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REVIEW ARTICLE

CAR-T therapy in mantle cell lymphoma: a literature review

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Abstract

Mantle cell lymphoma (MCL) is a rare lymphoma derived from mature B cells with the presence of translocation t(11;14) resulting in cyclin D1 overexpression, with a variety of clinical symptoms and a variable course. Despite better understanding regarding its pathogenesis, and the use of aggressive immunochemotherapy with autologous bone marrow transplantation, this disease is still considered incurable, with median overall survival of five years. Patients with refractory and relapsed disease have a poor prognosis and the traditional cytotoxic therapy is insufficiently effective in this group of patients. New therapies such as Bruton's tyrosine kinase inhibitors (BTKi), B-cell lymphoma-2 (BCL-2) inhibitors, and immunomodulatory drugs have produced high response rates, but the duration of response is limited, and patients have another relapse diagnosed.

Recently adopted immunotherapy with chimeric antigen receptor (CAR) T-cells directed against the CD19 receptor on lymphoma cells seems to be promising in the population of refractory and relapsed MCL patients. In July 2020, the United States Food and Drug Administration approved brexucaptagene autoleucel CAR-T product for patients with MCL after two lines of therapy and treatment with Bruton kinase inhibitors. In this review, we briefly discuss the treatment options in patients with refractory and relapsed MCL, focusing on BTKi treatment as the targeted therapy required before CAR-T treatment. We summarize our knowledge of CAR-T cell therapy for MCL in clinical trials and real-world clinical practice, and consider the place of CAR-T in future MCL therapy.

Key words: mantle cell lymphoma, CAR-T, refractory, non-Hodgkin lymphoma, cellular therapy

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Introduction

Mantle cell lymphoma (MCL), a B-cell neoplasm, accounts for 2.5–6% of newly diagnosed non-Hodgkin lymphomas (NHL) and is characterized by a broad spectrum of clinical presentations and a highly variable course [1, 2]. MCL is much more frequent in men than in women (3:1) and median age at diagnosis is 60–70 years. The disease is incurable in most patients, and median overall survival is five years [2]. The primary genetic lesion is a translocation t(11;14)(q13;q32) that leads to overexpression of cyclin D1 (*CCND1*) and deregulates cell cycles with uncontrolled cell proliferation [3, 4]. According to the World Health Organization (WHO) 2016 updated classification for lymphoid malignancies, MCL is divided into two distinct entities based on different molecular pathways accounting for the pathogenesis [3, 5]. The nodal subtype occurs in 80-90% of cases, and is characterized by unmutated immunoglobulin heavy chain variable region genes (*IGHV*), sex determining region Y-box 11 (*SOX11*) overexpression, and generally higher genomic instability resulting in an aggressive clinical course. Most patients have advanced disease with nodal and/or frequent extranodal involvement including infiltration of bone marrow

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(50–80%), blood (50%), liver (25%) and gastrointestinal tract (20–60%) [1, 5, 6].

Conversely, the non-nodal, leukemic variant (10–20%) of MCL is characterized by more genetic stability, mutated *IGHV*, *SOX11* negativity and indolent biological behavior. Patients present leukemic disease with leukocytosis, splenomegaly (40%), and bone marrow infiltrations, and the disease resembles chronic lymphocytic leukemia in its course. Acquired genetic lesions during the course of the disease might affect clinical behavior and worsen the prognosis [1, 5].

There are many factors that predict survival outcomes in MCL. The classic clinical factors for a poor outcome include older age, male sex, elevated lactate dehydrogenase, poor Eastern Cooperative Oncology Group (ECOG) performance status, elevated leukocyte count in the blood, advanced stage, and membership of a high-risk group according to the MCL International Prognostic Index (MIPI) [7]. A strong biological prognostic factor is the degree of tumor proliferation expressed as Ki-67 proliferation index [8]. The Ki-67 proliferation index enhances the value of the MIPI score. Other important biomarkers comprise the blastoid variant of MCL, complex karyotype, *TP53* mutation or overexpression, and *MYC* translocation or overexpression [1, 9].

Standard therapeutic approaches for MCL include cytotoxic and anti-CD20 monoclonal antibody immunotherapy. Induction chemotherapy with high-dose cytarabine consolidated with myeloablative chemotherapy and autologous stem cell transplantation (auto-SCT) has been adopted as management for young, fit, transplant-eligible patients [1, 10]. Older patients have been offered less intensive treatment including R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone), RB (rituximab, bendamustine), and VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisolone) [11]. Rituximab maintenance has improved overall survival (OS) and progression-free survival (PFS) post first line treatment. It is recommended to apply it for three years after auto-SCT consolidation in transplant-eligible patients, and after induction therapy in patients who are unfit for auto-SCT [12]. Chemo-free therapy with lenalidomide, Bruton's tyrosine kinase inhibitors (BTKi), and monoclonal antibodies has been tested in a few studies and offers great promise as future standard first line therapy, but its application is still at the clinical trial stage [13–15].

Despite improvements in the efficacy of the first line therapy, MCL is still an incurable disease, and nearly all patients will eventually relapse whatever their initial treatment. Median time to relapse ranges from less than two years (after less intensive therapy or in high-risk patients with *TP53* mutation) to more than 10 years after highly intensive cytarabine-based treatment. Patients with refractory and relapsed disease have a poor prognosis, and traditional cytotoxic therapy is insufficiently effective in this group of patients. Most patients require multiple lines over their disease course. Retreatment with chemotherapy is associated with a progressively lower response rate, shorter remission, and increased hematological toxicity [16].

In recent years, novel target therapies have shown promising activity in the relapsed/refractory (R/R) cohort. Ibrutinib, acalabrutinib, zanubrutinib, lenalidomide and bortezomib have achieved approval from the Food and Drug Administration (FDA) for relapsed and refractory MCL [17]. In July 2020, adoptive chimeric antigen receptor T-cell (CAR-T) immunotherapy with brexucabtagene autoleucel (brexu-cel), a CD19-directed genetically modified autologous T-cells for MCL treatment, received approval from the FDA [17]. This therapy has been intended for adult patients with R/R MCL who have received at least two lines of treatment, including at least one with BTKi.

In this review, we briefly discuss treatment options for patients with refractory and relapsed MCL lymphomas, focusing on BTKi as the targeted therapy required before CAR-T therapy. We summarize the existing data on CAR-T cells treatment as a new immunotherapy for MCL, and we discuss how CAR-T therapy fits into the current MCL treatment landscape.

Bruton tyrosine kinase inhibitors

Bruton's tyrosine kinase (BTK) is an enzyme involved in signal processing after the activation of B-cell receptor (BCR) on lymphoma cells. BTK's role is to participate in the differentiation, proliferation and survival of B lymphocytes and lymphoma cells. An adequate control of BTK activity is important for B-lymphocyte homeostasis. Uncontrolled activation of BTK and, indirectly, the nuclear factor kappa B (NFKB) pathway, is essential for lymphoma cell survival [18]. As mentioned above, three BTKi have been approved by the FDA for the treatment of patients with R/R MCL. They have demonstrated durable responses in relapsed and refractory disease settings, and also when MCL presents high-risk features including *TP53* mutations. BTKi have a common mechanism of action: they bind to the cysteine 481 in the ATP domain of BTK leading to irreversible inhibition. They differ in terms of selectivity, pharmacokinetics, toxicity, and dosage. Ibrutinib was the first BTK inhibitor of which the activity was confirmed in studies with refractory and relapsed MCL patients [19]. Three studies were performed: a pivotal phase II study PCYC 1104-CA, the phase II study MCL 2001, and the phase III study MCL 3001 [19–21]. A total of 370 patients with MCL receiving 560 mg of ibrutinib daily were analyzed [22]. Overall response rates (ORR) and complete remission (CR) rates were established for the three studies: 66% and 20%, respectively, with a median PFS of 13 months. Toxicities included diarrhea (40%), cough 22%, nausea 22%, peripheral edema 20%, atrial fibrillation 5%, and bleeding 5%. Ibrutinib is more effective

in the second line of treatment than in subsequent lines, with ORR of 78% and CR of 37% including a median PFS of 22 months for patients receiving second-line, compared to ORR of 69% and CR of 23% with a median PFS of 8 months among patients after two or more prior lines. Ibrutinib has also demonstrated activity in patients who progressed on bortezomib-containing regimens [22].

The second generation BTKi acalabrutinib and zanubrutinib have demonstrated better efficacy and toxicity profiles than ibrutinib. In the phase II multicenter ACE-Ly-2004 study, acalabrutinib demonstrated ORR of 81% and CR of 40% with a median duration of response of 26 months. Only 1.6% of patients required dose reductions and 6.5% discontinued therapy due to toxicity [23]. The activity of zanubrutinib has been shown in two phase II trials: BGB-3111-206 and BGB-3111-AU-003 [24, 25]. ORR was achieved in 84–90% of patients and CR was confirmed in 22–59% of patients. BTKi appears to be more effective in earlier lines if used in R/R disease settings. BTKi has become the preferred class of agents in second line treatment for MCL, but unfortunately these are not reimbursed in Poland.

Patients who relapse after BTKi have a very poor prognosis, with a median OS of 2.9 months. The optimal therapy for that high-risk group of patients is unknown. One treatment option may be immunochemotherapy with rituximab, cytarabine, and bendamustine [26]. This produces a high ORR (83%) but is not sustained (median PFS of 10 months) and can be used as a bridging strategy to other cell therapies.

Other strategies

Other agents such as lenalidomide and bortezomib were also approved by the FDA, but in monotherapy they have proved less effective in relapsed and refractory disease than in untreated MCL patients. FDA approval for lenalidomide is based on the results of the NHL-002, NHL-003, MCL 001 EMERGE and SPRINT studies. Response to treatment ranged from 28–57%, but the rate of CR was only 7.5%, and the median duration of response (DOR), PFS, and OS were 16.6, 4, and 19 months, respectively. The addition of rituximab to lenalidomide allows for a response in 57% (CR 36%) with a median DOR of 18.9 months, a median PFS of 11.1 months, and a median OS of 24.3 months [27]. The activity of bortezomib in MCL has been demonstrated in several studies. Monotherapy with bortezomib allows for an ORR of 41% and a CR of 20% in heavily pretreated patients (phase II PINNACLE study). The median DOR was 9.2 months. The addition of bortezomib to CHOP chemotherapy induced an ORR of 82% in patients with refractory and relapsed MCL. The combination of rituximab, bendamustine and bortezomib results in ORR of 83% and a 2-year PFS of 47% [27]. Venetoclax is a potent, selective inhibitor of BCL-2 whose activity was also demonstrated in 28 patients with MCL: ORR 75%, CR 21%, median PFS 14 months (phase I study). Venetoclax in combination with ibrutinib acts synergistically and induces ORR of 62% and CR of 42% [27]. Other intensively studied therapies include monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, and CDK4/6 inhibitors as a monotherapy or with other active drugs.

Allogeneic stem cell transplantation

Although allogeneic stem cell transplantation (allo-SCT) is a potentially curative treatment, it is not widely used in relapsed or refractory MCL patients [27]. The risks of early mortality (20%), acute graft-versus-host disease (GvHD) (40%) and chronic (30%) GvHD contribute to the choice of this therapy in patients with relapsed after auto-SCT and other targeted therapies [28]. High non-relapse mortality occurs in 10–24% of patients, even with reduced intensity conditioning. The 5-year OS and PFS are 40–60% and 30–50% respectively [29–31]. Most studies have been retrospective and have usually involved a small number of patients. Recent studies have shown that patients undergoing allo SCT therapy have long-term remission, which may suggest curative potential of this therapy [31–33].

CAR-T products in MCL

The first data on CD19 directed CAR-T activity in MCL disease was reported in a phase I/II study in 2016 [34]. Since then, four CD19 targeted CAR-T cell constructs have been approved by the FDA [17]. Three of them are intended for relapsed and refractory aggressive B cell lymphoma after two prior lines of therapy: axicabtagene ciloleucel based on the results of the ZUMA 1 trial [35], tisagenlecleucel based on the JULIET trial [36, 37], and lisocabtagene maraleucel based on the TRANSCEND-011 trial [38]. One CAR-T product, brexucabtagene, was approved for relapsed and refractory MCL based on the ZUMA 2 study [39]. The first promising results of treatment with lisocabtagene in patients with relapsed and refractory MCL have also been published [40]. Due to the short cut-off time of the data, this still requires confirmation in a long-term follow-up.

The major early toxicities following CAR-T therapy include cytokine release syndrome (CRS), macrophage-activation syndrome, immune effector cell-associated neurotoxicity syndrome (ICANs), tumor lysis syndrome (TLS), cytopenias, infections, and cardiotoxicity [41]. Late complications (28 days after infusion) comprise delayed TLS/CRS/ICANs, prolonged cytopenias, B cell aplasia, hypogammaglobulinemia and associated infections [41]. Various toxicity scales are used in the assessment of CRS, but the Lee scale is the most commonly used [42–44]. The 10-point ICE scale — immuno-effector cell encephalopathy has been

used to assess neurotoxicity [44]. Rest toxicity is usually assessed on the Common Terminology Criteria for Adverse Events (CTCAE) or CARTOX — CAR-T therapy associated toxicity scale [43, 44].

Brexucabtagene autoleucel (brexu-cel, Tecartus) is a CD19-directed genetically modified autologous CAR-T immunotherapy approved in July 2020 for adult relapsed and refractory MCL patients. Brexu-cel is a second generation CD19-directed CAR. It comprises an external domain with single-chain variable fragment linked via a hinge to transmembrane domain and two intracellular CD28/CD3ζ domains: CD28 is a costimulatory domain and CD3ζ is a signaling domain [45, 46]. It is transduced into T-cells using a gamma-retrovirus vector [47]. Binding to CD19 receptor on lymphoma cells CAR-T cells stimulates mechanisms of signaling via CD3ζ domain that leads to activate T-cells. CAR-T cells trigger a cascade of cytokines that facilitate neoplasm destruction, and mediate apoptosis of lymphoma through direct release of granzyme B and perforin [48]. The costimulatory domain CD28 improves CAR-T cell expansion, persistence and anti CD19 activity [50].

Brexu-cel has the same CAR construct as axicabtagene autoleucel (axi-cel), the CAR-T approved for aggressive lymphomas. The important difference is to be found in the manufacturing process after collection of autologous mononuclear cells from peripheral blood by leukapheresis [39]. The harvest product is rich in CD4, CD8 and lymphoma cells. During the manufacturing process, it is exposed to magnetic beads that are coated with anti-CD4 and CD8-antibodies to enrich the product with T-cells and remove any CD19 expressing malignant cells [51]. Then the product depleted CD19 cells are cultured with interleukin 2 (IL-2) followed by transduction of the CAR gene with a gamma-retrovirus vector. The CAR-T product is harvested and undergoes quality assurance testing prior to release. Each single infusion bag dedicated to the individual patient contains approximately 68 mL of anti-CD19 CAR-T cells dispersion, yielding a target dose of 2×10^6 viable anti-CD19 CAR-T cells per kilogram of body weight (range 1×10^6 to 2×10^6 cells per kg body weight) with a maximum number of viable anti-CD19-CAR--T cell of 2×10^8 per kg body weight. Before infusion, the CAR-T product must not be irradiated and no leukocyte depletion filter must be used for infusion [52].

The role of brexu-cel for patients with relapsed and refractory MCL was investigated in the multicenter phase II ZUMA-2 trial [39]. This was the first clinical trial with CAR-T in this population. The results of this study have contributed to the approval of brexu-cel by the FDA for patients with relapsed and refractory MCL. The study cohort contained patients who had received up to five prior therapies, with at least one line including BTK inhibitors. Sixty eight of 74 enrolled patients were administered brexu-cel infusion. Median age was 65 (range: 38–79), and high-risk features of disease such as blastoid or pleomorphic morphology, Ki-67 >30%, and *TP53* mutation were reported in 31%, 82% and 17% of patients respectively. Forty two patients (62%) had disease that had not responded to BTKi, and in 18 (26%) patients the relapse occurred during BTKi treatment. Therefore, 88% of the treated patients were considered to have disease refractory to BTKi. Bridging therapy was given to 25 patients, and 75% of them received BTKi, mainly ibrutinib. A primary efficacy analysis showed that brexu-cel induced high incidence of ORR (93%) and CR (67%) in the first 60 assessed patients. Looking at the entire study population, 85% of patients responded to CAR-T infusion with 59% of patients achieving CR. The response to CAR-T administration was fast and it deepened over time. The median time to initial response was 1.0 month (range: 0.8–3.1) and median time to complete remission was three months (range: 0.9–9.3). Over half of the patients who initially had a partial response or stable disease achieved CR with a longer follow up, and 57% of 60 patients were still in remission at 12 months. Minimal residual disease (MRD) was investigated in 29 patients, and 83% of them had no detectable disease four weeks post infusion. 15/19 (79%) had no detectable MRD six months after infusion. The responses to CAR-T were similar among various subgroups. Patients with a high MIPI score had a similar response to those with a low MIPI score (94% vs. 92%). Also, the use of bridging therapy did not affect response to brexu-cel. Follow up ranged between 7–32 months with a median of 12 months, with PFS and OS of 61% and 83% respectively [39].

All 68 patients experienced at least one adverse event of any grade, with adverse events of grade 3 or more in 99% of patients. Most common toxicity was hematological complications (94%) followed by neutropenia (85%), thrombocytopenia (51%), and anemia (50%). In 26% of patients, cytopenia grade 3 was detectable more than 90 days after CAR-T infusion. The next most common adverse events were infections (32%) grade 3 with pneumonia (9%), and cytomegalovirus infection (2%). CRS in any grade and CRS of grade 3 were reported in 91% and 15% of patients respectively. Median time to CRS was two days (range: 1–13), all symptoms of CRS resolved within a median 11 days, and no patient died of CRS. A total of 63% of patients developed neurological events (NEs), but none of them was fatal. NEs of grade 3 or more occurred in 31% of patients, and median time to NE onset of any grade was seven days. A total of 16 (24%) patients who received brexu-cel died, mainly due to progressive disease (21%) or because of grade 5 adverse events (3%) attributed to lymphodepleting chemotherapy [39].

Apart from the ZUMA study, there are some reports of the efficacy and safety of brexu-cel use in MCL patients (*see* Tables I, II) [53–56]. The first report was based on data from the standard of care practice from centers in the US Lymphoma CAR-T Consortium [53]. In this study, a total of 107 patients underwent leukapheresis, and 93 (87%)

Table I. Comparison of efficacy between ZUMA-2 study and other reports

Study [ref.]	Number of patients who received Brexucel	ORR [%]	CR [%]	Median follow-up in months	Median PFS	Median OS
ZUMA-2 [39]	60	93	67	12.3 (7–32)	NR	NR
US Lymphoma CAR-T Consortium [53]	92	88	66	12	NR	NR
US academic center [54]	52	88	69	4.1	NR	NR
DESCART — France [55]	48	87.2	63.8	3.3 (1–10)	6.3 months	NR
European study [56]	28	89	61	5 (1–10)	NR	NR

ORR — overall response rate; CR — complete remission; PFS — progression-free survival; OS — overall survival; NR — not reached

Table II. Comparison of toxicity between ZUMA-2 study and other reports

Study [ref.]	Number of patients who received Brexucel	CRS grade 3 in [%]	ICAN grade 3 in [%]	Neutropenia grade 3 in [%]	Persistent cytopenia +100	TRM in [%]
ZUMA-2 [39]	60	15	31	16	26	3
US Lymphoma CAR-T Consortium [53]	92	8	35	UNK	UNK	UNK
US academic center [54]	52	14	37	37	15	9
DESCART — France [55]	48	8.7	8.7	UNK	UNK	1
European study [56]	28	5	26	15	12	0

CRS — cytokine release syndrome; ICAN — immune effector cell-associated neurotoxicity syndrome; TRM — treatment-related mortality; UNK — unknown

patients were administered brexu-cel. Median age was 67 years (range: 34–89). Looking at the study population, more patients had unfavorable factors such as blastoid or pleomorphic morphology (45%), *TP53* (46%), Ki-67 >30% (77%), high risk MIPI (32%), and central nervous system (CNS) involvement (7%), and 73% of patients would have not met the ZUMA-2 trial eligibility criteria. Prior BTKi treatment had been given for 82% of patients, and refractory disease was reported in 44%. Bridging therapy was applied in 60 (65%) patients, including ibrutinib (45%), venetoclax (23%), chemotherapy (32%), CD20 monoclonal antibodies (43%), and others. Median follow up was three months (range: 0.1–9). At 30 days post infusion, ORR and CR were 86% and 64% respectively.

Interestingly, patients with a high-risk disease feature had high incidences of response and complete remission: the ORR/CR rates were 94%/70% for blastoid/pleomorphic variants, 82%/50% for *TP53* mutation, and 88%/67% for those who did not meet eligibility criteria for the ZUMA study. 3 months PFS was 80.6% and 6 months OS was 82.1%. CRS occurred in 88% of patients, but only 8% had CRS of grade 3. Neurological complications appeared in the same percentage, 58%, of patients as in the ZUMA-2 study, also a grade 3 NAs (33%). The authors confirmed encouraging results in activity and safety of brexu-cel in relapsed and refractory disease in real world practice, especially as 75% of patients would never receive CAR-T as participants in the ZUMA-2 study [54].

A second study concerns a safety and efficacy analysis of 52 patients treated with brexu-cel in 12 US academic centers [55]. Median age was 66 (range 47–79): seven patients had a history of CNS involvement, 50% of patients relapsed within 24 months of their initial treatment, all patients had previously received BTKi, and 77% of patients received a bridging therapy mainly including BTKi. The ORR and CR were 88% and 69% respectively. With a median follow up of 4.2 months, the estimated 6 months PFS and OS rates were 82.7% and 89% respectively. Patients with CNS involvement had no relapse at the final follow up. The incidence of adverse events were similar as in previously described reports: CRS occurred in 84% of patients with 10% grade 3, median time to CRS onset to max grade was five days (range: 0–10), and neurotoxicity of any grade developed in 57% of patients with a median time to onset of seven days. In 31% of patients, NEs of grade 3 or more were observed. One patient died due to neurotoxicity. Persistent neutropenia and thrombopenia were detectable in 12–15% of patients. Fatal infections occurred months after infusion: septic shock on +40 day and COVID infection on +80 day. Two patients died due to progressive disease. No adverse factors were found for survival in univariate analysis [54].

We now turn to two works from European centers. The first report was from DESCAR-T, the French national registry for all patients treated with CAR-T, and contained real-life data regarding the use of brexu-cel in relapsed and refractory MCL in France [55]. A total of 57 patients were

registered, and CAR-T cell product was ordered for 55 patients, but only 47 of them were infused with brexu-cel. Two patients decided against CAR-T. Eight patients did not administer the CAR-T product due to disease progression (three patients), manufacturing failure (three), infection (one) and cardiac disease (one). Most patients were treated with a median three lines of treatment (range: 2–8), and 30% of them presented a high-risk MIPI score. All patients received BTK inhibitors as one line of therapy. Median time between leukapheresis and CAR-T infusion was 56 days (range: 35–134) and up to 87% of patients required bridging therapy. The results of treatment were assessed in 42 patients and were similar to those in earlier studies: ORR in 88% and CR in 61.9% of patients. At 6 months, PFS was 57.9%. CRS and neurotoxicity were observed in 79% and 48.9% respectively. Up to 30% of patients required intensive therapy, although CRS and neurological events of grade 3 occurred in 8.5%.

The second report was from seven sites in three European countries [56]. Twenty eight patients were included, but only 19 (68%) received a CAR-T cell infusion. Median age was 67 (range: 51–78) and 89% were male. Unlike the other report, most of the patients had a high risk Mantle Cell Lymphoma International Prognostic Index (MIPI) score (63%) and required bridging therapy (79%), most patients had progressive (53%) or stable (27%) disease, and only 20% of patients responded to bridging therapy. There was a high incidence of ORR (89%) and CR (68%). A median PFS and a median OS were not reached, and at 6 months PFS and OS were 91% and 83% respectively. The toxicity did not differ from other reports, 89% of CRS and 63% of neurotoxicity of any grade, with low incidence of CRS grade 3 or more (5%) and neurotoxicity grade 3–5 (26%). Two patients required treatment in the Intensive Care Unit [56].

In summary, all reports have confirmed the high efficacy of CAR-T therapy with a high percentage of CR in a population with a very poor prognosis (Table I). The median time of follow up in all studies is very short. Toxicity is manageable and acceptable with a low incidence of grade 3 CRS (Table II). The results of all reports require the confirmation to be found in a longer follow up [39, 53–56].

Lisocabtagene maraleucel (liso-cel) is a another CD19-directed genetically modified autologous cellular immunotherapy provided as a defined composition of CD4+ and CD8+ CAR-T cells. CAR is constructed from extracellular FMC63 monoclonal antibody-derived single chain variable fragment, immunoglobulin G4 hinge region, CD28 transmembrane domain, and intracellular 4-1BB (CD137) co-stimulatory domain and CD3ζ signalling domain [45, 57]. During the manufacturing process of liso-cel, CD4+ and CD8+ are separated from the leukapheresis product and independently activated, expanded and administered as two separate infusions at equal target doses of CD^8 and CD^4 CAR-T [57, 58]. Separate activation of CD4 and CD8 cells allows liso-cel to be administered as a defined product, and reduces the dose variability of CD4 and CD8 components. A single dose of liso-cel contains 50–110 × 10^6 CAR-T-positive T-cells. In addition to CAR, genetically modified CD4 and CD8 cells coexpress a non-functional epidermal growth factor receptor that can serve as a surrogate for CAR expression. CAR binding to CD19 expressed receptors on the lymphoma surface, and normal B cells that induce activation and proliferation of CAR-T, release of proinflammatory cytokines and cytotoxic killing cells. The 4-1BB signalling enhances the expansion and persistence of liso-cel [50, 59].

Impressive results on the clinical activity of liso-cel in patients with R/R MCL who attended the ongoing phase I TRANSCEND-NHL study (NCT 02631044) were presented to the American Society of Hematology (ASH) annual meeting in 2020 [40]. Forty one patients had undergone leukapheresis, but only 32 received liso-cel, at a dose level of 50 × 10^6 (n = 6), or at a dose level of 100 × 10^6 CAR-T cells. Median age for 32 patients was 67 (range: 36–80). High risk factors for treatment failure such as blastoid morphology, high Ki-67, TP53 mutation, and complex karyotype were found in 37.5%, 72%, 22% and 34% of patients respectively. Most patients had been heavily pretreated with a median three (range: 1–7) prior treatment lines. Twenty eight patients had been treated with BTKi (87.5%), and 11 (34%) had acquired resistance to BTKi. ORR and CR were achieved in 27 (84%), and 19 (59%) patients, but better results were obtained for the higher dose 100 × × 10^6. Treatment-emerging adverse events (TEAE) occurred in 27 (84%) patients. Toxicity occurred more frequently at the higher dose level of liso-cel infusion (100 × 10^6 CAR-T cells). Over 30% of patients had hematological complications such as neutropenia (41%), anemia (34%), thrombocytopenia (31%), and prolonged cytopenia grade 3 (34%), CRS occurred in 50% of patients, mainly in 1–2 grade, and only one patient developed CRS grade 4. Median time to onset of CRS was six (range: 2–10) days. Nine patients (28%) developed neurological events (NE) with one third grade 3; no NEs grade 4–5 were reported. Median time to NE onset was eight days (range: 2–25). Serious TEAEs grade 5 occurred in two patients, i.e. tumor lysis syndrome and cryptococcal meningoencephalitis. We are awaiting final results that will confirm these findings [50].

Little is known about the long-term efficacy and safety with 4-1BB based CAR-T cells in MCL. Promising results were reported in three high risk patients with relapsed and refractory MCL. All three achieved complete remission and remained in CR during a follow up of 25–34 months. Long-term B cell depletion was observed in two patients, and no recovery of serum immunoglobulin was observed in two patients. However, they did not develop any serious infections [60].

In the above studies, the main emphasis was on toxicity and response according to the Lugano criteria. A work focused on the eradication of minimal residual disease (MRD) was presented by Chinese researchers from the Shenzhen center (NCT0385786) [61]. Two patients, including one with MCL disease with MRD presentation, were administered anti-CD19 scFv TCRz cells: 41BB CAR-T. Before the administration of cells, in the patient with MCL the presence of genetic abnormalities such as TP53, ATM and NOTCH were found. One month after the administration of CAR-T cells in the next-generation sequencing (NGS) test, no genetic changes were found, TP53 negativity was confirmed on day 180 after the infusion. At the end of the observation, TP53, ATM and NOTCH were still negative. The residual disease was fully eradicated. A second patient with Burkitt lymphoma had also eradicated MRD from bone marrow, confirmed at 42 days post infusion. This report also comprised patients who received CAR-T due to refractory aggressive lymphoma. One patient with MCL was included: he had a high tumor burden, and had received two prior lines of therapy. He achieved metabolic PR in the first course of CAR-T and progressed after 29 months of PR. He was reinfused once more and achieved CR within one year. After 65 months, the patient was in CR. This report confirmed the high activity of CAR-T cells in MCL, and the possibility of eradicating MRD in patients with persistent lymphoma cells [61].

Bispecific CAR-T cells might be another therapeutic option for R/R MCL. Bispecific CAR-T cells aim at two tumor target antigens and could reduce the risk of relapse. The first human phase I dose escalation and dose expansion (NCT03019055) [62] trial with bispecific 4-1BB–CD3ζ anti CD20, anti CD19 (LV20.19) CART included 22 patients with relapsed and refractory NHL (seven with MCL) or chronic lymphocytic leukemia. All patients received 4-1BB–CD3ζ (LV20.19) CAR-T. CRS of grade 3-4 occurred in 5% of patients and neurotoxicity grade 3–4 in three (14%) patients. At 28 days, ORR was 82% with complete remission in 64% of patients. For relapsed and refractory MCL, 4/7 patients achieved a durable response with CR.

The development of allogeneic (allo) CAR-T might be the future direction of cellular therapy for R/R MCL. Off-the shelf allo CAR-T could overcome some disadvantages or limitations of autologous CAR-T such as manufacturing failure or variable T-cell fitness and composition [63]. The T-cells for allo CAR-T cells are yielded from healthy donors. Then, like auto lymphocytes, the allo-T cells undergo a manufacturing process to achieve anti CD19-directed CAR-T. They might be used on demand, also repeating doses if needed. This therapy might become an alternative to autologous CAR-T. The disadvantages of such therapy comprise a risk of GvHD, a rejection risk, an unknown risk of mutagenesis, profound immunosuppression with a high infection risk, and unknown long-term safety [64].

Last year, the American Society of Transplantation and Cellular Therapy (ASTCT), the Center of International Blood and Marrow Transplant Research (CIBMTR), and the European Society for Blood and Marrow Transplantation (EBMT) issued recommendations regarding the role, timing and sequence of autologous hematopoietic cell transplantation (auto-HCT), allogeneic hematopoietic cell transplantation (allo-HCT), and CAR-T cell therapy in patients with newly diagnosed and R/R MCL [65].

For first-line treatment, the consolidation of auto-HCT is the standard of care for patients eligible for this procedure. The role of allo-SCT and CAR-T therapy for *TP53* mutation patients as a first line treatment is not fully established and these therapies should be conducted within clinical trials. The optimal time for CAR-T therapy has not been determined. Due to the cost and availability of other active therapies, it has been recommended to use CAR-T therapy in patients who cannot tolerate or fail BTKi therapy.

In December 2020, the European Medicines Agency (EMA) approved CAR-T therapy for relapsed and refractory patients after two lines of systemic therapy including therapy with at least one BTKi. The ASTCT, the CIBMTR and the EBMT agree with the EMA's recommendation. In patients with the presence of *TP53* mutation, CAR-T therapy may be considered in the second line. The allo-SCT procedure is indicated when CAR-T is unsuccessful or impossible [65].

Conclusion

MCL is a rare, aggressive and incurable disease. Its treatment remains a challenge, especially in patients who have relapsed or refractory disease after treatment with Bruton's tyrosine kinase inhibitors. Allo-SCT remains the only potentially curative treatment option, but due to the high risk of early death posed by acute and chronic GvHD, this treatment is rarely chosen. A promising option is CAR-T cell therapy for MCL patients with disease that is relapsed and refractory to BTK inhibitors. The two CAR-T constructs, brexucaptagene and lisocaptagene, show high activity in this poor prognosis population. Brexucaptegene autoleucel has been approved by the FDA for patients after at least two lines of treatment and BTKi therapy (ZUMA-2 study). Various studies confirm the effectiveness and safety of brexucel. The therapy is also effective in patients with *TP53* mutation. Lisocel is also highly effective and safe in patients with refractory and recurrent MCL, but due to the short follow-up time, this needs to be confirmed in a long-term observation. Due to the cost of CAR-T cells and the availability of other active therapies, it has been recommended to use CAR-T therapy only in patients who cannot tolerate or who fail BTKi therapy. New directions in the development of cell therapies include treatment with bispecific CAR-T or allo-CAR-T.

Conflict of interest
None.

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Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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