hess et al. 2009[23]
Ibrutinib vs temsirolimus	139 vs 141	III	Relapsed or refractory	72% vs 40% (p<0.0001)	19% vs 1%	14.9m vs 6.2m (p<0.0001)	Median not reached vs 21.3 m (p=0·1324)	Dreyling et al. 2016[30]

Abbreviations: ASCT: autologous stem cell transplantation; m: months; OS: overall survival; R-CHOP: rituximab, cyclophosphamide, doxorubicin; vincristine, prednisone; VR-CAP: bortezomib, rituximab, cyclophosphamide, doxorubicin; prednisone.

Ibrutinib, the Bruton's tyrosine kinase (BTK) inhibitor, is even more active in MCL with excellent tolerability and a modest side-effect profile[21]. In a phase II study with single-agent ibrutinib, 68% of patients achieved an objective response. Interestin gly, 38 (34%) of 111 patients had transient lymphocytosis, similar to patients with chronic lymphocytic leukemia treated with this drug[21]. Ibrutinib in combination with rituximab was also investigated in relapsed or refractory MCL in a phase II trial[22]. Fifty patients received continuous oral ibrutinib at a dose of 560 mg daily until progressive disease or unacceptable toxic effects. Rituximab 375 mg/m^2 was administered intravenously once per week for four weeks during cycle 1, then on day 1 of cycles 3-8, and thereafter once every other cycle for up to two years. At a median follow-up of 16.5 months, 44 (88%) patients responded, including 22 (44%) who achieved a complete response. The combination of ibrutinib and lenalidomide is currently under investigation in previously-treated MCL (NCT02460276). In 2013, ibrutinib was approved by the FDA for MCL patients previously treated with one or more earlier therapies.

Several clinical studies have demonstrated that temsirolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is an active drug when used in monotherapy in previously-treated patients with MCL. In a pivotal multicenter, randomized phase III trial performed in patients with relapsed or refractory MCL, temsirolimus significantly prolonged median PFS in comparison with standard treatment[23]. However, OS was only slightly longer. However, ibrutinib treatment resulted in significant improvement in PFS and better tolerability in comparison with temsirolimus in patients with relapsed or refractory MCL[30]. Temsirolimus has been approved by the European Medicines Agency (EMA) for MCL patients with relapsed or refractory disease.

Preclinical data and early clinical trials suggest that several other agents may have clinical applications in the treatment of MCL in the near future. These drugs are being explored in phase I and II studies and show exquisite promise in MCL. In particular, second-generation anti-CD20 monoclonal antibo dies, including obinutuzumab and ofatumumab, are more potent than the conventionally-used rituximab. The BCL-2 inhibitor venetoclax and the phosphatydilinosytol 3-kinase δ inhibitor idelalisib and second generation BTK inhibitor acalabrutinib showed some activity in MCL[31]. Patients are currently being recruited for a phase I/Ib study of venetoclax combined with ibrutinib in relapsed/refractory MCL (NCT02419560). The next-generation proteasome inhibitor carfilzomib has also demonstrated activity in MCL and is undergoing clinical testing in MCL; moreover, ibrutinib synergizes with carfilzomib and is cytotoxic to carfilzomib-resistant cell lines. Currently, a phase I single-arm safety and dose-finding trial of combined ibrutinib and carfilzomib administration in patients with refractory/relapsed MCL is ongoing (NCT02269085). Acalabrutinib is a highly-selective, potent, covalent inhibitor of BTK with minimal off-target activity observed in pre-clinical trials and high clinical activity in CLL and MCL[32,33]. Acalabrutinib was granted breakthrough therapy designation by the FDA in August 2017 for the treatment of patients with MCL who have received at least one prior therapy based on results from the Phase II ACE-LY-004 clinical trial, which evaluated the safety and efficacy of acalabrutinib in patients with relapsed/refractory MCL who have received at least one prior therapy (NCT02970318).

In the future, the most effective therapy of MCL will most probably be based on combinations of targeted agents, either combined with each other or with chemo-immunotherapy. Several clinical studies are currently ongoing to establish the best combinations of new agents with existing therapies.

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Declaration of interest

The author has no conflicts of interest that are directly relevant to the content of this article.

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