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Research Article

In Mantle Cell Lymphoma, Low-Frequency Ppm1d Gene Mutations Linked To Poorer Response To Cd19 Targeted Car-T Cell Therapy.

Katj Sepel[1]*, Lynn Bennger[2], Ulke Bacher[3] and Tomas Pabst[2]*.

[1]*Department for Biomedical Research, University of Bern, 3008 Bern, Switzerland.*
[2]*Department of Medical Oncology, University Hospital Bern, 3010 Bern, Switzerland.*
[3]*Department of Hematology, University Hospital Bern, 3010 Bern, Switzerland.*

Abstract

One uncommon subtype of B-cell lymphoma with a high recurrence rate is mantle cell lymphoma (MCL). In patients with diffuse large B-cell lymphoma (DLBCL) treated with CD19 CAR-T-cell treatment using tisa-cel, somatic mutations in the PPM1D gene were linked to unfavorable outcomes; this finding may also hold true for patients with mantle cell lymphoma undergoing brexu-cel CAR-T-cell therapy.

Methods:This study assessed the impact of low-frequency PPM1D mutations on the safety and effectiveness of brexu-cel CAR-T-cell treatment in the first 16 r/r MCL patients admitted to Inselspital Bern. We also ascertained the prevalence of PPM1D mutations in the peripheral blood cells of MCL patients prior to CAR-T-cell infusion.

Results: With variable allele frequencies (VAF) ranging from 0.011 to 0.099, low-frequency PPM1D gene mutations were present in 25% of cases. The PPM1D mutant (PPM1Dmut) and PPM1D wild-type (PPM1Dwt) groups' clinical responses were compared, and the median progression-free survival was 1 against 32 months (p = 0.07) and the median overall survival was 1.5 versus 27 months (p = 0.001).

Conclusions: According to our research, individuals with mantle cell lymphoma receiving CAR-T-cell therapy may have worse outcomes if they have low frequency PPM1D gene mutations in their peripheral blood cells.

Keywords : *mantle cell lymphoma (MCL); chimeric antigen receptor T-cell (CAR-T); protein,phosphatase Mg/Mn-dependent 1D (PPM1D); wild-type p53-induced phosphatase 1 (Wip1); next-generation sequencing (NGS).*

INTRODUCTION

A unique subtype of mature B-cell non-Hodgkin lymphoma (NHL), mantle cell lymphoma (MCL) [1] has a varied clinical course that includes silent, slow-growing, indolent forms as well as symptomatic, aggressive, fast-growing variants [2]. MCL is frequently a widespread illness with occasionally leukemic appearance, whereas DLBCL typically manifests as a rapidly expanding localized lymphoma [3]. Combination immuno-chemotherapies R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin) comprise the initial treatment. High-dose chemotherapy (HDCT), autologous stem cell transplantation (ASCT), and maintenance therapy with rituximab are the next steps in the treatment process [4-6]. All MCL patients may receive maintenance therapy with rituximab and chemotherapy regimens comprising rituximab and cytarabine, but only transplant-eligible patients may receive consolidation therapy with autologous stem cell transplantation [7].A chimeric anti-CD20 monoclonal antibody called rituximab has demonstrated effectiveness in treating individuals with lymphoid cancers that express CD20 [8]. New treatments that target Bruce's tyrosine kinase have just received regulatory approval [9]. Progression-free survival was considerably increased when ibrutinib treatment was combined with conventional chemommunotherapy [10]. The TRIANGLE research demonstrated improved efficacy when ibrutinib was added to the conventional treatment of younger, transplant-eligible patients with mantle cell lymphoma [11]. As first-line therapy for MCL, combination treatments involving ibrutinib and either the monoclonal antibody

***Corresponding Author:** Katj Sepel, Department for Biomedical Research, University of Bern, 3008 Bern, Switzerland.
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rituximab or the proteasome inhibitor bortezomib are well tolerated and efficacious [12,13], although their duration of action is constrained.The need for new therapeutic choices is highlighted by the fact that a significant percentage of patients may experience repeated relapses, require additional treatment lines, and perhaps develop refractory disease. Chimeric antigen receptor (CAR) T-cell treatments are novel immunotherapeutic approaches for the treatment of relapsed or refractory lympho-proliferative cancers. As of right now, four FMC63-based anti-CD19 CAR-T-cell products have been approved for use in medicine: axicabta-gene ciloleucel (axi-cel, Yescarta©, Kite-Pharma Inc., Santa Monica, CA, USA); tisagen-lecleucel (tisa-cel, Kymriah©, Novartis, Basel, Switzerland); lisocabtagene maraleucel (lisa-cel, Breyanzi©, Juno Therapeutics Inc., Seattle, WA, USA); and brexucabta-gene autoleucel (brexu-cel, Tecartus©, Kite-Pharma Inc., Santa Monica, CA, USA). In 2018, Axi-cel and Tisa-cel received approval for the treatment of DLBCL, transformed follicular lymphoma (trFL), and acute lymphoblastic leukemia (ALL) [14].In 2021, Lisa-cel received approval to treat DLBCL, and in 2024, it was authorized to treat follicular lymphoma. In 2020, Brexu-cel received approval for the treatment of patients with relapsed or refractory MCL [15]. Brexu-cel is an anti-CD19 CAR-T-cell product that uses the same FMC63 design as axi-cel, tisa-cel, and lisa-cel. However, it is made using a different method since it contains the particular T-cell selection and lymphocyte enrichment required for MCL action [16]. With an overall response rate of 93% and lasting remissions in over 60% of responding patients, the phase II ZUMA-2 trial has shown encouraging outcomes with CAR-T-cell therapy in MCL patients who relapsed after taking BTK inhibitors [17]. In a similar vein, we reported that CAR-T-cell therapy was successful and well tolerated in a real-world environment for the first patients treated at our institution, including older and extensively pretreated patients [18]. Relevant toxicities such as cytokine release syndrome (CRS) and immunological effector cell-associated neurotoxicity syndrome (ICANS), which need for anti-inflammatory medication, may be brought on by CAR-T-cell infusion [19,20].

Clonal hematopoiesis (CH) is the term used to describe the proliferation of hematopoietic cell clones, which is accompanied by variations in myeloid and lymphoid clonal hematopoiesis [23,24] and an increase in somatic mutations with age [21,22]. Although other driver genes have subsequently been identified, the most significant CH driver genes are PPM1D, TP53, DNMT3A, ASXL1, and TET2 [25]. Very low variation allele frequency (VAF) TP53 mutations can occur in tumor cell populations, and in the setting of immuno-chemotherapy, the presence of these tiny TP53 clones (VAF < 1.0%) was linked to a lower survival rate [26]. Leukemogenesis, disease progression, response to treatment, including CAR-T-cell therapy, and the effectiveness and toxicity of immunotherapies have all been impacted by the presence of CH, which has been connected to inflammation and cancer [27].There are, however, some findings that show CH in DLBCL patients had no impact on therapy response, prognosis, or toxicity generated by CAR-T cells [28]. Hematopoietic stem cells benefit from mutations in CH driving genes [29]. CH has an impact on stem cell transplant recipients' survival and engraftment. CH was found in more than 30% of lymphoma patients who had received ASCT, with PPM1D being the most common driver change [30,31].

The protein phosphatase Mg2+/Mn2+-dependent 1D (PPM1D, Wip1), which targets the tumor suppressor protein p53 and other proteins involved in DNA damage response, is encoded by six exons of the PPM1D gene on chromosome 17q [32]. Both bone marrow and peripheral blood contain mature cells, such as neutrophils, macrophages, and B and T lymphocytes, as well as hematopoietic stem and progenitor cells that express PPM1D [33]. Compared to other CH-driver gene mutations, the growth of PPM1D mutant clones was more frequent in lymphoma patients receiving R-CHOP [34]. Low-frequency PPM1D gene mutations may have an impact on how well CD19-targeted CAR-T-cell treatment works in DLBCL patients [35]. In the future, powerful and selective allosteric PPM1D inhibitors may be used to treat lymphoma patients with PPM1D mutations [36–38].

This retrospective study aimed to assess the safety and effectiveness of CD19 brexu-cel CAR-T-cells in MCL patients by analyzing the prevalence of low-frequency PPM1D gene mutations in the peripheral blood mononuclear cells (PBMC) of the first 16 r/r MCL patients enrolled for CAR-T-cell therapy at the Inselspital Bern.

RESOURCES AND PROCEDURES

Research in Clinical Practice

Patients receiving brexu-cel CAR-T-cell therapy for relapsed or refractory MCL were examined in this retrospective single-center study conducted at the Inselspital, University Hospital Bern, Switzerland. 16 consecutive patients with relapsed or refractory MCL who were treated with brexu-cel between January 2019 and August 2022 made up the cohort under analysis. Written informed consent was provided by each patient for the use of laboratory and clinical data in study. All patients underwent clinical follow-up at one, three, six, one, one year, and one year after receiving CAR-T-cell therapy. Three and six months after receiving a CAR-T-cell infusion, the patients had PET-CT imaging.

Survival endpoints were the main results. The time between CAR-T-cell infusion and the advancement of the disease, death, or last follow-up was measured by progression-free survival (PFS) and OS.

At the final follow-up on August 18, 2023, PFS and OS were

censored; this date also served as the data cutoff. GraphPad Prism version 10 (GraphPad Software, San Diego, CA, USA) was used to compute survival curves (Kaplan–Meyer) and conduct univariate statistical analysis. Patient age, the international prognostic index (IPI), prior treatment lines, prior radiation, the requirement for bridging therapy prior to CAR-T-cell infusion, remission status at the time of CAR-T-cell treatment, the number of complete responses prior to CAR-T therapy, prior ASCT, lactate dehydrogenase (LDH) prior to lympho-depleting therapy, the occurrence of cytokine release syndrome (CRS), and other parameters were examined for their possible prognostic significance.ICANS, or immune effector cell-associated neurotoxicity syndrome, respectively. An established ddPCR test was used to track the kinetics of CAR-T-cell constructs in peripheral blood [30]. Twenty copies/μg of DNA was the limit of detection. To assess the incidence of CRS and infections, peak blood levels of IL-6 and C-reactive protein (CRP) were measured during the course of treatment [30]. 100 days, six months, and a year following CAR-T-cell infusion were the follow-up dates. Frequencies and percentages were used to summarize the categorical data, while medians and ranges were used to summarize the continuous variables.

Gene Analysis of PPM1D

Mononuclear cells (PBMC) obtained from the peripheral blood of 16 consecutive patients with relapsed or refractory MCL prior to CAR-T-cell infusion, as well as eight people without a history of malignant illness, were used to harvest genomic DNA.The earlier descriptions were followed by bioinformatics and NGS amplicon sequencing [35].

Gene Analysis of CD19

As previously mentioned, exons 3 and 4 of the CD19 gene were amplified and sequenced using genomic DNA [39].

RESULTS

PPM1D Mutation Prevalence in r/r MCL

In peripheral blood mononuclear cells (PBMC) obtained from the 16 patients with r/r MCL who were enrolled in CD19-targeted CAR-T-cell treatment, we used NGS amplicon sequencing to find mutations in exon 6 of the PPM1D gene. A PPM1D gene mutation with a variable allele frequency (VAF) > 0.01 was required for inclusion. With three in-del, one nonsense, and three missense mutations, we were able to identify seven low-frequency PPM1D gene mutations in four MCL patients (4/16, 25%) (Table 1, Figure 1). These samples included two with a single in-del mutation, one with a nonsense and a missense mutation, and one with an in-del and three missense mutations. The PBMC DNA samples had PPM1D mutations with a VAF ranging from 0.011 to 0.099.

Features of the Clinic

Univariate analysis was used to assess the clinical features of the 16 patients with relapsed or refractory MCL who were enrolled in Brexu-cel CAR-T-cell therapy (Table 2). The median age at initial diagnosis was 65 (range: 48–80 years). 88% of individuals had stage IV original illness. The majority of the PPM1Dmut subgroup (n = 4) had a high-risk score on the Mantle Cell Lymphoma International Prognostic Index (MIPI), while the majority of the PPM1Dwt subgroup (n = 12) scored in the intermediate risk category.

In both groupings, the average number of treatment lines was four, and all patients had extensive pretreatment. Additionally, the majority of the PPM1Dmut (3/4, 75%) and a minority of the PPM1Dwt (5/12, 42%) subgroups had received high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation (ASCT). There were discrepancies between the two groupings in terms of complete remissions to prior treatments: seven patients in the PPM1Dwt subgroup (7/12; 54%) had 17 CR, whereas the four patients in the PPM1Dmut subgroup (1/4; 25%) had just one CR.

Most r/r MCL patients received bridging therapy, which include the anti-CD20 monoclonal antibody rituximab in combination with bendamustine, cytarabine, dexamethasone, oxaliplatin (R-BAC, R-DHAO), or the BTK inhibitor ibrutinib, to lessen the lymphoma burden prior to CAR-T-cell infusion. The two groupings had different target antigen variations (p = 0.02): only 25% of PPM1Dwt patients had the CD19 gene single nucleotide polymorphism rs2904880, whereas all PPM1Dmut patients did. When FMC63-anti-CD19-CAR-T-cell therapy was administered to DLBCL patients, the presence of rs2904880 was linked to better treatment results [26].

Clinical Results and CAR-T-Cell Therapy

Before receiving a CAR-T cell injection, one patient with a low-frequency PPM1D mutation passed away from progressive illness. With two days of washout before Brexu-cel CAR-T-cells (day 0), the majority of patients with relapsed/refractory MCL (n = 15) received chemotherapy for three days with 300 mg/m2 cyclophosphamide and 30 mg/m2 fludarabine (day −5 to −3) for lympho-depletion. Univariate analysis was used to assess the specifics of CAR-T-cell therapy and clinical results (Table 3). The median age of patients receiving CAR-T-cell therapy was 72 years old, with a range of 56 to 81 years. For the PPM1Dwt and PPM1Dmutpatient populations, the median time from initial diagnosis and CAR-T-cell infusion was 4.5 and 1.5 years, respectively (p = 0.17). Prior to lympho-depletion, the PPM1Dwt patients had lower median LDH levels (180 U/L vs. 320 U/L, p = 0.04), suggesting variations in the course of the disease.

The illness status of the two subgroups differed at the time of CAR-T-cell infusion (p = 0.009): all patients in the

PPM1Dmut subgroup had progressive disease, whereas the majority of patients in the PPM1Dwt subgroup (58%) had remitting or stable disease.Following CAR-T-cell infusion, a few of individuals experienced low-grade cytokine release syndrome (CRS).Three patients experienced low grade 1/2, three more experienced high grade 3/4, and six patients (40%) experienced immune effector cell-associated neuro-toxicity syndrome (ICANS). Patients with and without mutations in the PPM1D gene had comparable frequencies of CRS and ICANS. Anakinra, dexamethasone, and tocilizumab were used to treat toxicity symptoms. The PPM1Dmut subgroup had higher levels of inflammatory markers such as ferritin, IL-6, and C-reactive protein (CRP) (CRP, 82 mg/L vs. 37 mg/L, p = 0.077; ferritin, 5115 µg/L vs. 1501 µg/L, p = 0.031; IL-6, 639 pg/mL vs. 412 pg/mL, p = 0.77). The PPM1Dmut subgroup had a longer median time to peak IL-6 levels (25 vs. 7 days, p = 0.01). Both categories responded differently to treatment (p = 0.027). Only one patient (33%) of the PPM1Dmut fraction had complete response (CR) six months following CAR-T-cell infusion, whereas CR was common in the PPM1Dwt cohort (92%) three months after CAR-T-cell infusion. Five patients (42%) died with a median survival period of 27 months, and three patients (25%) relapsed within 6 months following CAR-T-cell infusion in the PPM1Dwt subgroup (n = 12). With a median survival period of 1.5 months following CAR-T-cell infusion, the disease advanced in two of the three patients in the PPM1Dmut subgroup, and all of them died. The PPM1D wt and PPM1Dmut MCL patients had considerably different survival times from CAR-T-cell infusion to disease progression and death.In the PPM1Dwt population, the median survival was considerably longer than in the PPM1Dmut population (27 months vs. 1 month, p = 0.001; Figure 2). Nine patients—five PPM1Dwt and four PPM1Dmut—had progressing illness at the time of CAR-T-cell infusion. One of the three PPM1Dmut patients (33%) and four of the five PPM1D patients injected during progressing disease (80%) achieved a full response to CAR-T-cell treatment.

DISCUSSION

16 consecutive patients with relapsed or refractory MCL who underwent brexu-cel CAR-T-cell therapy between 2019 and 2022 were included in our retrospective single-center analysis. The MCL patients in this study had previously received a number of treatment modalities, including consolidation therapy, which included high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT); maintenance therapy, which included rituximab; and first-line therapy, which involved the alternating application of combined immuno-chemotherapies RCHOP and R-DHAP.A new treatment option for relapsed or refractory lympho-proliferative cancers is chimeric antigen receptor (CAR)-T-cell therapy. We reported a markedly worse survival outcome in patients with CH-related PPM1D mutations in a prior study on CD19 targeted CAR-T-cell therapy in r/r DLBCL treated with axi-cel or tisa-cel:p = 0.004 for 5 versus 37 months. Most patients in the PPM1Dmut subgroup experienced only partial remission (60%) and a shorter length of relapse-free survival (3 versus 12 months; p = 0.07), whereas the DLBCL PPM1Dwt subgroup experienced complete remission (56%), the most common treatment outcome [22]. In comparable lymphoma treatment regimens, we expected a correlation between PPM1D mutations and a worse response to CD19 CAR-T-cell therapy. In fact, the PPM1Dmut population's overall and relapse-free survival durations were significantly reduced in r/r MCL patients treated with brexu-cel in this trial (1 versus 27 months; p = 0.001). While 92% of the PPM1Dwt cohort experienced complete response (CR), only 33% of the PPM1Dmut cohort experienced CR following CAR-T cell infusion.Our findings point to a negative prognostic and perhaps predictive effect of PPM1D mutations in brexu-cel-treated individuals with relapsed or refractory MCL. Furthermore, despite variations in the particular therapies, such as T-cell selection and lymphocyte enrichment in brexu-cel production, patients with PPM1D-mutated lymphoma who received FMC-63-based CAR-T-cell therapies showed worse outcomes in both the r/r MCL and r/r DLBCL settings. This suggests a shared association between PPM1D gene mutation and CAR-T-cell response.

In our larger r/r DLBCL cohort [22] and the smaller r/r MCL cohort (this study), 20% of patients with highly pretreated lymphoma had low-frequency PPM1D gene mutations. The bulk of the stop-gain alterations in the six PPM1D exon mutations that were found resulted in intruncated protein products that would not be efficiently targeted for degradation by the cellular APC/C complex [42]. These mutations were similar to those that had been previously reported [18,40,41]. Cancer patients with a history of chemotherapy and radiation exposure have been found to have a higher prevalence of PPM1D somatic mutations [17,21,29,43]. Pre-treatment LDH serum levels and post-treatment serum levelsof inflammatory markers, including CRP, ferritin, and IL-6, differed in the PPM1Dwtversus PPM1Dmut populations with elevated levels in the PPM1Dmut MCL and DLBCLpopulations and negative association with clinical results.Prior research has linked aggressive disease and unfavorable clinical outcomes to elevated ferritin levels in lymphoma patients' sera [44]. Similarly, decreased survival rates in lymphoma patients undergoing anti-CD19 CAR-T-cell therapy had previously been linked to increased CRP blood levels >30 mg/L [10].

The two MCL subgroups, however, had different baseline and pretreatment characteristics. The majority of PPM1Dwt MCL patients had intermediate risk scores on the Mantle Cell Lymphoma International Prognostic Index (MIPI), whereas

the majority of PPM1Dmut subgroup members had high risk scores. As a result, the median time between initial diagnosis and CAR-T-cell infusion was longer for the PPM1Dwt subgroup than for the PPM1Dmut patients. Radiation therapy, HDCT, and ASCT had been performed on the majority of PPM1Dmut patients and the minority of PPM1Dwt individuals. Previous radiation and chemotherapy were associated with CH mutations in the TP53 and PPM1D genes [17]. In myeloma and lymphoma, HDCT with melphalan has been linked to a high direct mutagenic impact [45,46].Furthermore, the two MCL subgroups differed in their illness status at the time of CAR-T-cell infusion. All of the PPM1Dmut MCL patients had progressive disease at CAR-Tcell infusion, in contrast to the majority of MCL patients in the PPM1Dwt subgroup, who either achieved CR or had stable disease (58%). Given that DLBCL patients with bulky disease had worse results than those treated with CAR-T-cell therapy, the disease status at the time of CAR-T-cell infusion may have an impact on the outcome [47]. 92% of PPM1Dwt patients in the small MCL cohort experienced a full response to CAR-T-cell therapy, including four out of five PPM1Dwt patients (80%) who received infusions during the course of their disease, but just one out of the three PPM1Dmut patients (33%).Additionally, the frequency of CD19 rs29048800 varied across the two groupings, with the PPM1Dmut individuals having a higher prevalence. Better treatment outcomes for DLBCL treated with FMC63-anti-CD19-CAR-T-cell therapy were linked to the presence of rs2904880 [26]. Here, CD19 rs2904880 did not improve the result of brexu-cel treatment for mantle cell lymphoma when combined with mutations in the PPM1D gene.

PPM1D inhibitors might offer patients with PPM1Dmut a new therapeutic option in the future. There are small molecule inhibitors of PPM1D, such as the powerful and specific allosteric inhibitor GSK2830371. Furthermore, bispecific antibodies provide a viable and well-tolerated alternative for patients whose mantle cell lymphoma recurs following CAR-T therapy, and other treatments may still be taken into consideration following CAR-T-cell failure.

CONCLUSIONS

According to our data, PPM1D mutations may have a negative prognostic effect on patients receiving brexucel CD19 CAR-T-cell treatment for relapsed or refractory MCL. The results of the CAR-T-cell therapy and the existence of a PPM1D mutation, however, might not be causally associated given the limited number of patients in our study. Other factors, such as increasing disease at the time of CAR-T-cell infusion, a lower frequency of full remissions to prior therapies, and initial adverse risk disease, may be responsible for MCL patients' poor response to brexu-cel therapy. Future analyses of larger cohorts of MCL patients undergoing CD19 CAR-T-cell treatment are necessary to validate the detrimental effects of lowfrequency PPM1D mutations.

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