Editorial Commentary

How to treat older patients with mantle cell lymphoma in the era of targeted drugs

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About 6% of all B-cell non-Hodgkin lymphoma (NHL) patients demonstrate the subtype mantle cell lymphoma (MCL) (1), with most of these being older people: the median age at diagnosis is 69 to 71 years. The prognosis is worsened by advanced age, poor performance status and the presence of comorbidities, and no curative regimens currently exist (2,3).

The choice of front-line treatment depends on the age, fitness level and comorbidities of the patient. In fit patients usually younger than 65 years, the treatment of choice is cytarabine and rituximab-based induction with subsequent autologous stem cell transplantation (ASCT) (4). However, most patients are older, and usually unfit. For these patients, no standard front-line therapy exists, and a range of treatment approaches are typically used to prolong response durations and overall survival (OS) (*Table 1*). The current standard of care is rituximab-based chemoimmunotherapy followed by rituximab maintenance (5-13). Among the different therapeutic regimens, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and RB (riuximab and bendamustine) are most commonly used for patients unsuitable for intensive treatment.

A large randomized study found R-CHOP followed by rituximab maintenance until progression has been confirmed to be effective and safe for MCL patients 60 years of age or older (5). Patients not eligible for high-dose therapy and ASCT were randomized to six cycles of rituximab, fludarabine, and cyclophosphamide (R-FC) or R-CHOP. Any patients who responded to induction treatment were then randomized to maintenance therapy with rituximab or interferon alpha. Complete response (CR) rates were 40% with R-FC and 34% with R-CHOP and did not differ statistically (P=0.10). However, disease progression was more common with R-FC (14%), than with R-CHOP (5%). After a median follow-up time of 7.6 years, median overall survival (OS) was 6.4 years after R-CHOP and 3.9 years after R-FC (P=0.0054).

Subsequently, a randomized study comparing bendamustine and rituximab (BR) with R-CHOP showed higher CR rate and longer progression-free survival (PFS) for BR, with a side-effect profile similar to R-CHOP. However, the OS was similar in both regimens (9). The combination of lenalidomide with bendamustine and rituximab (LBR) was also investigated in previously-untreated patients with MCL (11,13). In an open-label phase 1/2 trial, 51 treatment-naive patients older than 65 years (median age 71 years) received six cycles of LBR every four weeks for six cycles, followed by single lenalidomide (days 1–21), every four weeks for seven cycles. After six cycles, the CR rate was 64%, and 36% of the patients had negative minimal residual disease (MRD). Median PFS was 42 months, and 3-year OS was 73%. However, severe infections, including opportunistic infections, and high numbers of second primary

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Table 1 Larger studies in previously-untreated MCL patients unsuitable for ASCT

Study	Treatment	Patients, N	Median age (range, years)	ORR (CR)	Median PFS	Median OS
Kluin-Nelemans *et al.* 2020 (5)	R-FC *vs.* R-CHOP	246 *vs.* 239	70 [60–83] *vs.* 70 [61–87]	78 (40%) *vs.* 86 (34%)	26 *vs.* 28 months	3.9 *vs.* 6.4 years
Robak *et al.* 2015, 2018 LYM-3002 (6,7)	R-CHOP *vs.* VR-CAP	244 *vs.* 243	66 [34–82] *vs.* 65 [26–88]	89 (42%) *vs.* 92 (53%)	14.4 *vs.* 24.7 months	55.7 *vs.* 90.7 months
Rummel *et al.* 2013 StiL (8)	BR	46	64 [34–83]	93 (40%)	35 months	NR
Flin *et al.* BRIGHT (9)	BR *vs.* R-CHOP or R-CVP	36	60 [28–84]	94 (50%)	5-year 40%	5-year 59%
Visco *et al.* (10)	RBAC500	57	71 [67–75]	91 (91%)	3-year 76%	NR
Ruan *et al.* (11)	Lenalidomide + Rituximab	38	65 [42–86]	92 (64%)	3-year 80%	3-year 89%
Jain *et al.* (12)	Ibrutinib + Rituximab	50	71 [69–76]	96 (71%)	3-year 87%	3-year 94%

ASCT, autologous stem cell transplantation; BR, bendamustine plus rituximab; CR, complete response; MCL, mantle cell lymphoma; NR, not reached, ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone; R-BAC, rituximab, bendamustine, cytarabine; R-FC, rituximab, fludarabine, and cyclophosphamide; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone.

malignancies were observed, which can limit the use of this regimen.

The VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone) regimen, in which the vincristine in R-CHOP has been replaced by bortezomib, has been increasingly adopted for older MCL patients. The large, randomized LYM-3002 study compared VR-CAP with R-CHOP for previously-untreated MCL patients unsuitable for ASCT (*Table 1*) (6,7). In this study, 487 adult patients were randomized to receive six to eight 21-day cycles of R-CHOP or VR-CAP. The CR rate was significantly higher in the VR-CAP group (53%) than in R-CHOP group (42%) (P=0.007). In addition, PFS was longer in the VR-CAP arm (24.7 months) than in the R-CHOP arm (P<0.001). Median treatment-free interval was 40.6 and 20.5 months, respectively (P<0.001). Most importantly, OS improved by almost three years in VR-CAP group (VR-CAP 90.7 months and R-CHOP 55.7 months, P<0.001). However, hematologic toxicity was more common in patients treated with VR-CAP than with R-CHOP.

More recently, Bruton tyrosine kinase (BTK) inhibitors were introduced for the treatment of B-cell lymphoid malignancies (14). Three of them, ibrutinib, acalabrutinib and zanubrutinib, have been approved by FDA and EMA for the treatment of relapsed or refractory MCL (*Table 2*) (15,18,19). However, these targeted drugs have been used much less in the front-line treatment of MCL patients than in relapsed or refractory patients. Jain *et al.* reported the results of a phase 2 study with a chemotherapy-free combination containing ibrutinib and rituximab in 50 older, previously-untreated patients with MCL (12). Ibrutinib was given with rituximab for two years. The median age of the patients was 71 years (range, 69–76 years). Of the patients, 16% demonstrated a high-risk simplified MCL international prognostic index. Low (<30%) Ki-67% was noted in 38 patients (76%) and moderately high (≥30–50%) in 12 (24%). However, high risk patients with Ki-67% ≥50% and blastoid morphology were not included into the study due to probability of the lower activity of BTK inhibitor in this patient population. The overall response (OR) rate was 96% including 71% CR. The 3-year PFS was 87% and OS 94%. However, neither median PFS nor OS were reached, and no deaths were observed during the study. Treatment was well tolerated. Grade 3 or higher cytopenia was observed in less than 5% of patients, and hospitalization for infections was noted in 10%. The results indicate a lower rate of myelosuppression and risk of hospitalization for infections than previously found for

Table 2 Characteristics of BTK inhibitors active in MCL

Drug (reference)	Characteristics	T1/2 (hours)	IC50 (nM)	Dosing	Clinical trials in MCL	Approval for MCL
Ibrutinib (PCYC-1102) (15)	Covalent irreversible C481	4–8	0.5	420 mg	Wang *et al.* 2013 (15) – RR, Ibrutinib, phase 1/2 BRUIN study; Jain *et al.* 2022 (12) – TN, Ibrutinib + Rituximab, phase 2; Maddocks *et al.* (16) – RR, Ibrutinib + Rituximab + Bendamustine, phase1/1b; Tam *et al.* 2018 (17) – RR; Ibrutinib + Venetoclax phase 2	FDA RR 2013; EMA RR 2014
Acalabrutinib (ACP-196) (18)	Covalent irreversible C481	0.9	5.1	100 mg twice a day	Wang *et al.* (18) – RR, Acalabrutinib, phase 2, ACE-LY-004)	FDA RR – 2017; EMA RR – 2020
Zanubrutinib (BGB-3111) (19)	Covalent irreversible C481	2–4	0.5	160 or 320 mg twice a day	Song *et al.* 2020 (19) – RR Zanubrutinib, phase 2	FDA RR – 2019; EMA RR – 2020
Orelabrutinib (ICP-022) (20)	Covalent irreversible C481	~1.5–4 h	1.6	150 mg	Song *et al.* 2020 (20) – RR, phase 2	Approval for RR MCL in China – 2020; FDA granted for RR MCL – 2021
Tirabrutinib (ONO/GS- (21,22)	Covalent irreversible C481	NA	5.6	80 mg	Rule *et al.* 2020 (21) – RR, Tirabrutinib, phase 2; Walter *et al.* 2016 (22) – RR, Tirabrutinib phase 1	No approval
Pirtobrutinib (LOXO-305) (23)	Non-covalent reversible	NA	0.85	200 mg	Mato *et al.* 2021; (23) – RR, Pirtobrutinib, phase 1/2 – BRUIN study.	No approval
Nemtabrutinib (ARQ 531) (24)	Non-covalent reversible	NA	0.85	65–100 mg	Woyach *et al.* 2019 (24) – RR, phase 1	No approval

BTD, breakthrough therapy designation; BTK, Bruton's tyrosine kinase; EMA, European Medicines Agency; FDA, Food and Drug Administration; IC50, half-maximal inhibitory concentration; MCL, mantle cell lymphoma; NA, not available; RR, relapsed and refractory.

chemoimmunotherapy or lenalidomide combined with rituximab. However, atrial fibrillation (AF) due to ibrutinib therapy was common. Grade 3 AF was noted in 11 (22%) patients. These results indicate that ibrutinib combined with rituximab is an effective and well-tolerated treatment for older patients with MCL. However, further studies are needed to confirm that the regimen is equal to, or better than, standard immunochemotherapy in this patient population.

BTK inhibitors are commonly used in patients with relapsed and refractory MCL (*Table 2*). In a phase 2 study, ibrutinib was used in 111 patients with relapsed or refractory patients with MCL. In this study, OR was 68%, including 21% CR, median PFS 13.9 months and median OS was not reached (15). Even better results were obtained in phase the 1/1b study when ibrutinib was combined with BR in previously-untreated and relapsed refractory patients, including 17 MCL patients (16). In this study, OR was noted in 16 (94%) including CR in 13 (76%) patients. In a phase 2 trial, ibrutinib was combined with rituximab in a relapsed/refractory setting. Most patients were older (median age 67 years) and heavily pretreated. At the median follow-up 47 months, 29 patients (58%) achieved CR and 12 were on treatment. Median PFS was 43 months and the median OS has not been reached. However, patients with blastoid morphology, a high-risk MCL International Prognostic Index score and high Ki67% had shorter survival. In addition, combined treatment with the BCL-2 antagonist venetoclax and ibrutinib showed significant activity in patients with MCL (17). However, a randomized comparison with standard therapies is needed before this therapy can be included alongside other regimens for previously-untreated older patients with MCL.

The second-generation BTK inhibitors acalabrutinib and zanubrutinib were also investigated in relapsed and refractory MCL (18,19). These agents are more selective

and less toxic than ibrutinib, due to their lower off-target activity. In a phase 2 study, 124 pretreated patients received acalabrutinib monotherapy (18). An ORR rate of 81% and CR of 40% were achieved, with median PFS of 22 months. As expected, acalabrutinib was better tolerated than ibrutinib in similar studies, with AF observed in 2.4% of patients and hypertension in 4.0%. Zanubrutinib was investigated in 86 patients with relapsed or refractory MCL in a phase 2, single-arm study (19). After a median follow-up of 18.4 months, the OR rate was 84% and CR rate 68.6%. Median PFS was 22.1 months. Treatment was well tolerated, with neutropenia (19.8%) and lung infection (9.3%) as the most common grade ≥3 adverse events (AE). Major bleeding events were observed in three patients and no AF was noted. However, no randomized trials comparing efficacy and safety of ibrutinib, acalabrutinib and zanubrutinib, in relapsed/refractory patients with MCL have been reported so far, and it is unclear whether one agent is more active and better tolerated than another. In addition, several irreversible and reversible BTK inhibitors have been developed recently, and clinical trials in MCL have been initiated (*Table 2*) (20-24).

In conclusion, ibrutinib and other BTK inhibitors have become the standard treatment in relapsed and refractory MCL. Indeed, Jain *et al.* (12) indicate that ibrutinib combined with rituximab is also an active and well-tolerated up-front treatment in older patients unsuitable for intensive chemotherapy and ASCT. However, further randomized trials on larger number of patients are needed to confirm the advantage of this targeted treatment over standard immunochemotherapy in previously-untreated MCL patients.

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