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Special Article - Acute and Chronic Myeloid Leukaemia

Advancement of Drugs for Myeloid Leukaemia: An Overview in the Developmental Process

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Abstract

Every year millions of people are being freshly diagnosed with cancer and a healthy amount is diagnosed with some form of myeloid leukaemia. Few decades ago treatment options for myeloid leukaemia were not so diverse and mortality rate amongst patients were very high. Things have changed dramatically due to the introduction of various treatment options; patients are being able to lead a healthy life prior to their medication period. Though conventional chemotherapy is still used but there are a variety of drugs that have been introduced which could replace chemotherapy and stem cell transplantation in near future as these new generation of drugs have a very specific mode of action and they have a minimal side effect. For example Tyrosine Kinase Inhibitor brought a revolution in the field of treatment for Chronic Myeloid Leukaemia as they bind to the ATP binding site of BCR-ABL gene, thus inhibiting the signaling process of cell division and controlling the number of tumor cell. Though Acute Myeloid Leukaemia has a higher mortality rate than Chronic Myeloid Leukaemia but some of the recent developments in the field of Immunotherapy are showing very promising result. Artificially modified T lymphocyte cell is used to differentiate the tumor cells thus controlling the cancer via body's own immune system. Some of the treatment options are still in developmental stage and some of them are not affordable by people all over the world, but the ongoing development shows a promising future in the treatment of myeloid leukaemia.

Keywords: Acute myeloid leukaemia; Chronic myeloid leukaemia; BCR-ABL; Tyrosine kinase inhibitor; CAR-T cell immunotherapy; Chemotherapy

Abbreviations

AML: Acute Myeloid Leukaemia; CML: Chronic Myeloid Leukaemia; APL: Acute Promyelocytic Leukaemia; RBC: Red Blood Cell; WBC: White Blood Cell; TKI: Tyrosine Kinase Inhibitior; IFN: Interferon; BCR: Break Point Clusture Gene; ABL: Abelson Tyrosine Kinase Gene; CAR: Chimeric Antigen Receptor; SOS: Sinusoidal Occlusive Syndrome; ATRA: All-trans Retinoic Acid; ATO: Arsenic Trioxide; GSH: Glutathione; TCR: T cell Receptor; scFV: Single Chain Antibody FV; TYK: Tyrosine Protein Kinase; JAK: Janus Kinase; GO: Gemtuzuma Ozogamicin

Introduction

Acute Myeloid Leukaemia or AML is a rare type of disease mostly affecting adults and its incidence increases with the increase in ages, although about 1.2% of cancer deaths are caused by AML [1]. It's also known as acute myelocytic, myelogenous or granulocytic leukaemia. AML is primarily caused by outgrowth and build-up of abnormal white blood cells in the bone marrow which reduces the number of RBC, platelets and normal WBC. There are also several risk factors resulting in some chromosomal abnormalities which could be responsible for AML but the real reason is still a mystery. General symptoms consist of easy bruising, bleeding, anaemia, tiredness, prone to infection. AML could be fatal if left untreated and it has a very fast growth rate. Due to the several subtypes of AML, prognosis could vary. AML has a better survival rate for people aging less than 60 years with 35-40% comparing to the 5-15% aging more than 60 years [2]. There are some pre leukemic blood disorders such as myeloproliferative disease (MPS) and myelodysplastic syndrome (MDS) that can mature and turn into AML [3]. Prolonged exposure to several chemotherapy agents such as alkylating agents [4], epipodophyllotoxins and anthracyclines [5] have been known to increase the risk of AML. Chromosomal translocation between 8 & 21 and 15 & 16 and inversion of 16 brings some cytogenetic changes which results in a subtype of AML known as Acute Promyelocytic Leukaemia (M3 or APL) [6]. Chronic Myeloid Leukaemia or CML is a rare myeloproliferative neoplasm or myelodysplastic syndrome typically caused by outgrowth and accumulation of abnormal WBC in bone marrow just as AML. CML affects relatively less number of people and they have a longer incubation time than AML but it is difficult to cure a CML than AML. Generally CML is caused by the translocation of chromosomes which activates oncogenes or deactivates tumor suppressor genes [7]. Other form of chromosomal defects contains deletion. Another main cause of CML is the deformation in Philadelphia chromosomes [8].

There are several treatments available regarding CML. Five distinct and well known treatment for CML available are Tyrosine Kinase Inhibitor (TKIs), Bone Marrow Transplant, Interferon alpha-2b (IFN-α2b), Myelosuppressive or Leukopheresis therapy and Splenectomy [9]. Most of the times the growth of a tumor cell in CML depends upon the activation of break point clusture gene (BCR) at chromosome 22 and Abelson tyrosine kinase gene (ABL) at chromosome 9, together known as BCR-ABL tyrosine

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Table 1: List of the drugs used in case of acute myeloid leukaemia.

List of Drugs	Use/ Mode of action/ Source
Cytarabine (ara-C) & Anthracycline	"7+3", used with induction chemotherapy
All-*trans*-retinoic acid (ATRA)	Used in case of M3 subtype or APL, used with induction chemotherapy. It causes the terminal differentiation of the APL cells.
Gemtuzumab Ozogamicin (Mylotarg)	Used for people who were unable to withstand high dose of chemotherapy. The drug was first come in 2000 and used till 2010 until it was withdrawn.
Arsenic Trioxide	Specific to M3 subtype only. Used in case of relapsed APL.PML-RAR alpha gene is known to cause the arrest of myeloid cell development at promyelocyte stage which accumulates in the bone marrow. ATO degrades the PML-RAR alpha gene, thus have great effect towards the APL.
Daunorubicin Hydrochloride	Used as remission induction therapy, mainly adults are treated.
Doxorubicin Hydrochloride	Chemotherapy medication
Thioguanine	Remission induction therapy, remission consolidation therapy
Cyclophosphamide	Chemotherapy medication, suppresses the immune system.
Immunotherapy by CAR-T cell	Recent advancement
Allogenic (ALLO) stem cell transplantation	Existing approach
Bone marrow Transplantation	Existing approach

kinase complex which forms the deformities in the Philadelphia chromosome. Imatinib (Gleevec) is considered as the very first drug that inhibits BCR-ABL Tyrosine kinase [10]. Dasatinib is an also a TKI more specifically BCR-ABL TKI which is used orally to prevent CML in those patients who are intolerant to Imatinib [11]. Nilotinib (AMN107) is also a TKI used in case of Imatinib intolerance. Radotinib (IY5511) [12] and Bosutinib (SKI-606) [13,14] are recently developed in case to the intolerance of the prior treatment. Sometimes BCR-ABL genes undergo a specific kind of mutation (T315I) which alters the protein binding site of Imatinib and other similar drugs, thus resulting in a futile treatment. Omacetaxine mepesuccinate or homoharringtonine (HHT) is used for in case of adult patients when multiple TKIs are intolerant by the patients [15]. It is a type of natural drug obtained from *Cephalotaxus harringtonia*. IFN-α2b is one of the oldest methods for treatment of CML but due to its higher toxicity comparing to TKIs, it is almost obsolete nowadays [16].

Chemotherapy is the main way of treating AML. It is divided into three phase, Induction chemotherapy, Post-remission chemotherapy and Consolidation chemotherapy. Alone a chemotherapy is not that much effective so a Stem cell transplantation or a bone marrow transplantation is recommended (only if the patients is able to tolerate a transplantation) in most of the times. Allogeneic (ALLO) stem cell transplantation (i.e. using donated stem cell) is done in case of patients suffering from AML [17]. This induction chemotherapy is given with (except in case of M3 subtype of AML) cytarabine (ara-C) and an anthracycline [18]. The induction Chemotherapy routine is also denoted by "7+3" because the cytarabine is given to the patients continuous IV infusions for 7 days consecutively and as IV push, anthracycline is given for 3 days consecutively [19]. Acute promyelocytic leukaemia (APL) or the M3 subtype of AML is treated with all-*trans*-retinoic acid (ATRA) with addition to induction chemotherapy, almost universally [20]. For older people aging over 60 years with relapsed AML who are unable to withstand high dosages of chemotherapy, Gemtuzumab Ozogamicin (Mylotarg), a monoclonal antibody linked cytotoxic agent is being used as a replacement [21] but the drug was withdrawn from the market by its manufacturer, Pfizer in the year of 2010 [22]. US FDA approved Arsenic trioxide for the treatment of relapsed APL and this compound is specific to the M3 subtype of AML like ATRA [23]. Another more recent advancement in the field of treatment of AML is Immunotherapy by CAR-T cell. The T-cells in patients body is modified so that they could produce special receptors on their surface which is known as chimeric antigen receptors (CARs). CARs are protein in nature which detect a specific kind of antigen released by the tumor cell and destroy them. They are generally produced in laboratory to expand rapidly and then after rapid growth they are infused in the patient's body to kill the cancer cells and when present in the patient's body, they can also multiply [24].

Acute myeloid leukaemia

AML is a fatal form of myeloid leukaemia affecting almost all the age groups. Accumulation of abnormal WBC in bone marrow results in AML. AML has a very fast growth rate and patients die very quickly if left untreated, prior to the diagnosis. Anaemia, tiredness, bruising, bleeding and prone to infection are some of the very common side effects rather symptoms in case of AML. There are some pre occurred diseases which could turn in to AML. Chemotherapy was the main mode of treatment alongside stem cell transplantation. As the science advances there are a lot of new treatment options introduced in the market which are proving a lot more efficient than conventional stem cell transplantation or chemotherapy. The lists of drugs in use and under development are enlisted in table 1.

Drugs used in the treatment of acute myeloid leukaemia

"7+3" Chemotherapy: Chemotherapy is the most common method used against AML. The anti-cancer drugs are administered orally, injected into the cerebral spinal fluid (CSF) or under the skin to control or eradicate the cancer cells. Cytarabine (ara-C) & Anthracycline is a combination of drugs, denoted by the "7+3". The administration of drug is based on 7 days of continuous application of Cytarabine (ara-C) of which the first 3 days an infusion of Anthracycline antibiotic is simultaneously given. In more recent times Cytarabine (ara-C) is used with the integration of Gemtuzuma Ozogamicin. A study has shown that 28-30% disease free survival rate could be achieved through this process of medication. However, prior to stem cell transplantation (SCT), GO could cause sinusoidal occlusive syndrome (SOS) after re-induction process [25]. In recent

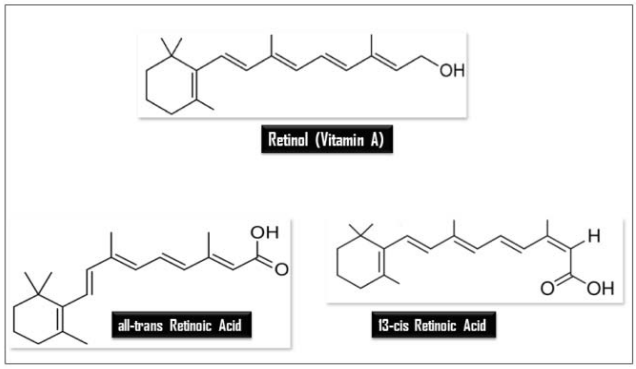

Figure 1: Schematic representing structure of Vitamin A and its derivative (ATRA and 13-cis RA).

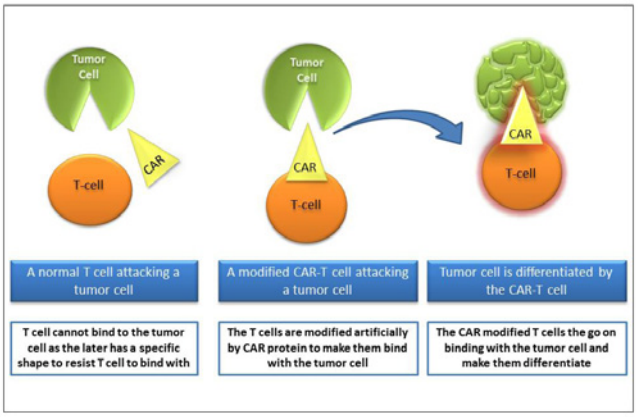

Figure 2: Schematic diagram representing the CAR-T cell mediated tumor cell differentiation.

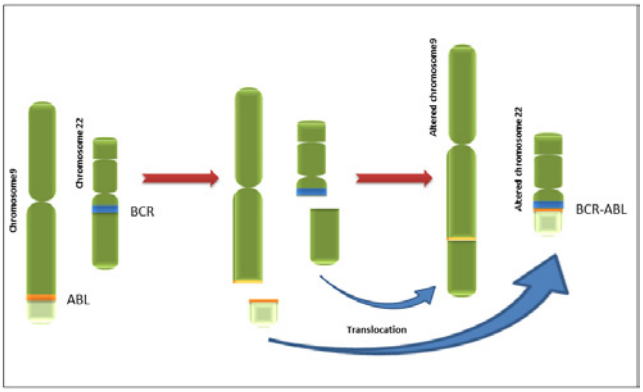

Figure 3: Schematic representation showing pathogenesis of philadelphia chromosome.

times Daunorubicin Hydrochloride is being used with Cytarabine in the chemotherapy process. Similar to Daunorubicin, Doxorubicin Hydrochloride is also used as a chemotherapy drug. They both inhibit the enzyme Topoisomerase II, which prevent the DNA from supercoiling. Due to the inhibition of Topoisomerase II, DNA undergo supercoiling, thus terminating the transcription. AS they both have various side effects and may damage the heart due to prolonged application, their usage is very much limited.

Differentiating leukaemia cells with retinoic acid: Another popular method for treating AML is using All-*trans*-retinoic acid (ATRA) by Differentiating therapy. ATRA is A Vitamin A derivative as shown in Figure 1, specifically used for the M3 subtype. Complete remission could be achieved through ATRA medication. Studies have proven that ATRA has a better remission rate than chemotherapy. ATRA has a 72% complete remission rate than chemotherapy, which has complete remission rate of 69% [26]. The mechanism by which ATRA acts on the cancer cell is still a mystery, but on a molecular basis, laboratory experiments show that ATRA drive APL cells to differentiate and prevent them from proliferating. Laboratory tests shows that ATRA drive the primary cancerous promyelocytes to differentiate in their final form, reducing the number of abnormal cells and allowing the normal cells to outgrow in the bone marrow. Recent studies have shown that ATRA and 13-cis Retinoic Acid (13-cis RA) have the same impact over APL cells but due relatively lower toxicity level in 13-cis RA; it is preferred over ATRA [27].

Arsenic trioxide targeting BCR-ABL positive acute myeloid leukaemia: In recent times, a more chemo-free treatment is being introduced and one of the widely used methods of chemo free treatment is Arsenic trioxide or ATO (As2O3). BCR-ABL derived AML is a pretty rare subtype which is now included as a provisional entity by World Health Organisation classification of myeloid malignancies, revised in 2016. Typically, BCR-ABLoncoprotein is related with CML but recent studies have shown that BCR-ABL positive AML is a new and distinct subgroup [28]. BCR-ABL oncoprotein is targeted by ATO by the p62/SQSTM1-mediated localization of the oncoprotein to the autolysosomes and successive degradation mediated by the protease cathepsin B. In general, ATO alters the autophagic process to approach BCR-ABL and later promoting its degradation [29]. ATO is also used in case of APL. The PML-RAR alpha gene causes the termination of myeloid cell development in the promyelocyte stage which later accumulates in the bone marrow to cause APL. APL was mainly treated with ATRA but nowadays it is used in combination with ATO. APL cells are very much sensitive towards ATO which causes apoptosis, angiogenesis and growth arrest. ATO also degrades the PML-RAR alpha gene and causes differentiation [30,31]. ATO also interacts with Glutathione (GSH) related enzymes. It is proposed that ATO activates the Jun N-terminal kinase (causes arsenic induced apoptosis), activator protein-1 and inhibit the dual-specificity phosphatises [30].

Stem cell transplantation as a substitute for chemotherapy: Allogenic (ALLO) stem cell transplantation is popular among aging patients or patients with rejection to chemotherapy. It is a type of transplantation where the donor is genetically non identical with the patient. Recent studies have proved that Allogenic Stem Cell Transplantation is very much successful for the elderly patients. Before the transplant, patient's allograft acceptance is checked to ensure that there will be no autoimmune response from the patient's body towards the newly transplanted stem cells. Even in normal patients, chemotherapy after transplantation has better survival chance than normal chemotherapy.

CAR mediated T-cell immunotherapy: One of the latest

Table 2: List of the drugs used in the treatment of chronic myeloid leukaemia.

List of Drugs	Use/ Mode of action/ Source
Interferon alpha-2b (IFN-α2b)	High toxicity compare to TKIs, almost obsolete. It targets the CML stem cells.
Imatinib (Gleevec)	Very first generation of drug. Tyrosine Kinase Inhibitor.
Dasatinib	Tyrosine Kinase Inhibitor.
Nilotinib (AMN107)	Tyrosine Kinase Inhibitor.
Radotinib (IY5511)	Tyrosine Kinase Inhibitor.
Bosutinib (SKI-606)	Tyrosine Kinase Inhibitor.
Omacetaxinemepesuccinate or homoharringtonine (HHT)	It is a type of natural drug obtained from *Cephalotaxus harringtonii.* Used when the patient is resistant to multiple Tyrosine Kinase Inhibitor or the patient acquires the BCR-ABL-T315I mutation. It is a natural alkaloid that inhibits protein synthesis and induces cell
Splenectomy	Existing approach but have post operative complications like infections, thrombocytosis and hepatomegaly.
Myelosuppressive or Leukopheresis therapy	The therapy is used along with TKIs to control the WBC count.
Bone Marrow Transplant	Existing approach

advancement in the field of AML medication is immunotherapy by CAR-T cell. Blood is drawn from the patient and the immature T cells are isolated. The isolated T cells are then modified with Chimeric Antigen Receptor which helps the T cells to bind with the tumor cells more firmly and destroy them. CARs are a kind of protein that is specially modified to link a target cell ligand recognition domain to signaling regions from the T-cell receptor (TCR). The most common ligand recognition domain is a single chain antibody Fv (scFv) which recognize a surface molecule of a tumor cell shown in Figure 2. The CAR modified T cells are then left to mature artificially and after maturation, then the cells are incorporated in the patient's body to fight of cancer. CAR-T cell immunotherapy was first developed for B cell malignancies but myeloid leukaemia has also been effectively targeted with CAR-T cells [24,32].

Chronic myeloid leukaemia

Chronic Myeloid Leukaemia is a less fatal type of myeloid leukaemia and complete remission could be achieved through medications nowadays. Formation of BCR-ABL gene due to the translocation of chromosome 9 and chromosome 22 or Philadelphia chromosome results in the CML (Figure 3). This event also results in deactivation of tumor suppressor gene which further results in growth of tumor cell in the body. Interferon was primarily used as the main mode of treatment but due to various side effects it was replaced by TKIs. The lists of drugs in use and under development are enlisted in Table 2.

Medication used for the treatment of chronic myeloid leukaemia

Interferon mediated treatment to eradicate malignant cells: CML has a lot more survival rate than AML and due to the recent development of many advance drugs; it has a high complete remission rate. IFN-α2b, an antiviral drug, is the first generation of drugs used to treat CML. It was developed in the biotech company BIOGEN, cofounded by molecular biologist Charles Weissmann, University of Zurich. Interferons are a batch of signaling proteins, released by the host cell upon the presence of tumor cell in host body. IFN-α2b binds to its receptor, IFN-α Receptor 1 and 2 (IFN-αR1/2). Upon ligand binding the Non-receptor tyrosine-protein kinase (TYK2) protein associated with IFN-αR1 is phosphorylated which in turn phosphorylates Janus kinase 1 (JAK1) associated with IFN-αR2. This kinase transduces signal by phosphorylating signal transducer and activator of transcription (STAT) 1 and 2 through JAK1 and TYK2 respectively. The phosphorylated STATs then dissociate from the receptor, which is a heterodimer and form an interferon transcription factor with p48 (Neucleotide excision repair protein) and interferon regulatory factor 9 (IRF9) to form the interferon stimulate transcription factor-3 (ISGF3). Then ISGF3 translocates to the nucleus where it transcribe several genes involved in cell cycle control, cell differentiation, apoptosis and immune response which in turns help to eradicate malignant cells from the body [33].

Stem cell transplantation is being out-dated: Like AML, bone marrow transplantation was an early form of treatment. Due to the fact that cancer cells cannot be eradicated from the body completely, they tend to invade the bone marrow and infect it. Thus occurring of relapses was very much common. So, nowadays transplantation is very much obsolete to treat CML.

Development of tyrosine kinase inhibitors: Over the course of last 15 years, treatment for CML has been dramatically improved with the development of Tyrosine Kinase Inhibitors (TKIs), specifically BCR-ABL TKIs which specially target BCR-ABL. BCR-ABL is an activated form of tyrosine kinase complex protein, which causes Philadelphia chromosome translocation. Normal functioning TK requires other cellular messaging protein to activate and initiate cell division. On the other hand, BCR-ABL TK requires none such proteins to activate. They activate on their own and also activate a number of cell cycle controlling proteins and enzyme, which result in uncontrolled cell division. Our body could not control this type of cell division and the number of malignant cell increase rapidly. TKIs bind to the ATP binding site of BCR-ABL, thus inhibiting the enzyme activity and controlling the cell division. Imatinib is the first generation TKI drug that came into market at 2001. It destroys the malignant cells by inhibiting the BCR-ABL enzyme and allows the normal cells to grow in the bone marrow but as there is always a chance of survival of a single malignant cell, so the treatment has to be continued indefinitely. There a series of oncogenic proteins that blocks the action of Imatinib. The resistance was caused by a mutation in the BCR-ABL which is known as T315I mutation. When a single Cytosine to Thymine base pair substitution occurs at position 944 of the ABL gene sequence, which is codon '315' of the

ABL protein, resulting in amino acid Threonine being substituted by Isoleucine at that position. This resistance to Imatinib was later solved by introducing a couple of second generation TKIs which are more potent to inhibit BCR-ABL. Dasatinib was the first drug of generation 2 TKI which was first approved in 2007. Dasatinib is very much powerful to inhibit the activity of BCR-ABL TK. Nilotinib in 2010 and Radotinib in 2012 joined Dasatinib as the second generations of TKIs. In late 2012, Bosutinib was introduced as TKI when the patients were intolerant to prior the therapy.

Non kinase inhibitor as a backup for tyrosine kinase inhibitor: In recent years a non-kinase inhibitor, Omacetaxinemepesuccinate or homoharringtonine (HHT) is developed which is a protein synthesis inhibitor. The mechanism in which Omacetaxinemepesuccinate prevents the CML is still a mystery. Formerly known as Homoharringtonine (HHT), it is in clinical trial long before the inception of Imatinib. Nowadays patients are treated with Omacetaxinemepesuccinate when they face 2 or 3 TKI reistance. One disadvantage of this drug is that it has a substantial myelosuppression and some patients could require transfusion. Though the responses from treatment with this drug are not so exciting but it is good to have a treatment option open for patients when the all other treatment options fails.

Discussion

Two decades ago myeloid leukaemia was almost incurable. As the science progresses, many medications were introduced to treat the cancer, but not all the treatment options were successful. In the past, complete recovery rate was very much low, due to which it was a terrorizing feeling if one was diagnosed with cancer because available treatments could only prolong one's life period by a mere of few years and those treatments were very much costly.

CML is now treated with various TKIs, but prior to that complete remission was hardly observed. Stem cell transplant and chemotherapy were the first generation of treatment for patients diagnosed with CML. These treatments resulted in very little complete remission and they only could delay the median survival time up to 3-5 years from the time when patients were first diagnosed with CML.IFN-α2b, cytarabine and various steroids were used in the early years but they showed very little amount of cure amongst patients and death was inevitable. In the beginning of 21st century a revolution in the field of treatment for CML broke out due to the invention and use of BCR-ABL TKIs. These kinase inhibitors specifically target the BCR-ABL mutation caused by Philadelphia Chromosome translocation. IRIS, a globally conducted studies showed the effectiveness of TKIs over conventional IFN-α2b and cytarabine combination. Recent studies have found that BCR-ABL undergoes a specific kind of mutation i.e. T315I mutation which alters the ATP binding site of TKI resulting in resistance towards TKI.

Resistance towards the prior treatment led to develop a kind of non kinase inhibitor Omacetaxinemepesuccinate to treat CML.

Unlike CML, AML do not have that high complete remission rate. Comparing to CML, AML grows very rapidly and the patients experience acute symptoms more quickly. Chemotherapy using Cytarabine &Anthracycline combination and a bone marrow transplantation or stem cell transplantation could slow down the rate of growth of AML but in maximum cases they cannot cure the disease completely. In recent times some new drugs are being used in chemotherapy such as Gemtuzuma Ozogamicin, Doxorubicin Hydrochloride and Danurubicin Hydrochloride. Treatments options were enriched prior to the introduction of ATRA and ATO. ATRA, specific to the APL, differentiate the tumor cell thus controlling their number in patient's body which help them to lead a normal life for a long period of time. A recent study have shown that the Philadelphia chromosome translocation is causing AML is case of some patients. This distinct sub type of AML is being treated with ATO which has been approved by WHO. There are some recent advancement also being observed in the treatment of AML and one of the distinct treatment method ios immunotherapy by CAR-T cell where T cells from patient's body is being modified to fight of tumor cells. This process is still in experimental stages but we can surely say that it will bring on a revolution in the field of AML.

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