Leukemia insights

OCTOBER 2021

MONTHLY EDITION

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

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In this month's Leukemia Insights newsletter, written by Naval Daver, M.D., and Abhishek Maiti, M.D., and sponsored in part by the Charif Souki Cancer Research Fund, we summarize the immune and cellular therapy clinical trials available for patients with acute myeloid leukemia (AML) at our institution. Learn more about our Leukemia program.

Immunotherapies and Cellular Therapies for Patients with Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is an aggressive cancer of white blood cells that commonly presents in patients with a median age of 68 years. Intensive chemotherapy remains the mainstay for frontline therapy for younger patients, while lower-intensity venetoclax-based regimens are now the standard approach for older/unfit patients. However, 5%-30% of younger patients and 10%-40% of older patients may not respond to frontline treatment. Treatment failure is an especially major issue for patients with *TP53* mutant AML, adverse-risk cytogenetics, secondary AML following prior chemotherapy, AML arising from prior blood disorders or cancers, or AML with persistent minimal residual disease (MRD) pre- or post-stem cell transplant. Among patients requiring salvage therapy for AML, response rates are 20%-40%, with median overall survival less than 6-7 months.

Most of our current treatments, both approved and investigational, focus on disrupting cell intrinsic pathways via receptor tyrosine kinase targeting, promoting apoptosis, or leveraging epigenetic pathways that support cancer sustenance. However, leukemia cells frequently evade such treatments through evolution and outgrowth of resistant clones. Immunotherapies have been highly successful for solid tumors, lymphoma, acute lymphocytic leukemia (ALL), and multiple myeloma. We currently are developing several promising cellular and immunotherapy options for patients with AML. Such therapies are often better tolerated than conventional chemotherapy due to more manageable side effect profiles. Below we summarize some of the immune and cellular therapy clinical trials available for patients with AML at our institution (**Table 1**).

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It's the easiest way to stay current with information on the latest leukemia news, research, and resources. View archived issues.

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Immunotherapies

Macrophage Checkpoint Inhibitors

Several clinical trials are evaluating CD47-SiRPa antibody-based combination approaches. Such therapies block the "do not eat me" signal that leukemia cells can use to evade phagocytosis by disrupting the CD47-SiRPa interaction, unleashing macrophages to attack cancer cells. This new immunotherapy approach using the combination of azaciticine and the anti-CD47 antibody magrolimab has shown promising activity in the treatment of newly diagnosed older/unfit patients with AML and myelodysplastic syndrome (MDS) with encouraging CR/CRi rates, safety, and survival (Daver N et al, EHA 2020; Sallman D et al, ASH 2020). Even higher response rates have been observed with the "triple therapy" of azacitidine, venetoclax and magrolimab. This is of particular interest for patients with *TP53*-mutated AML who do not seem to benefit from available high- and low-intensity therapies, with response rates of 14%-50% and a dismal median overall survival of 2-7 months. The combination of azacitidine and magrolimab has shown response rates of 70% with encouraging median survival duration in ongoing single-arm studies. We currently have trials with four CD47-SiRPa antibodies: magrolimab, ALX148, TTI-622, and lemzoparlimab. Additional trials with bispecific antibodies (BiTEs) that simultaneously engage the innate immune system via CD47 blockade and the adaptive immune system via T-cell engagement are opening soon.

Bispecific T-Cell Engagers (BiTEs)

Bispecific T-cell engagers (BiTES) are essentially proteins with two arms. With one arm the protein latches onto the leukemia cell and with the other arm the protein binds to endogenous T-cells. Once the leukemia and immune cells are in close proximity to one another, the immune cells release cytokines and enzymes against the leukemia cells, killing them. BiTEs have shown promising activity and are approved for other leukemias, including acute lymphoblastic leukemia, (e.g. blinatumomab). Multiple clinical trials are evaluating BiTEs (with targets including CD33, CD123 and FLT3) in relapsed/refractory and MRD-positive AML. They appear to be most effective in relapsed/refractory patients with a low disease burden or in those in remission but with MRD positivity. We are focusing our efforts on these patient populations, especially those who are MRD-positive prior to or after allogeneic stem cell transplant.

Targeting Specific Leukemia Antigens

Clinical trials are evaluating antibodies targeting specific leukemia antigens, including CD70 (cusatuzumab) and LILRB4 which enable eradication of leukemia cells through multiple mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC) and co-inhibitory immune checkpoint inhibition. In addition, antibody-drug conjugates (ADCs) that work by targeted delivery of chemotherapy to leukemia cells expressing antigens such as CD123 (IMGN632) are showing high efficacy in ongoing clinical trials, especially when combined with azacitidine or azacitidine with venetoclax.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors remove the brakes from our immune system, thus unleashing it to kill leukemia. Several ongoing trials at our institution are evaluating checkpoint inhibitors targeting PD-1, CTLA-4, TIM-3, and OX40, among others. Among these, PD-1 checkpoint inhibitors are already approved by the Food and Drug Administration for the treatment of multiple solid tumors. These are used in combination with standard therapies to harness synergistic effect and seem to be most effective in

patients with extra-medullary AML or patients who are post allogeneic stem cell transplant with maintained donor chimerism.

Cancer Vaccines and Other Immunotherapy Approaches

Galinpepimut-S is a peptide vaccine against the protein WT-1 that is highly expressed on leukemia cells and may help generate immune responses against leukemia. It is being evaluated as maintenance therapy, as well as in combination with the checkpoint inhibitor pembrolizumab as salvage therapy in patients with relapsed/refractory AML. Inhibition of IRAK4, in combination with standard azacitidine and venetoclax, can help augment response through inhibition of toll-like receptor signaling leading to decreased IL-6 levels and may be particularly effective against leukemia with splicing factor mutations. We have a clinical trial with the IRAK4 inhibitor CA-4948, given in combination with azacitidine and venetoclax.

Cellular Therapies

Cellular therapies currently being investigated include immune cells (T and natural killer [NK] cells) that are engineered to express new receptors called chimeric antigen receptors (CAR), which can target and kill leukemia cells or, in the case of NK-cells infused at high cell numbers (up to 1 – 1.5 billion cells weekly), generate potent ADCC. Ongoing AML CAR-T cell trials include autologous cells targeting CD123 and CLL-1 proteins on leukemia cells. For these therapies, the patient's T-cells are collected via leukapheresis, expanded and engineered to express specific receptors to target leukemia cells, and then given back to patients. These cells expand in the patient's body and seek out and kill leukemia cells. This approach is of high interest for particularly resistant subsets of AML such as relapsed/refractory *TP53*-mutated AML or AML with other adverse cytogenetic or molecular aberrations, as well as for MRD-positive disease.

In addition, NK cell therapy options include modified NK cells as well as CAR NK cells, both of with are allogeneic, or off-the-shelf (from healthy donors). The off-the-shelf approach eliminates the wait time, which can be an issue when using autologous products, as cells are readily available. In addition, these off-the-shelf therapies can be a solution for patients who may not have sufficient T-lymphocytes to be harvested and engineered, which is not uncommon either due to overwhelming leukemia or prior chemotherapies. One ongoing phase I clinical trial with FT538 -- where NK cells obtained from a pluripotent stem cell line (iPSC) are modified via serial manipulations to increase ADCC against AML, persistence and serial killing -- has shown promising responses in early data, and, again, is especially of interest in patients with a low disease burden or AML in remission with positive MRD. NKX101 is another ongoing CAR-NK cell approach where donor-derived healthy NK cells are engineered to express a receptor specific for NKG2D proteins on leukemia cells. NK-based therapies appear to have much lower rates of cytokine release syndrome and neurotoxicity compared with CAR-T cells.

Summary

In summary, there are several cellular and immunotherapy clinical trial options for younger and older patients with AML who are newly diagnosed, relapsed/refractory, MRD-positive, or appropriate for maintenance therapy. Several of these approaches have yielded encouraging response rates in the patients treated so far, and others are early in phase I trials but are biologically highly promising. Such cellular and immunotherapy options have generally favorable safety profiles, and may offer a chance for durable responses in patients who have AML with adverse mutations or cytogenetics, or patients who do not have any available standard therapy options.

Table 1. Overview of cellular and immunotherapy options for patients with acute myeloid leukemia

Immuno/cellular therapy target	Agent / regimen	Newly diagnosed	Relapsed / refractory	Phase	NCT Number
Cellular therapies					
CLL-1 CAR-T cell	KITE-222		✓	1	NCT04789408
NK cells	FT538		✓	1	NCT04023071
NKG2D CAR-NK cell	NKX101		✓	1	NCT04623944
CD123 CAR-T cell	UCART123 v1.2		✓	1	NCT03190278
Immunotherapies					
CD47 antibody	Magrolimab with low-intensity or intensive chemotherapy	✓	✓	2	NCT04778410
CD47 antibody	Magrolimab, Azacitidine		✓	1	NCT03248479
CD47 antibody	Magrolimab, azacitidine vs standard therapy for TP53 mutant AML	✓	✓	3	NCT04778397
CD47 antibody	Evorpacept, venetoclax, azacitidine	✓	✓	1 | 2	NCT04755244
CD123xCD3 BiTE	Vibecotamab		✓	1	NCT02730312
CD123xCD3 BiTE	Flotetuzumab		✓	1 | 2	NCT02152956
CD33xCD3 BiTE	AMG 330		✓	1	NCT02520427
CD33xCD3 BiTE	AMV564, pembrolizumab		✓	1	NCT03144245
CD33xCD3 BiTE	JNJ-67571244		✓	1	NCT03915379
FLT3 BiTE	AMG 427		✓	1	NCT03541369
LILRB4 antibody	IO-202		✓	1	NCT04372433
PR1/HLA-A2 antibody	Hu8F4		✓	1	NCT02530034
CD123 ADC	Azacitidine, IMGN632, Venetoclax	✓	✓	1 | 2	NCT04086264
CD123 ADC	Azacitidine, SL-401, Venetoclax	✓	✓	1	NCT03113643
ROR1 ADC	VLS-101		✓	1	NCT03833180
OX40 antibody	OX40, Venetoclax, Avelumab, Glasdegib, Gemtuzumab Ozogamicin, Azacitidine		✓	1 | 2	NCT03390296
PD-1 antibody	Nivolumab, venetoclax, azacitidine	✓	✓	2	NCT02397720
PD-1, TIM-3 antibody	HMA, PDR001, MBG453		✓	1	NCT03066648
TIM-3 antibody	MBG453, Venetoclax, Azacitidine		✓	2	NCT04150029
CD70 antibody	Cusatuzumab, Azacitidine, Venetoclax		✓	1	NCT04150887
CD70 antibody	SEA-CD70		✓	1	NCT04227847
IRAK4 inhibitor	CA-4948, Azacitidine, Venetoclax		✓	1 | 2	NCT04278768
WT-1 vaccine	Galinpepimut-S vs best available therapy		✓	3	NCT04229979
WT-1 vaccine, PD-1 antibody	Galinpepimut-S, Pembrolizumab		✓	1 | 2	NCT03761914

Announcements

Bridging Oncology and Primary Care Education Series

MD Anderson Cancer Center is featuring an online educational series for all health care provider specialties. This series will feature specialized presentations covering: Gastroenterology, Internal Medicine, Dermatology/Melanoma, Hematology, Breast, Gynecologic Oncology, Immunology, Thoracic and Head & Neck, COVID Related Topics and Hot Topics. The modules are pre-recorded and will be available through July 15, 2021–February 1, 2022. To view more details or register, go to http://mdanderson.org/ccc21.

Leukemia Faculty Contacts

Completing these studies in a timely manner will allow us to move quickly on positive leads. We appreciate referrals and will make every effort, once a patient is enrolled on a study, to continue as much of the care as possible through the referring oncologist. We also will keep you apprised of the patient's progress. View our faculty roster.

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