CAR T-Cell Therapy for CLL: A New Addition to Our Treatment Toolbox?

Lorenzo Iovino, MD, PhD,[1,2] and Mazyar Shadman, MD, MPH[1,2]

[1]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, Washington

[2]Medical Oncology Division, Department of Medicine, University of Washington, Seattle, Washington

Corresponding author:
Mazyar Shadman, MD, MPH
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N; D5-396
Seattle, WA 98109
Email: mshadman@fredhutch.org

Abstract: Treatment of high-risk chronic lymphocytic leukemia (CLL) has undergone a revolution in recent years with the introduction of novel agents. Bruton kinase inhibitors (BTK) inhibitors, such as ibrutinib, acalabrutinib, and zanubrutinib, are effective at controlling CLL in all lines of therapy, including in patients with high-risk features. BTK inhibitors can be used in sequence or in combination with the BCL2 inhibitor venetoclax. As a result, standard chemotherapy and allogeneic stem cell transplant (allo-SCT)—once major treatment approaches in high-risk patients—are used much less commonly in the current era. Despite the outstanding efficacy of these novel agents, a proportion of patients still experience disease progression. Chimeric antigen receptor (CAR) T-cell therapy has received regulatory approval for several B-cell malignancies in which it has shown efficacy, but it remains investigational for CLL. Several studies have shown the potential for long-term remission in CLL with CAR T-cell therapy, with a favorable safety profile compared with conventional approaches. This review focuses on selected literature on CAR T-cell therapy for CLL, including the interim results of key ongoing studies, with an emphasis on recent research.

Keywords
B-cell lymphoma, CAR T cells, cell therapy, CLL

Introduction

The introduction of novel agents for the treatment of chronic lymphocytic leukemia (CLL) has improved clinical outcomes in recent years for patients with high-risk disease. Despite this, CLL remains an incurable disease, and treatment of patients with double-refractory CLL after failure of both Bruton tyrosine kinase (BTK) inhibitors and the BCL2 inhibitor venetoclax (Venclexta, AbbVie/Genentech) is an unmet need.[1-5] Allogeneic stem cell transplant (allo-SCT) is the only potentially curative treatment for CLL, but its use is limited given the high rates of treatment-related mortality and morbidity. Chimeric antigen receptor (CAR) T-cell therapy is now part of standard care for

several lymphoid malignancies but remains investigational for CLL. However, a number of studies have shown the potential for long-term remissions in CLL, with a favorable safety profile compared with allo-SCT. This review focuses on the potential use of CAR T-cell therapy in CLL, including the interim results of notable ongoing studies and future directions.

Clinical Experience With CAR T-Cell Products in CLL

CAR T cells are genetically modified T cells that are forced to express a chimeric receptor designed to recognize an antigen of interest on the surface of tumor cells.[6] CD19 is a surface marker that is expressed on the majority of CLL cells and is the target antigen for the approved CAR T-cell constructs.[7,8] The currently approved CAR T-cell products are autologous, meaning that the T cells are collected from the patients and transfected with the CAR construct. The structure of current CAR T cells includes: (1) a single-chain variable domain of a single-chain variable fragment (scFv) antibody that confers the antigen specificity; (2) a transmembrane domain; (3) a signal transduction domain of the T-cell receptor (TCR), allowing for intracellular activation; and (4) an intracellular costimulatory domain.[9] Recognition of the antigen of interest causes the activation of the CAR T cell through the signal transduction domain of the TCR, leading to T-cell activation and expansion, and to cytokine production.[9] The killing mediated by CAR T cells is both direct and indirect.[10]

The US Food and Drug Administration (FDA) has approved the use of 4 CAR T-cell products as treatment for patients with B-cell non-Hodgkin lymphoma (NHL). All of these products are autologous and target the surface molecule CD19 and differ from each other based on the type of CAR construct and the type of T cells used as a source. Axicabtagene ciloleucel, also known as axi-cel (Yescarta, Kite), consists of an scFv extracellular domain targeting CD19 proteins with CD3ζ signal transduction domain, and a CD28 costimulatory domain.[11,12] Brexucabtagene autoleucel, also known as brexu-cel (Tecartus, Kite), consists of an scFv extracellular domain targeting CD19 proteins with CD3ζ signal transduction domain and a CD28 co-stimulatory domain.[13] Tisagenlecleucel, also known as tisa-cel (Kymriah, Novartis), involves a murine anti-CD19 scFv, a CD8 transmembrane domain, a 4-1BB costimulatory domain, and a CD3ζ signal transduction domain.[14-16] Lisocabtagene maraleucel, also known as liso-cel (Breyanzi, Juno/BMS), consists of a murine anti-CD19 scFv, a 4-1BB costimulatory domain, and a CD3ζ signal transduction domain. It is also derived from CD8+ and CD4+ central memory T-cell subsets in equal ratios.[17,18]

None of these FDA-approved CAR T-cell products have indications in CLL, even though the very first report for proof of concept of CAR T-cell efficacy in B-cell malignancies was in CLL.[19] The modest efficacy of CAR T-cell therapy in initial CLL studies, along with the rapid development of targeted agents for CLL and lack of an immediate need for or interest in an alternative treatment modality for treatment of patients with CLL, likely explains the slow pace of CAR T-cell development for CLL.

In 2020, long-term results became available from a study of axi-cel in 43 patients with relapsed or refractory (R/R) B-cell lymphoma that was conducted by the group at the National Institutes of Health.[20] In this trial, 8 patients with CLL received axi-cel. The median age was 61 years, and the median number of previous treatments was 4. No patients had received previous allo-SCT, and no data were available regarding the previous use of novel agents. The results showed an objective response in 7 patients (88%), with a median duration of response of 82 months. The 5-year overall survival (OS) rate was 100%, and the median event-free survival was 40.5 months. No specific data on toxicities (cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome [ICANS]) were reported. The ZUMA-8 trial was designed to evaluate the safety and efficacy of brexu-cel in patients with R/R CLL (NCT03624036). Results on 15 patients were recently reported at the 2022 American Society of Hematology annual meeting that showed objective responses in 7 of 15 patients as of the data cutoff date, including 2 patients with complete responses (CRs).[21] This is notable, considering that 80% of the patients had received more than 3 prior lines of therapy, 27% had a deletion in 17p, and 47% presented with a complex karyotype. However, adverse events of grade 3 or higher were reported in all patients (100%).

Investigators at the University of Pennsylvania studied an anti-CD19 CAR T-cell therapy (ultimately developed as tisa-cel) in 14 heavily pretreated patients with R/R CLL.[22] The average age was 66.9 years, and patients had received a mean of 5.3 previous lines of treatment. Six patients (43%) had a *TP53* aberration. An overall response occurred in 8 of 14 patients (57%), with 4 CRs and 4 partial responses (PRs). Responses were durable in most patients, with remission lasting longer than 10 years in the first 2 patients treated. Nine patients (64%) developed cytokine release syndrome of any grade, including all 8 patients who showed signs of response. Measurable residual disease (MRD) was not detectable in the bone marrow using next-generation sequencing in patients who achieved a CR, suggesting that disease eradication may be possible in some patients with advanced CLL.

Table 1. Selected Studies Using CAR T-Cell Therapy for Chronic Lymphocytic Leukemia

Study	University of Pennsylvania[23]	Fred Hutchinson Cancer Center[24]	TRANSCEND 004[25]	ZUMA-8[21]	Fred Hutchinson Cancer Center (+ibrutinib)[33]
Target costimulatory domain	CD19/4-1BB	CD19/4-1BB	CD19/4-1BB	CD19/CD28	CD19/4-1BB
N	32	24	23	15	19
LD with Cy-Flu (%)	62%	87%	100%	100%	100%
Del(17p)/*TP53* mut	28%	58%	96%	27%	74%
Prior BTKi	28%	100%	100%	100%	100%
BTKi-refractory	NR	79%	74%	NR	94%
ORR	44%	74%	82%	47%	83%
CR	28%	21%	45%	13%	22%
CRS, all grades	59%	83%	74%	80%	74%
CRS, grade >3	11%	8%	9%	7%	0%
ICANS, all grades	25%	33%	39%	73%	26%
ICANS, grade >3	9%	25%	21%	20%	26%
OS	64 mo	NR	NR	NR	64% at 1 y
PFS	1 mo	8.5 mo	1 y	NR	38% at 1 y

Allo-SCT, allogeneic stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; CRS, cytokine release syndrome; Cy/Flu, cyclophosphamide/fludarabine; del, deletion; ICANS, immune effector cell-associated neurotoxicity syndrome; LD, lymphodepletion; mo, month; mut, mutation; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; uMRD, undetectable minimal residual disease; y, year.

The median OS was 29 months, and the median progression-free survival (PFS) for treated and evaluable patients was 7 months.

The University of Pennsylvania group also published the long-term outcomes of a randomized trial comparing 2 dose levels of a CD19-targeted CAR T-cell therapy in a cohort of patients with relapsed CLL.[23] Various types of lymphodepleting chemotherapy were used. More than one-quarter (28%) of the patients were at high risk for *TP53* aberration, 28% of the patients had prior exposure to BTK inhibitors, and 3% of the patients had prior exposure to venetoclax. The overall response and CR rates were 44% and 28%, respectively. Achievement of a CR was an important predictor of both PFS and OS. The CR rate was 59%, and the rate of ICANS was 25%.

The Fred Hutchinson Cancer Center group treated 24 patients using a 4-1BB CD19-targeted CAR T-cell therapy in a cohort of 24 patients previously exposed to ibrutinib (Imbruvica, Pharmacyclics/Janssen), of whom 25% were also refractory to venetoclax.[24] Among 19 patients who received cyclophosphamide and fludarabine for lymphodepletion and who underwent restaging, the overall response rate (ORR) and CR rate at day 28 were 74% and 21%, respectively. Having a high tumor burden and a lower number of prior treatments were associated with a higher likelihood of response. Interestingly, 88% of patients obtained undetectable MRD (uMRD) by flow cytometry, and 58% of those patients were also negative at the molecular level by next-generation sequencing. Investigators reported a strong correlation between the achievement of uMRD by next-generation sequencing after treatment and PFS (not reached vs 8.5 months, respectively).

The updated results of the TRANSCEND-CLL-004 trial using liso-cel were recently published.[25] A total of 23 patients were treated in the monotherapy cohort, of whom 11 had previously progressed on BTK inhibitors and venetoclax (double refractory). The researchers reported an ORR of 82%, with a complete remission/complete remission with incomplete blood count recovery rate of 45%. The response rates also were high in the subgroup of patients who were in progression after BTK inhibitors and venetoclax. At 12 months, half of the responses were durable, and 2 of the responders progressed beyond 12 months. Failure to achieve uMRD after CAR T-cell therapy was a strong predictor of treatment failure in the form of either relapse or Richter transformation (RT). The median duration of PFS at 24-month follow-up was 18 months in the entire cohort and 13 months in the double-refractory group.

Although clinical responses to CAR T-cell therapy have been promising, management of patients with active progressive CLL after failure of both BTK inhibitors and venetoclax can be challenging when preparing them for CAR T-cell therapy, and these patients have dismal outcomes.[26] In a series of 28 patients, the median OS after CAR T-cell therapy failure was only 7 months in double-refractory patients vs 16.4 months in patients who only had BTK inhibitors or venetoclax failure before CAR T-cell therapy. An outline from selected publications using CAR T cells in R/R CLL is reported in the Table.

In conclusion, even though none of the 4 FDA-approved CAR T-cell products for NHL are currently approved for CLL, an approval in relapsed CLL may be expected in near future based on the most recent data with liso-cel. For now, CAR T-cell therapy in CLL is for use in clinical trials.

When CLL Goes Out of Control: CAR T Cells in RT and B-Cell Prolymphocytic Leukemia

CLL that has transformed to aggressive high-grade B-cell lymphoma via RT is difficult to treat, and finding novel therapeutic strategies remains an unmet need. The response to first-line regimens such as rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is in the range of 30% and options are limited for relapsed disease, with no current standard of care.[27]

In a recent study, Benjamini and colleagues[28] reported high CR rates in 5 of 8 treated patients (71%) when they used a CD19-targeted CAR T-cell therapy with a CD28 costimulatory domain. Importantly, 4 patients received CAR T-cell therapy as the first treatment after RT diagnosis, and all patients had progressive disease before CAR T-cell therapy. Despite the small number and the short follow-up, observation of a high rate of CRs is promising. Kittai and colleagues reported the results of axi-cel in 9 patients with RT.[29] Eight of 9 patients obtained a response. At a median follow-up of 6 months, 6 patients remained in remission, although at the time of publication 1 patient had received allo-SCT and 3 patients remained on a BTK inhibitor. As more data with a longer follow-up for CAR T-cell therapy in RT patients are awaited, consideration of cellular immunotherapy trials for these patients remains a reasonable option, but clinical trials (CAR T-cell therapy and non–CAR T-cell therapy) should be prioritized.

The Union Makes Us Strong: CAR T-Cell Therapy in Combination With TKIs

The addition of ibrutinib to CAR T-cell therapy has been demonstrated to be beneficial for many T-cell functions, including an increased efficacy and a lower rate of toxic effects.[30] Preclinical studies demonstrated that treatment with ibrutinib restored CLL patients T-cell functions, and that concurrent ibrutinib treatment enhanced CAR T-cell activity and engraftment in xenograft models of leukemia.[31] Given the potential for an improved efficacy and safety profile, Gauthier and colleagues from the Fred Hutchinson Cancer Center investigated the concurrent use of ibrutinib with a 4-1BB CD19-targeted CAR T-cell therapy in patients with ibrutinib-resistant CLL.[32,33] The authors compared a cohort of patients who received ibrutinib alongside CAR T-cell therapy vs a cohort of patients in which ibrutinib was discontinued after documented resistance. The patient characteristics of the 2 groups were comparable; the response rates were significantly higher in patients who received ibrutinib compared with the non-ibrutinib ones. In the ibrutinib group, the overall response and CR rates were 83% and 22%, respectively, and uMRD status was achieved in 72% and 61% of patients using flow cytometry and next-generation sequencing, respectively. Despite the equivalent level of CAR T-cell therapy expansion, concurrent use of ibrutinib was associated with a lower median cytokine release syndrome grade compared with patients who did not receive ibrutinib, with no patients in the ibrutinib group developing cytokine release syndrome grade greater than or equal to 3 vs 11% in the non-ibrutinib group. Achievement of uMRD was noted to be a strong predictor of PFS, with a 1-year PFS of 59% in patients who had no detectable disease by next-generation sequencing.

In the TRANSCEND CLL 004 trial, 19 patients received combination therapy with liso-cel and ibrutinib.[25] All patients had R/R disease after treatment with ibrutinib, and 58% had prior exposure to both BTK inhibitors and venetoclax. Cytokine release syndrome occurred in 14 patients (74%), with 5% experiencing grade 3 cytokine release syndrome. Neurologic events were reported in 32% of patients, with 16% experiencing grade 3 neurologic events. Investigators reported an ORR of 95% and a complete remission/complete remission with incomplete blood count recovery rate of 63%; uMRD was achieved in 89% of patients by flow cytometry in peripheral blood, and in 79% of patients by next-generation sequencing in the bone marrow. Of 17 patients who achieved uMRD in the blood, only 1 patient progressed owing to RT. Neither of the 2 patients with progressive disease during the 10-month follow-up had achieved uMRD after CAR T-cell therapy treatment.

Recently, Gill and colleagues reported promising results of a clinical trial testing the use of autologous humanized CD19-directed CAR T cells with 4-1BB costimulatory domain (huCART19) in a cohort of 19 patients who did not achieve a CR after 6 months of therapy with ibrutinib.[34] After a median follow-up of

41 months, 18 patients had developed cytokine release syndrome and 5 patients had developed ICANS. The 3-month CR rate was 44% at 12 months. The study showed that the combination of BTK inhibition and CAR T-cell therapy led to a high proportion of deep responses, with 72% of patients obtaining uMRD. The estimated OS and PFS at 48 months were 84% and 70%, respectively. Of 15 patients with uMRD at 3 or 6 months, 13 remained in ongoing CR at last follow-up.

Concurrent use of ibrutinib with CAR T-cell therapy seems to be a feasible approach, with potential efficacy and safety benefits. From a practical standpoint, these are valuable data that support the use of ibrutinib around the time of CAR T-cell therapy. The potential advantages or disadvantages of using next-generation BTK inhibitors, which have higher specificity for BTK, in combination with CAR T-cell therapy remains an important clinical question that needs investigation in the upcoming years. Some preclinical studies have showed that the addition of the second-generation BTK inhibitor acalabrutinib (Calquence, AstraZeneca) to liso-cel is able to improve the performance of CAR T-cell therapy.[35] Clinical trials are needed to test the safety and efficacy of this association in the clinical setting. At the Wuhan Union Hospital in Wuhan, China, a phase 3 trial is testing zanubrutinib (Brukinsa, BeiGene), another second-generation BTK inhibitor, in combination with CAR T-cell therapy in several B-cell malignancies, including CLL (NCT05020392).

In summary, for patients who experience treatment failure with novel agents, the combination of BTK inhibition, especially with ibrutinib, and CAR T-cell therapy seems to potentiate the effect of cell therapy and provide prolonged remissions. It is not clear whether part of these results depend directly on the previous in vivo use of BTK inhibitors. Generating CAR T cells from patients who received novel agents as the only or immediate therapy before leukapheresis may be a more efficient process in terms of cell senescence and in vivo persistence of CAR T cells after infusion, especially compared with CAR T cells generated from patients with other types of lymphoid malignancies with previous exposure to chemotherapy-based therapies. However, given the potential side effects of CAR T cells, although partially mitigated by BTK inhibitors, it remains to be determined whether this approach should be proposed to all eligible BTK inhibitor-refractory patients or to be limited to patients with high-risk disease.

Future Directions: Novel CARs and Novel Targets

Whereas the CAR T-cell products discussed here target the CD19 antigen, clinical trials are examining alternative tumor antigens as the next frontier of cell therapy. Among these alternative targets is CD20, which is largely expressed on the surface of mature B cells and is the most commonly targeted molecule by monoclonal antibodies. Currently, a phase 1/2 multicenter trial in patients with R/R CD20-positive CLL is ongoing in the United States (NCT05360238).

Bispecific CAR T cells are CAR products bearing CARs against 2 different tumor targets. Some of these agents have been tested in patients with CLL. Shah and colleagues enrolled 3 patients with CLL in a phase 1 trial of dose escalation with an anti-CD20/CD19 CAR T-cell product; 2 out of the 3 patients were in CR at day 28 after CAR T-cell infusion.[36]

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an antigen that is expressed on a variety of human cancer cells.[37] A multicenter trial utilizing an anti-ROR1 CAR T-cell product in CLL is expected to start enrollment in the near future (NCT02706392). More therapeutic options for CLL patients are expected to be developed, similar to other B-cell malignancies. Some molecules, such as B-cell maturation antigen (BCMA), are expressed in CLL cells and are already targeted by CAR T-cell products approved in other diseases, but studies of these cell products in CLL are not currently available.

Generating CAR T cells from third-party sources is an active area of research. The goals are to reduce the cost of treatment, improve treatment efficacy, and have cell products that are ready to use in cases of leukapheresis failure. Examples of third-party CAR T-cell products are allogeneic CAR T-cell products, CAR natural killer cell (CAR-NK) products, and CAR natural killer T-cell (CAR-NKT) products. The use of off-the-shelf donor cells that have not been previously exposed to lymphotoxic treatments and a manufacturing process that eliminates the need for the patient to undergo leukapheresis make these options attractive. Allogeneic CAR T cells were first generated in patients who had experienced CLL relapse after allo-SCT, which was previously utilized as a treatment for young patients who had high-risk disease and a suitable donor. The anticancer effect of donor-derived immune cells, known as graft-versus-leukemia, represents the beginning of the cell immunotherapy era. In the era of cell therapy for B-cell NHL, allo-SCT is still a suitable and safe option in patients who experience relapse after anti-CD19 CAR T-cell therapy.[38,39]

Despite high rates of durable responses, patients with CLL still experience a considerable rate of relapse after allo-SCT. One option to restore antitumor activity is to perform donor lymphocyte infusions using lymphocytes isolated from the peripheral blood of the stem cell donor. Because there is now a way to manipulate this product,

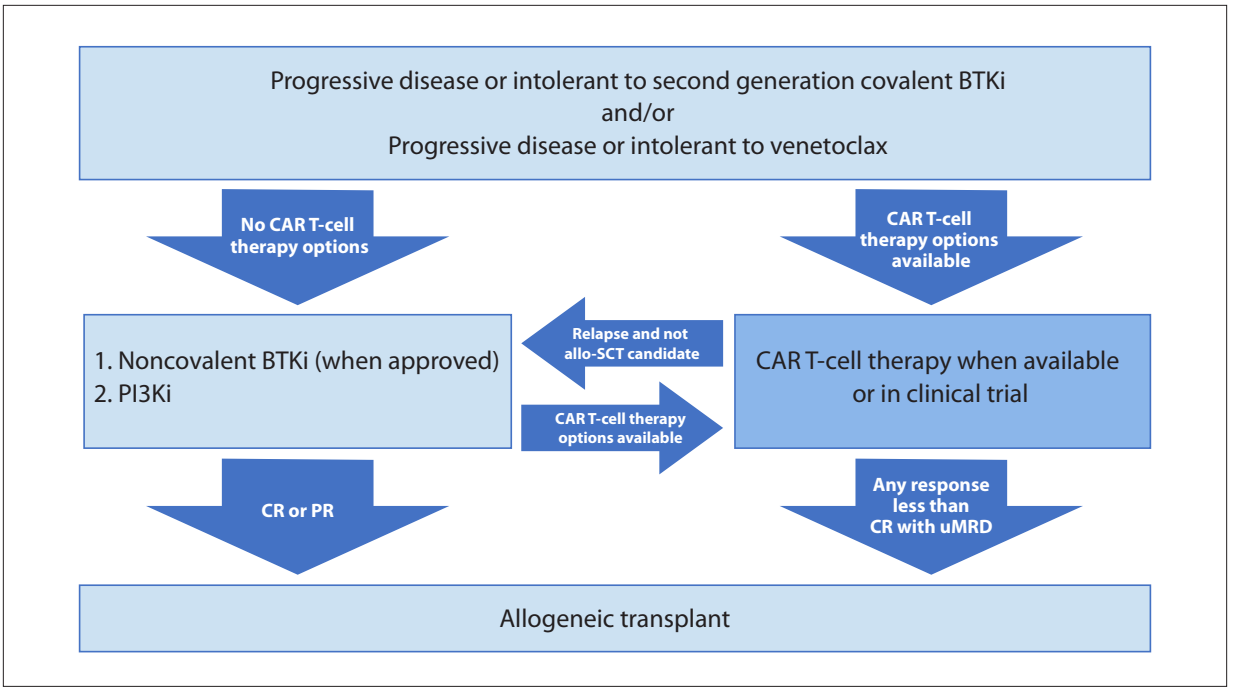

Figure. Proposed algorithm for referral of patients with chronic lymphocytic leukemia to CAR T-cell therapy.

Allo-SCT, allogeneic stem cell transplant; BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete response; PI3Ki, phosphoinositide 3-kinase inhibitor; PR, partial response; uMRD, undetectable minimal residual disease.

CAR T cells were generated from donor-derived T cells in a 2016 study.[40] Twenty patients with B-cell NHL and relapse after allo-SCT received anti-CD19 CAR T cells generated from donor T cells. Among them, 5 patients had CLL. Overall, 8 patients obtained remission, which included 6 CRs and 2 PRs. The response rate was highest for acute lymphoblastic leukemia, but responses also occurred in CLL and lymphoma. The longest ongoing CR was more than 30 months in a patient with chronic CLL.

Allogeneic CAR T cells can also be generated by third-party donors and used outside of the context of allo-SCT as an "off-the -shelf" product. One ongoing trial is testing the safety and efficacy of PBCAR0191, an allogeneic, off-the-shelf CD19-targeting CAR T-cell product, in patients with R/R CD19+ NHL (NCT03666000). The preliminary results of the study were presented in 2021, and the CR rates with PBCAR0191 are comparable to those observed with autologous CAR T-cell therapy in this population.[41]

A group at the MD Anderson Cancer Center reported results with CAR-NK therapy targeting CD19, without human leukocyte antigen matching and using cord blood cells as a source. The study included 5 patients with CLL (1 with RT), 3 of whom had CR after treatment.[42] Although these results are promising, all therapy patients subsequently were started on post-remission therapy given the presence of persistent or subsequent MRD.

Conclusion: When to Use CAR T-Cell Therapy in CLL

In the current era, treatment of CLL requires a multidisciplinary approach. A full overview of all the treatment option goes beyond the scope of this paper, but appropriate timing and sequence of novel agents, CAR T-cell therapy, and allo-SCT require expertise from CLL and cellular immunotherapy experts. For these reasons, seeking guidance from experienced academic centers is highly recommended.

In the early stages of CLL treatment, the common sequence of novel agents includes using either BTK inhibitors or venetoclax followed by the other agent in cases of disease progression or major intolerance to the first class of drugs.[43] Patients with CLL, even those with high-risk cytogenetics and molecular disease, usually respond to novel agents in earlier lines of treatment, and cell therapy is not recommended in that setting. However, given that the safety and efficacy profile of CAR T-cell therapy is expected to improve over time, the CLL community needs to start planning for studies to test the feasibility of integrating CAR T-cell treatment in earlier lines of therapy.

CAR T-cell therapy (in a clinical trial or after approval) is a reasonable option for patients with disease progression on, or true intolerance to, a BTK inhibitor or venetoclax. The authors recommend using CAR T-cell therapy if available before allo-SCT (Figure). The favorable toxicity profile, shorter treatment duration, and possibility of long-term remissions in a significant proportion of patients are reasons for such an approach. Allo-SCT should be considered for transplant-eligible patients who show signs of MRD after CAR T-cell therapy. The discussion about moving forward with allo-SCT is critical before the disease burden becomes prohibitory for transplant. Even though MRD negativity seems to have a strong correlation with improved outcomes, it is too early to give any strong recommendation about maintenance or intensification therapy for patients who have persistence of MRD after CAR T-cell therapy.

CAR T-cell therapy has the potential to become a major player in achieving the common goal of a time-limited and potentially curative treatment of CLL. Allo-SCT remains a backup plan for patients with poor response to the novel agents, especially in those with a suboptimal response to CAR T-cell therapy.

Because no FDA-approved CD19 CAR T-cell therapies are available for CLL, enrollment in a clinical trial using alternative CAR T-cell products that are supported by preliminary published data (ie, anti-CD20 CAR T-cell therapy, allogeneic CAR T-cell therapy, CAR-NK therapy, or CAR-NKT therapy) is a reasonable option to consider.

Disclosure

Dr Iovino has no competing interests to declare. Dr Shadman has received research funding from Mustang Bio, BMS, Pharmacyclics, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Genmab, MorphoSys/Incyte, and Vincerx; and has done consulting for AbbVie, Genentech, AstraZeneca, Pharmacyclics, BeiGene, BMS, MorphoSys/Incyte, Kite, Eli Lilly, Mustang Bio, Regeneron, ADC Therapeutics, Fate Therapeutics, and MEI Pharma.

References

1. Venclexta (venetoclax) [prescribing information]. North Chicago, IL: AbbVie Inc; 2020.
2. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188-1200.
3. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225-2236.
4. Kater AP, Wu JQ, Kipps T, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. *J Clin Oncol*. 2020;38(34):4042-4054.
5. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial. *J Clin Oncol*. 2018;36(19):1973-1980.
6. Sterner RC, Sterner RM. CAR-T cell therapy: current limitations and potential strategies. *Blood Cancer J*. 2021;11(4):69.
7. Zelenetz AD, Gordon LI, Chang JE, et al. NCCN Guidelines® Insights: B-cell lymphomas, version 5.2021. *J Natl Compr Canc Netw*. 2021;19(11):1218-1230.
8. Hallek M, Al-Sawaf O. Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. *Am J Hematol*. 2021;96(12):1679-1705.
9. Fischer JW, Bhattarai N. CAR-T cell therapy: mechanism, management, and mitigation of inflammatory toxicities. *Front Immunol*. 2021;12:693016.
10. Benmebarek MR, Karches CH, Cadilha BL, Lesch S, Endres S, Kobold S. Killing mechanisms of chimeric antigen receptor (CAR) T cells. *Int J Mol Sci*. 2019;20(6):1283.
11. Yescarta (axicabtagene ciloleucel) [package insert]. Kite Pharma; 2022.
12. Neelapu SS, Dickinson M, Munoz J, et al. Primary analysis of ZUMA-12: a phase 2 study of axicabtagene ciloleucel (axi-cel) as first-line therapy in patients with high-risk large B-cell lymphoma (LBCL) [ASH abstract 739]. *Blood*. 2021;138(suppl 1).
13. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382(14):1331-1342.
14. ClinicalTrials.gov. Tisagenlecleucel in adult patients with aggressive B-cell non-Hodgkin lymphoma (BELINDA). https://clinicaltrials.gov/ct2/show/NCT03570892. Accessed March 24, 2021.
15. Kymriah (tisagenlecleucel) [package insert]. Novartis; 2019.
16. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448.
17. Bristol Myers Squibb announces positive topline results from phase 3 TRANSFORM trial evaluating Breyanzi (lisocabtagene maraleucel) versus chemotherapy followed by stem cell transplant in second-line relapsed or refractory large B-cell lymphoma. https://news.bms.com/news/details/2021/Bristol-Myers-Squibb-Announces-Positive-Topline-Results-from-Phase-3-TRANSFORM-Trial-Evaluating-Breyanzi-lisocabtagene-maraleucel-Versus-Chemotherapy-Followed-by-Stem-Cell-Transplant-in-Second-line-Relapsed-or-Refractory-Large-B-cell-Lymphoma/default.aspx. Accessed June 22, 2021, 2021.
18. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396(10254):839-852.
19. Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med*. 2011;365(8):725-733.
20. Cappell KM, Sherry RM, Yang JC, et al. Long-term follow-up of anti-CD19 chimeric antigen receptor T-cell therapy. *J Clin Oncol*. Nov 10 2020;38(32):3805-3815.
21. Davids MS, Kenderian SS, Flinn IW, et al. ZUMA-8: a phase 1 study of KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in patients with relapsed/refractory chronic lymphocytic leukemia [ASH abstract 3319]. *Blood*. 2022;140(suppl 1):7454-7456.
22. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Sci Transl Med*. 2015;7(303):303ra139.
23. Frey NV, Gill S, Hexner EO, et al. Long-term outcomes from a randomized dose optimization study of chimeric antigen receptor modified T cells in relapsed chronic lymphocytic leukemia. *J Clin Oncol*. 2020;38(25):2862-2871.
24. Turtle CJ, Hay KA, Hanafi LA, et al. Durable molecular remissions in chronic lymphocytic leukemia treated with CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. *J Clin Oncol*. 2017;35(26):3010-3020.
25. Siddiqi T, Soumerai JD, Dorritie KA, et al. Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL. *Blood*. 2022;139(12):1794-1806.
26. Shadman M, Gauthier J, Khajavian S, et al. Relapsed or refractory CLL after CD19-specific CAR-T therapy: treatment patterns and clinical outcomes [ASH abstract 4249]. *Blood*. 2019;134(suppl 1).
27. Tadmor T, Levy I. Richter transformation in chronic lymphocytic leukemia: update in the era of novel agents. *Cancers (Basel)*. 2021;13(20):5141.
28. Benjamini O, Shimoni A, Besser M, et al. Safety and efficacy of CD19-CAR T cells in Richter's transformation after targeted therapy for chronic lymphocytic leukemia [ASH abstract 545]. *Blood*. 2020;136(suppl 1).
29. Kittai AS, Bond DA, William B, et al. Clinical activity of axicabtagene ciloleucel in adult patients with Richter syndrome. *Blood Adv*. 2020;4(19):4648-4652.
30. Ruella M, Kenderian SS, Shestova O, et al. The addition of the BTK inhibitor ibrutinib to anti-CD19 chimeric antigen receptor T cells (CART19) improves responses against mantle cell lymphoma. *Clin Cancer Res*. 2016;22(11):2684-2696.

31. Fraietta JA, Beckwith KA, Patel PR, et al. Ibrutinib enhances chimeric antigen receptor T-cell engraftment and efficacy in leukemia. *Blood*. 2016;127(9):1117-1127.
32. Gauthier J, Hirayama AV, Hay KA, et al. Comparison of efficacy and toxicity of CD19-specific chimeric antigen receptor T-cells alone or in combination with ibrutinib for relapsed and/or refractory CLL [ASH abstract 299]. *Blood*. 2018;132(suppl 1).
33. Gauthier J, Hirayama AV, Purushe J, et al. Feasibility and efficacy of CD19-targeted CAR T cells with concurrent ibrutinib for CLL after ibrutinib failure. *Blood*. 2020;135(19):1650-1660.
34. Gill S, Vides V, Frey NV, et al. Anti-CD19 CAR T cells in combination with ibrutinib for the treatment of chronic lymphocytic leukemia. *Blood Adv*. 2022;6(21):5774-5785.
35. Qin JS, Johnstone TG, Baturevych A, et al. Antitumor potency of an anti-CD19 chimeric antigen receptor T-cell therapy, lisocabtagene maraleucel in combination with ibrutinib or acalabrutinib. *J Immunother*. 2020;43(4):107-120.
36. Shah NN, Johnson BD, Schneider D, et al. Bispecific anti-CD20, anti-CD19 CAR T cells for relapsed B cell malignancies: a phase 1 dose escalation and expansion trial. *Nat Med*. 2020;26(10):1569-1575.
37. Zhao Y, Zhang D, Guo Y, et al. Tyrosine kinase ROR1 as a target for anti-cancer therapies. *Front Oncol*. 2021;11:680834.
38. Shadman M, Gauthier J, Hay KA, et al. Safety of allogeneic hematopoietic cell transplant in adults after CD19-targeted CAR T-cell therapy. *Blood Adv*. 2019;3(20):3062-3069.
39. Zurko J, Ramdial J, Shadman M, et al. Allogeneic transplant following CAR T-cell therapy for large B-cell lymphoma. *Haematologica*. 2023;108(1)98-109.
40. Brudno JN, Somerville RP, Shi V, et al. Allogeneic T cells that express an anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease. *J Clin Oncol*. 2016;34(10):1112-1121.
41. Shah BD, Jacobson CA, Solomon S, et al. Preliminary safety and efficacy of PBCAR0191, an allogeneic, off-the-shelf CD19-targeting CAR-T product, in relapsed/refractory (r/r) CD19+ NHL [ASCO abstract 7516]. *J Clin Oncol*. 2021;39(15)(suppl).
42. Liu E, Marin D, Banerjee P, et al. Use of CAR-transduced natural killer cells in CD19-positive lymphoid tumors. *N Engl J Med*. 2020;382(6):545-553.
43. Wierda WG, Byrd JC, Abramson JS, et al. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 4.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020;18(2):185-217.