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Jacobs Journal of Cancer Science and Research

Review article

Novel Approaches in Treatment of Adult AML

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Received: 11-17-2015

Accepted: 01-18-2016

Published: 02-26-2016

Abstract

Acute myeloid leukemia (AML) is cancer of the blood cells. This cancer specifically affects red blood cells, platelet forming cells and other white blood cells in the body; its incidence is very low in the United States with less than 3% of cancer diagnoses being for AML. Traditionally, this disease would be treated with chemotherapy or radiation therapy. Immunotherapy is a new way to fight this cancer. This therapy stimulates one's own immune system to fight the malignant tumor. In this paper, we discuss the causes, epidemiology, and potential immunotherapeutic techniques to fight AML.

Keywords: Acute Myeloid Leukemia; Cancer; Tumor; Immunotherapy; Blood Cells

Abbreviations

AML: Acute Myeloid Leukemia;
MABs: Monoclonal Antibodies;
SCT: Stem Cell Transplantation;
LFS: Leukemia-Free Survival;
TKI: Tyrosine Kinase Inhibitors;
TAA: Tumor-Associated Antigens;
IL: Interleukin

Introduction/Epidemiology

Acute Myeloid Leukemia (AML) represents less than 3% of all cancers [1]. According to data collected in the United States (US) in 2010, AML has an age-standardized rate of incidence of 23.5 per 100,000. In 2009, the overall five year survival rate of 24.9% was estimated in the US [2]. According to the American Cancer Society, in 2014 more than 18,860 new cases of AML were diagnosed in the US. In the same year, 10,460 cases of death were also reported [3]. The US, Australia, and west European countries have a higher incidence rate in comparison with the other countries [4].

AML includes different types of histopathological and genetic characteristics. The male-to-female ratio is 1.5:1, with a predominance of male over female [5] and higher incidence observed, above the age of 50 years [2]. The symptoms of AML include: anemia, shortness of breath, fatigue, recurrent infection, bruising and unusual bleeding [6].

The risk factors that are associated with AML include: hereditary genetic disorders, like Down syndrome, severe congenital neutropenia, Shwachman–Diamond syndrome, Dyskeratosiscongenita and Fanconi Anemia, environmental exposures to ionizing radiation, benzene, cigarette smoking and pesticides, chemotherapy with Topoisomerase II inhibitors, alkylating chemotherapy, anthracyclines, and anti-tubulin agents.[7] Incidence of AML increases with age. Age also has a negative impact on AML prognosis and chances of cure.

The pathophysiology of AML constitutes alteration in genes at several locations [8]. The molecular basis was explained by several mechanisms such as nucleophosmin mutations, CCAAT/enhancer binding protein alpha mutations, Fms-like Tyrosine Kinase 3 Mutations, FLT3 Internal Tandem Duplications, FLT3 tyrosine kinase domain (FLT3/TKD) mutations, core binding factor (CBF) associated KIT Mutations, CBF associated Janus-kinase-2 gene (JAK2) Mutations, RAS Mutations, isocitrate dehydrogenase mutations, mixed-lineage leukemia (MLL) gene mutations, polo like kinases aberrations, WT1 mutations, RUNX1 (AML1) mutations, mutations of DNMT3A gene and mutations of TET2 gene.

Immunotherapy

A. Monoclonal Antibodies: The aim of the monoclonal antibodies (mAb) is targeting the leukemic cells through adherence via specific antigens expressed on their surface. This is followed by the process of antibody-dependent cell cytotoxicity (ADCC) that helps to clear out these leukemic cells with or without the complement activation process. Antibodies can be used either in conjugated or unconjugated form with radioisotopes or immunotherapeutics [9]. Anti-CD33 antibody is widely used as a treatment for AML patients. One of the most important immunoconjugate is gemtuzumab ozogamicin.

1. Gemtuzumab Ozogamicin: It is an antibody-drug conjugate containing recombinant, humanized, anti-CD33 monoclonal antibody attached to the cytotoxic antitumor antibiotic calicheamicin. In this conjugate, the antibody binds to and is internalized by tumor cells, expressing CD33 antigen (a sialic acid-dependent glycoprotein commonly found on the surface of leukemic blasts), thereby delivering the attached calicheamicin to CD33-expressing tumor cells. Calicheamicin binds to the minor groove of DNA, causing double strand DNA breaks and resulting in the inhibition of DNA synthesis [10,11].

2. Radiolabeled Anti-CD33 Antibody: It is conjugated with radio nucleotides. Labeling of these antibodies is done using α-emitters like 225Ac, 213Bi and 211At with or without β-emitters like 131I, 90Y and 188Re. These α-particles are known to show better specificity in targeting a single cell as compared to β-particles. β-particles, being high-speed electrons, create a field that result in the irradiation of even those cells that do not express antigens. According to the clinical trial data, labeling HuM195, an anti-CD33 antibody with 213Bi, with cytarabine results in complete remission rates of AML patients [12,13].

3. BC8-SA[14]: It is an immunologic conjugate of monoclonal antibody, along with streptavidin. This conjugate adheres to the tyrosine phosphatase CD45 and leads to the cytotoxicity of the tumor cell through streptavidin-based internalization.

4. Nivolumab [15]: It acts as a PD-1 inhibitor and improves the potential of immune system. It adheres to PD-1 and stimulates the T-cell based immune response, thus resulting in tumor cell death.

5.Ipilimumab [16]: It is a CTLA4 antigen inhibitor. It augments the activation of T-cells and inhibits B7-1 and B7-2 based pathways.

6. Basiliximab [17]: A recombinant, chimeric, human-murine monoclonal antibody directed against the alpha subunit of the interleukin-2 receptor (IL-2R alpha) with immunosuppressant activity. Basiliximab selectively binds to and blocks IL-2R alpha, which is expressed on the surface of activated T-lymphocytes, thereby preventing interleukin-2 binding and inhibiting the interleukin-2-mediated activation of lymphocytes.

B. Stem Cell Transplantation:

Allogeneic Stem Cell Transplantation (SCT) is the most common type of SCT, which is used to treat AML. In this type of transplantation, the stem cells are obtained from another person, whose HLA type closely resembles that of the patient. The most successful donors are often a close relative, or more specifically, a brother or sister. If the HLA of the close relatives do not match, stem cells can be obtained from a matched unrelated donor (MUD). However, use of such stem cells might lead to several complications. Umbilical cord stem cells can also be used. Such cells come from the blood obtained from the umbilical cord and placenta after the birth of the baby and the cord is cut.

In AML, allogeneic SCT is more widely used as compared to autologous SCT. This is due to the fact that leukemia occurs in blood and bone marrow, hence if the cells of the patients are re-infused into them, there are chances that some of the leukemia cells might also re-enter the body. The donor cells are more beneficial due to their "graft-versus-leukemia" effect. As soon as these donor cells are given to the patient, they can identify foreign leukemia cells and attack them. This effect is not observed in autologous stem cell transplantation.

Due to the serious risk and side effects of allogeneic transplantation, patients need to be younger and healthy to be suitable candidates. Finding a matched donor can be another challenge. One of the major and serious complications associated with allo-SCT is graft-versus-host-disease (GVHD). Symptoms include itching, mouth sores, skin rashes, diarrhea and nausea. Liver and lungs may be damaged. Fatigue and muscle ache are some other symptoms.

Non-myeloablative Transplant (Mini-Transplant): Older people who cannot withstand standard allogeneic transplant or are using high dose chemotherapy, may undergo this procedure. In this procedure, the patients are subjected to a lower dose of chemotherapy, which destroys the bone marrow cells

partially. After this, the allogeneic donor stem cells are infused in them. It reduces the toxicity; however, the major complication is GVHD.

Autologous Stem Cell Transplantation (ASCT) acts as an important treatment therapy for the patients affected with AML. However, the role of ASCT in the patients with first remission remains unclear. It has been reported that by using Phase-II and Phase-III data, ASCT can be utilized in the patients, who have favorable risk of cytogenetics. The relapse rate is decreased and Leukemia-free survival (LFS) rate is improved. Allogenic transplant can be of use for the patients having poor risk cytogenetics [18].

In a study conducted by City of Hope Medical Center, the consolidation therapy was used, along with high dose ara-C (HDAC), for about eight to ten doses [19]. This therapy was followed by the isolation of stem cells using G-CSF stimulation. The patients were then passed through the procedure of ASCT using a complete regimen of Total Body Irradiation (TBI), cyclophosphamide and etoposide. The results showed two year disease–free survival (DFS) in 61% of the patients who underwent transplantation.

In the successive study, idarubicin was given with HDAC and IL-2, after the transplantation. The results were quite encouraging, with approximately two years of DFS, in 68% of the patients.[20] Another group utilized the concept of intensive consolidation by using HIDAC with either etoposide or mitoxantrone under G-CF stimulation in collecting peripheral blood stem cells. DFS was projected at 71% in the first 42 remission patients. [21] Hence, ASCT acts as an important treatment therapy in selected patients with AML.

C. Adoptive T-cell Therapy:

Adoptive T cell therapy involves the isolation and ex vivo expansion of tumor specific T cells to achieve greater number of T cells that would be obtained by vaccination alone. The tumor specific T cells are then infused into patients with cancer in an attempt to give their immune system the ability to overwhelm remaining tumor via T cells which can attack and kill cancer. There is no adoptive therapy that is currently approved by FDA for AML. However, many adoptive therapies are under clinical trials in phase I–III, as mentioned in Table-1.

Biological	Clinical trial identifier number	Phase	Study design	Target
NK-92 (Neukoplast)	NCT00900809	Phase-I	Safety/Efficacy Study, Open Label	Tumor cell and Fc receptors
AKT-801	NCT01478074	Phase-I	Safety/Efficacy Study, Open Label	p53 epitope/MHC complexes

Table 1. Adoptive therapy [22, 23]

D. Vaccine Therapy [24–27]:

There is no FDA approved vaccine therapy, available for AML. Other vaccine therapies that are under clinical trial in phase I–III are listed below:

1. Autologous Tumor Cell Vaccine: It is a vaccine, formulated by isolating an individual's tumor cell. This vaccine exhibits immune-response against tumor-associated antigens (TAAs), generated through cytotoxic T-lymphocytes and leads to apoptosis.

2. Dendritic Cell-AML (DC-AML) Vaccine: Dendritic Cell-AML (DC-AML) vaccine identifies the cancer cells and generates a T-lymphocytes based response against them. It can be used in chemotherapy-resistant subjects.

3. G-Vax Leukemia Vaccine: It is a vaccine produced from the cancer cells of the patient. It generates a protein called GM-CSF that can further generate a strong immune response against the cancer.

4. OCV-501: A peptide cancer vaccine comprised of a peptide derived from Wilms tumor gene 1 (WT1) protein with potential immunomodulating and antineoplastic activities. Upon subcutaneous administration, WT1 peptide vaccine OCV-501 may stimulate a CD4-positive helper T-lymphocyte-mediated immune response against WT1 expressing cells. WT1 protein, a zinc finger DNA-binding protein, is overexpressed in leukemic cells and in some solid tumors.

E. Kinase Inhibitors:

There is no tyrosine-kinase inhibitor that is currently approved by FDA for AML. Some of the TK inhibitors that are under clinical trials in phase I–III are as mentioned in the Table- 2 below:

F. MAPK Inhibitors:

There is no MAPK inhibitor that is currently approved by FDA for AML. However, the below mentioned MAPK inhibitors are under clinical trial, as given in the Table-3.

G. mTOR Inhibitors:

There is no mTOR inhibitor that is currently approved by FDA for AML. However, the below mentioned mTOR inhibitor is under clinical trial, as given in the Table-4.

H. Proteasome Inhibitors [42, 43]

There is no proteasome inhibitor that is currently approved by FDA for AML. However, there are two proteasome inhibitors that are under clinical trial.

TK Inhibitor	Clinical trial identifier number	Phase	Study design	Target
Sorafenib	NCT01371981	Phase-III	Efficacy Study, Open Label	RAF kinase
Gefitinib	NCT00130702	Phase-II	Safety/Efficacy Study, Open Label	EGFR
Imatinib	NCT00509093	Phase-II	Efficacy Study, Open Label	TK Inhibitor.
AKN-028	NCT01573247	Phase-I/II	Safety/Efficacy Study, Open Label	FLT3, STK1 and SCFR
Dasatinib	NCT01876953	Phase-I/II	Safety/ Efficacy Study, Open Label	Src protein kinase
Giltertinib (ASP2215)	NCT02014558	Phase-I/II	Safety Study, Open Label	TK Inhibitor
KX2-391	NCT01397799	Phase-I	Safety Study, Open Label	Src Kinase
Cabozantinib	NCT01961765	Phase-I	Safety/Efficacy Study, Open Label	VEGFR-1,2,3, FLT3 and KIT
Trebananib	NCT01555268	Phase-I	Safety Study, Open Label	Ang 1&2
Pacritinib	NCT02323607	Phase-I	Safety Study, Open Label	JAK 2
MK-1775	NCT02381548	Phase- I	Safety Study, Open Label	WEE1

Table 2. TK Inhibitors [28–38]

MAPK Inhibitors	Clinical trial identifier number	Phase	Study design	Target
Trametinib	NCT01907815	Phase-II	Efficacy Study, Open Label	MAPK
Binimetinib (MEK-162)	NCT02049801	Phase-I	Safety Study, Open Label	MEK-1/2

Table 3. MAPK Inhibitors [39–40]

mTOR Inhibitors	Clinical trial identifier number	Phase	Study design	Target
Everolimus	NCT00636922	Phase-I	Safety/Efficacy Study, Open Label	FKBP-12

Table 4. mTOR Inhibitors [41]

1. Bortezomib: It is a 26 S proteasome inhibitor with anticancer properties. By inhibiting it, bortezomib hampers several signaling pathways. This results in cell cycle arrest, differentiation, and anti-angiogenesis. It also acts as NF-kappa B inhibitor and reduces cell survival, angiogenesis and growth of tumor.

2. Ixazomib: An orally bioavailable, second-generation proteasome inhibitor (PI) with potential antineoplastic activity. Ixazomib inhibits the activity of the proteasome, blocking the targeted proteolysis normally performed by the proteasome, which results in an accumulation of unwanted or misfolded proteins; disruption of various cell signaling pathways may follow, resulting in the induction of apoptosis. Compared to first generation PIs, second generation PIs may have an improved pharmacokinetic profile with increased potency and less toxicity. Proteasomes are large protease complexes that degrade unneeded or damaged proteins that have been ubiquinated.

I. Farnesyl Transferase Inhibitor:

There is no farnesyl transferase inhibitor that is currently approved by FDA for AML. However, the below mentioned transferase inhibitors are under clinical trial, as given in the Table 5.

Drug	Clinical trial identifier number	Phase	Study design	Target
Tipifarnib	NCT00093418	Phase-II	Safety/Efficacy Study, Open Label	TK Inhibitor

Table 5. Farnesyl transferase Inhibitor [44]

J. Cytokine Therapy:

Aldesleukin[45]: A recombinant analog of the endogenous cytokine interleukin-2 (IL-2) with immunoregulatory and antineoplastic activities. Aldesleukin binds to and activates the IL-2 receptor, followed by heterodimerization of the cytoplasmic domains of the IL-2R beta and gamma(c) chains, activation of the tyrosine kinase Jak3 and phosphorylation of tyrosine residues on the IL-2R beta chain, resulting in an activated receptor complex. Various cytoplasmic signaling molecules are recruited to the activated receptor complex and become substrates for regulatory enzymes that are associated with the receptor complex. This agent enhances lymphocyte mitogenesis, stimulates long-term growth of human IL-2 dependent cell lines, enhances lymphocyte cytotoxicity, induces Lymphokine-Activated Killer (LAK) cell and Natural Killer (NK) cell activities, and induces expression of interferon-gamma. Aldesleukin may induce T cell-mediated tumor regression in some tumor types.

K. Multikinase Inhibitor:

Midostaurin [46]: A synthetic indolocarbazole multikinase inhibitor with potential antiangiogenic and antineoplastic activities. Midostaurin inhibits protein kinase C alpha (PKCalpha), vascular endothelial growth factor receptor 2 (VEGFR2), c-kit, platelet-derived growth factor receptor (PDGFR) and FLT3 TKs, which may result in the disruption of the cell cycle, inhibition of proliferation, apoptosis and inhibition of angiogenesis in susceptible tumors.

L. Immunomodulators [47–49]:

The below mentioned immunomodulators are under clinical trial

1. Lenalidomide: A thalidomide analog with potential antineoplastic activity. Lenalidomide inhibits TNF-alpha production, stimulates T cells, reduces serum levels of the cytokines, such as vascular endothelial growth factor (VEGF) and basic

fibroblast growth factor (bFGF), and inhibits angiogenesis. This agent also promotes G1 cell cycle arrest and apoptosis of malignant cells.

2. Sargamostim: A recombinant therapeutic agent, which is chemically identical to or similar to endogenous human GM-CSF. Binding to specific cell surface receptors, sargramostim modulates the proliferation and differentiation of a variety of hematopoietic progenitor cells with some specificity towards stimulation of leukocyte production and may reverse treatment-induced neutropenias. This agent also promotes antigen presentation, up-regulates antibody-dependent cellular cytotoxicity (ADCC) and increases interleukin-2-mediated lymphokine-activated killer cell function; it may also augment host anti-tumoral immunity.

3. Pomalidomide: An orally bioavailable derivative of thalidomide with potential immunomodulating, anti-angiogenic and antineoplastic activities. Although the exact mechanism of action is yet to be fully elucidated, pomalidomide appears to inhibit TNF-alpha production, enhance the activity of T cells and NK cells and enhance antibody-dependent cellular cytotoxicity (ADCC). In addition, pomalidomide may inhibit tumor angiogenesis, promote cell cycle arrest in susceptible tumor cell populations and stimulate erythropoeisis.

M. Serine/ Threonine Kinase Inhibitors:

GSK2141795 [50]: An orally bioavailable inhibitor of the serine/threonine protein kinase Akt (protein kinase B) with potential antineoplastic activity is under clinical trial. Akt inhibitor, GSK2141795 binds to and inhibits the activity of Akt, which may result in the inhibition of PI3K/Akt signaling pathway, tumor cell proliferation and the induction of tumor cell apoptosis. Activation of the PI3K/Akt signaling pathway is frequently associated with tumorigenesis and dysregulated PI3K/Akt signaling may contribute to tumor resistance in a variety of antineoplastic agents.

Conclusion

Although, there is no currently FDA approved immunotherapeutic available for AML, a number of clinical trials are going on for various classes like MABs, adoptive therapy, vaccines, and targeted therapies. Stem cell transplantation is also an important treatment therapy for AML. Allogeneic stem cell transplantation is the most widely used and efficient treatment for the management of AML. Donor cells are more beneficial due to their "graft-versus-leukemia" effect. Non-myeloablative transplant method is another technique of allo-SCT, which is utilized in older people. It uses low dose chemo and radiation therapy, before allogeneic transplantation. ASCT has been utilized in favorable risk cytogenetics and allogenic transplantation in poor risk cytogenetics. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper pre-clinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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