Treatment of mantle cell lymphomas: Updated recommendations of the Belgian Hematological Society 2015

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*On behalf of the BHS Lymphoproliferative Working Party**

Mantle cell lymphoma is a rare B-cell non-Hodgkin's lymphoma characterised by a t(11;14) translocation resulting in overexpression of cyclin D1 and cell cycle dysregulation. Mantle cell lymphoma represents approximately 7-9% of all lymphomas in Europe.[1] Although new treatment regimens have improved the outcomes over the last decades, mantle cell lymphoma is still considered one of the worst prognosis B-cell non-Hodgkin's lymphoma with a median overall survival of less than five years.[2] In September 2014 the Belgian Hematological Society recommendations for the treatment of mantle cell lymphoma were published.[3] Since then, novel therapies such as ibrutinib and bortezomib have been approved by the European Medicines Agency in the treatment of mantle cell lymphoma. We present the new updated recommendations of the Belgian Hematological Society Lymphoproliferative Working Party. For young patients, the first line therapy remains an AraC-containing chemo-immunotherapy followed by high dose chemotherapy and autologous stem cell transplantation. For the main group of elderly patients, chemo-immunotherapy followed by maintenance with rituximab appears to be the gold standard. In relapse we can recommend treatment with BTK-inhibitor ibrutinib as first choice. Temsirolimus is reimbursed as third line treatment. Relapse patients should also be considered for allogeneic stem cell transplantation if eligible.
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Introduction

Mantle cell lymphoma (MCL) is a distinct B-cell non-Hodgkin's lymphoma subtype, characterised by a t(11;14) translocation resulting in overexpression of cyclin D1. MCL is a rare disease, representing approximately 7-9% of all lymphomas in Europe.[1] Although new treatment regimens have improved the outcomes over the last decades, MCL is still considered as one of the worst prognosis B-cell non-Hodgkin's lymphoma (NHL) with a median overall survival of less than five years.[2] The Belgian Hematological Society (BHS) Lymphoproliferative Working Party reviewed the available literature on treatment of MCL to make new updated recommendations on first line and salvage therapy for MCL. The authors are aware that some of the recommended treatment options (such as bendamustine, rituximab (R) and bortezomib) are currently not reimbursed in Belgium.

First line treatment

Localised or indolent disease

A small proportion of MCL (10-15%) display an indolent behaviour. For these asymptomatic, elderly patients 'watchful waiting' could be a good option.[2] Other patients (less than 20%) have limited stage disease at time of diagnosis and could benefit from involved field radiotherapy. A small retrospective study of 26 patients showed an improved progression free survival (PFS) for

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Table 1. Guidelines of the BHS: treatment recommendations for mantle cell lymphoma in Belgium.

Overall recommendations	Category
Inclusion in a clinical trial is advised	
First line treatment	
1. Fit for autologous stem cell transplantation	
• Induction with R-Chemotherapy with high dose cytarabine (e.g. 3x R-CHOP/3x R-DHAP)	I
• Consolidation with high dose chemotherapy and autologous stem cell transplantation	I
• Maintenance? Awaiting results from LyMa trial	
2. Non-eligible for autologous stem cell transplantation	
• 8 x R-CHOP + R maintenance q2months until progression (R not reimbursed)	I
• Alternative: R-bendamustine (not reimbursed), VR-CAP (reimbursement pending)	I
Salvage treatment	
1. Allogeneic stem cell transplantation if eligible	I I
2. If non-eligible for allogeneic stem cell transplantation:	
• Ibrutinib monotherapy at first relapse	I I
• Temsirolimus at second relapse	I
• Alternative: R-chemotherapy (R-Benda, R-DHAP, R-ICE, R-HAD)	I I

Table 2. Categories of evidence level.

Level I: Evidence obtained from at least one properly designed randomised controlled trial
Level II-1: Evidence obtained from well-designed controlled trials without randomisation
Level II-2: Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one centre or research group
Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

patients treated with regimens including radiotherapy (five years PFS 68 versus 11%).[4]

Advanced disease

Eligible for autologous stem cell transplantation

For younger and fit patients (<66 years, transplant eligible) we recommend the use of R-chemotherapy as induction treatment, followed by high dose chemotherapy and autologous hematopoietic stem cell transplantation (SCT). As published in the previous BHS guidelines, there is growing evidence that high dose AraC is probably one of the most important drugs in the treatment of MCL.[3] A large prospective, multicentre, phase III randomised controlled trial (RCT) of the European MCL Network with 455 young patients, showed that in comparison with R-CHOP (cyclophosphamide,

doxorubicin, vincristine and prednisolone) followed by autologous SCT, R-DHAP (dexamethasone, cytarabine, cisplatinum) alternating with R-CHOP followed by autologous SCT significantly increases PFS (3.8 versus 7.3 years) and overall survival (OS) (6.8 years versus not reached).[5] Preliminary results from the LyMa trial showed an improved complete response (CR) rate of 76% after induction with four cycles R-DHAP compared to alternating R-DHAP and R-CHOP.[6] The role of R maintenance after induction with chemo-immunotherapy (CIT) (4 x R-DHAP) and autologous SCT is currently still under investigation in the phase III RCT LyMa trial. An interim analysis showed a significant improvement in three year event free survival (EFS) in the R maintenance group compared to watchful waiting (3-y EFS 88.1% versus 73.4%).[7]

Non-eligible for autologous stem cell transplantation

For the main group of elderly patients, CIT followed by maintenance with R appears to be the gold standard. We note that R is not licensed nor reimbursed in Belgium for the treatment of mantle cell lymphoma. A large RCT from the European MCL Network with 560 elderly MCL patients, showed that induction therapy with R-CHOP (8 cycles/21 days) is superior compared to R-FC (fludarabine, cyclophosphamide, 6 cycles/28 days) in terms of overall response rates (ORR) (86% versus 78%) and 4-year OS (62% versus 47%). Additionally, R-FC was more toxic and had lower compliance rates. This study also demonstrated the benefit of R as maintenance (375 g/m^2 q2 months until progression) after R-CHOP compared to interferon alpha maintenance in terms of PFS (PFS after four years was 58% versus 29%, respectively). Furthermore, there was a significant improvement in four year OS (87% versus 63%) for patients who responded to induction with R-CHOP.[8] Treatment with VR-CAP (R-CHOP regimen, but replacing vincristine with bortezomib at a dose of 1.3 mg/m^2 body surface area) seems to be a good alternative to induction with R-CHOP. In a recently published phase III RCT, 487 newly diagnosed elderly (median age 66 years) MCL patients received VR-CAP or R-CHOP, showing significantly improved PFS (24.7 versus 14.4 months) and a trend towards improved four year OS (64% versus 54%) after VR-CAP induction, but at the cost of increased haematological toxicity.[9] Treatment with bendamustine combinations represents another attractive alternative therapy for elderly MCL patients. R-bendamustine was at least as effective as R-CHOP in a RCT with 94 patients (median PFS 35 versus 22 months) with fewer toxic effects, but a comparable OS.[10] Furthermore, combination treatment with rituximab 375 mg/m^2 (d1), bendamustine 70 mg/m^2 (d2-3) and cytarabine 800 mg/m^2 (d2-4) (RBAC) is highly active, but patients suffered from significant hematologic toxicity.[11] A recent phase II trial (n=57) adopted the RBAC schedule, but lowered the dose to 500 mg/m^2 (RBAC500) with a substantial reduction in toxicity and maintaining excellent responses (ORR 96%, CR 93%, estimated two year OS 83%).[12]

Salvage treatment

Despite the advances in first line treatment, most patients eventually relapse. There is no standard of care in this group. For younger patients allogeneic transplantation must be considered. A recent retrospective analysis showed an overall survival of 46% after two years in patients with relapse after autologous SCT.[13]

At first relapse we can recommend treatment with the BTK-inhibitor ibrutinib. An open label phase II registration trial of ibrutinib in 111 relapsed/refractory MCL patients showed excellent responses (ORR 67% and CR 23%) with durable remissions (PFS 13 months and OS 22.5 months) at a median follow-up of 26.7 months. Approximately one-third of patients remain progression free at 24 months. In addition, ibrutinib showed a favourable safety profile. The most common adverse events (AE) included diarrhoea (54%), fatigue (50%), nausea (33%) and dyspnoea (32%). Grade ≥3 bleeding events were haematuria (2%) and subdural hematoma (2%), but no fatal bleeding events were reported. This study led to the approval of ibrutinib for patients with MCL who have received one prior therapy.[14] It is reimbursed in this setting in Belgium since August 2015.

The mTOR inhibitor temsirolimus is currently approved and reimbursed for treatment of MCL at second relapse. A phase III RCT confirmed the superiority of temsirolimus compared to investigator's choice in terms of PFS (4.8 versus 1.9 months).[15] Results are also promising for temsirolimus in combination with CIT. A phase I/II study explored the combination of bendamustine, rituximab and temsirolimus (BeRT) in fifteen MCL patients, showing promising results (ORR 93% and CR 33%). A phase II trial is ongoing.[16]

The proteasome inhibitor bortezomib has been approved for the treatment of MCL in the United States, in Europe it is only approved as combination regimen VRCAP in first line treatment. A phase II trial with single agent bortezomib in 155 relapsed/refractory MCL patients showed durable responses (ORR 33%, CR 8% and DOR 9.2 months) with manageable toxic effects.[17] The

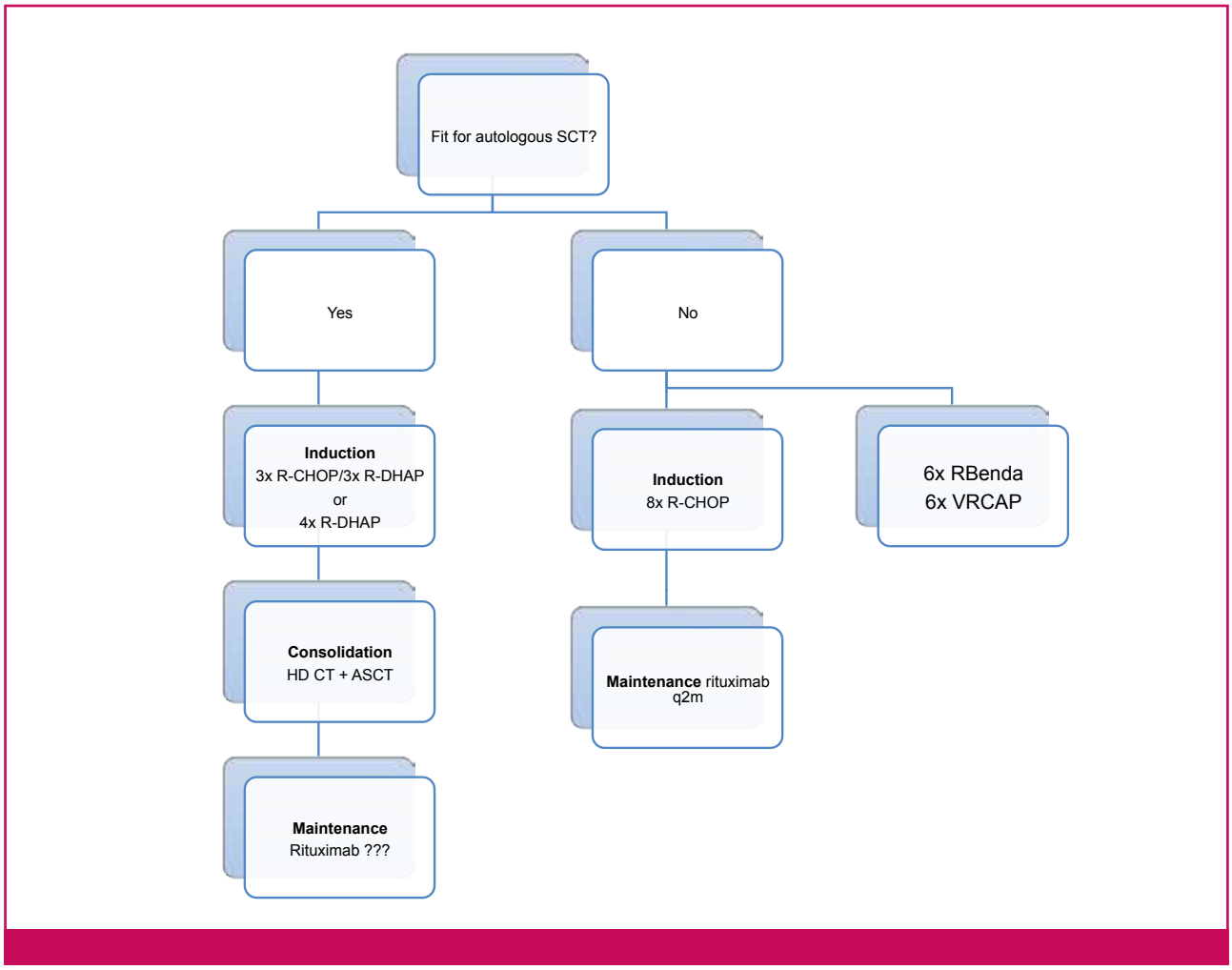

Figure 1. First line therapy.

addition of bortezomib to cytarabine is synergistic in vitro.[18] In a small German study, eight heavily pretreated MCL patients received therapy with bortezomib, high dose cytarabine and dexamethasone with/without rituximab, showing good responses (ORR 50%).[19] The combination is currently being studied in a phase III study of the European MCL Network (MCL 2005-01). Furthermore the combination of bortezomib and CHOP has recently been studied in a phase II RCT in first relapse MCL. Compared to CHOP the combination of bortezomib-CHOP showed improved ORR (48% versus 83%), CR (22% versus 35%) and median OS (11.8 versus 35.6 months).[20]

Several phase II trials investigated the use of single agent lenalidomide in relapsed/refractory MCL. Lenalidomide was well tolerated and active (ORR 28-53%).[21-24] Lenalidomide has been approved for treatment of MCL in the United States, but not in Europe. The combination of lenalidomide and R appears to increase responses with an ORR of 57% (CR 36%) as observed in 52 patients.[25]

Classical CIT such as R-bendamustine, R-DHAP, R-ICE (ifosfamide, carboplatinum and etoposide) or R-HAD (cytarabine and dexamethasone) can be used as an alternative to the novel therapies in relapsed MCL. A recent large multicentre randomised phase III study compared the efficacy and safety of R-Bendamustine and R-Fludarabine. R-Bendamustine was superior to R-Fludarabine in terms of ORR (84% versus 53%), CR (39% versus 16%), PFS (34 versus 12 months) and OS (110 versus 49 months) in the treatment of relapsed indolent or MCL.[26] Which patients should be treated with ibrutinib at first relapse and which patients could benefit from classical CIT remains a difficult question. In cases of early relapse (<24 months) or refractory disease, ibrutinib is probably preferred. Single-agent ibrutinib produces comparable ORR, independent of number of prior therapies or presence of refractory disease. However, less tumour bulk and non-refractory disease were associated with longer PFS and OS.[14] Among the three compounds approved in the United States (bortezomib,

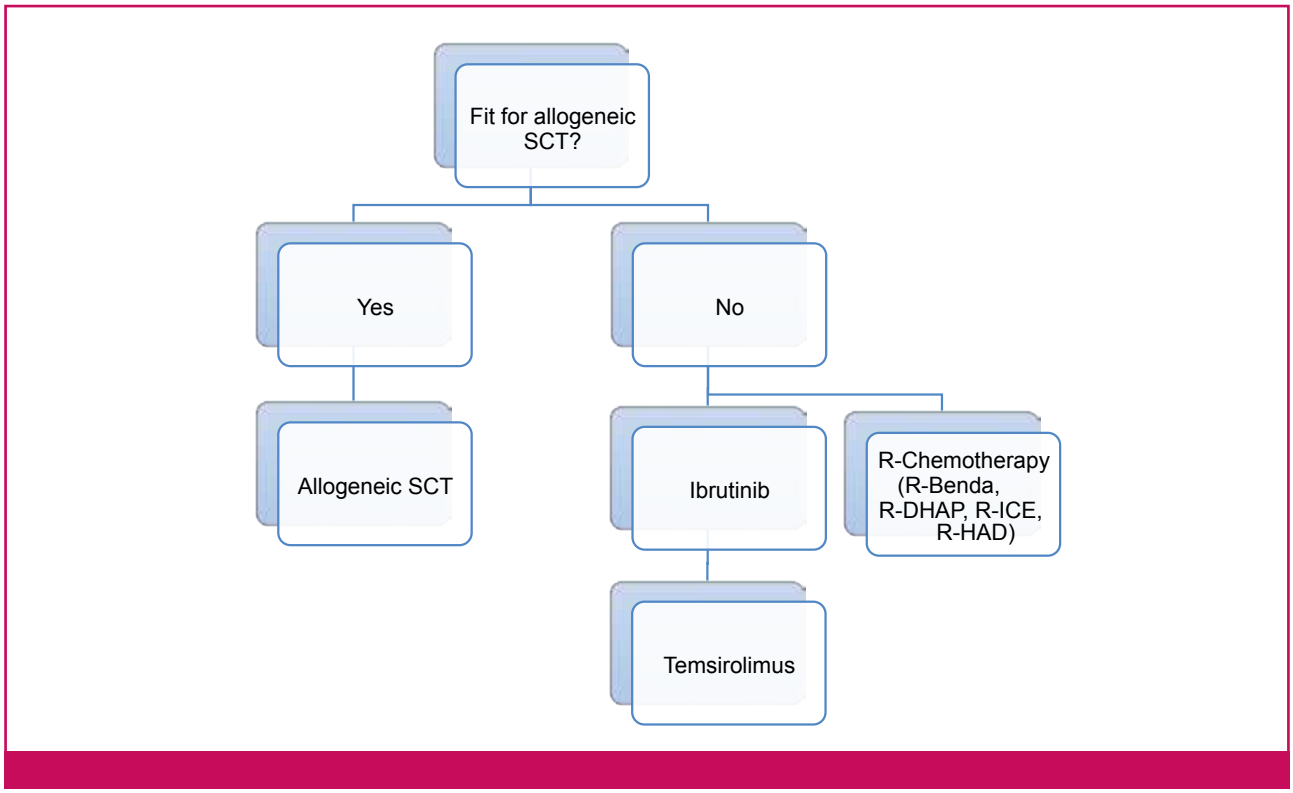

Figure 2. Salvage treatment.

ibrutinib and lenalidomide), ibrutinib has the highest response rate and longest duration of response (no randomised trial has been done).[14,17,21-24]

Conclusion

Mantle cell lymphoma remains a challenging disease. New treatment strategies are being studied in order to improve clinical outcome. Furthermore, novel targeted therapies such as ibrutinib, bortezomib, temsirolimus and lenalidomide have recently been developed and demonstrated excellent clinical activity in MCL patients. Treatment with ibrutinib has now been approved and reimbursed in first relapse in Belgium. In the future, RCTs with novel therapies in combination with classical chemotherapy will provide new treatment strategies.

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Key messages for clinical practice

1. **In young patients, R-chemotherapy including high dose cytarabine followed by high dose chemotherapy and autologous stem cell transplantation is the standard of care.**
2. **In elderly patients, 8 x R-CHOP followed by R-maintenance is the standard of care.**
3. **Ibrutinib monotherapy is recommended at first relapse. Alternatives are classical chemo-immunotherapy e.g. R-Benda, R-DHAP, R-ICE, R-HAD.**
4. **Temsirolimus is reimbursed at second relapse.**

3xDHAP 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. [abstract]. Blood 2012;120(21):151. ASH Annual Meeting Abstracts.

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