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# Treatment of Acute Myeloid Leukemia

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#### Abstract

Acute myeloid leukemia (AML) is the most common leukemia affecting adults. In this paper some chemotherapic treatments are described, including the mechanisms and chemical structure of those compounds. The best treatment consists in the mixture of a nucleotide analog and an anthracycline.

**Keywords:** Acute myeloid leukemia; Acute nonlymphocytic leukemia; Chronic myeloid leukemia

## Introduction

Acute myeloid leukemia (AML), also known as acute myelogenous leukemia or acute nonlymphocytic leukemia (ANLL) consists in a proliferation of the myeloid line of blood cells in the bone marrow (Figure 1). The normal bone marrow synthesizes a small number of blood stem cells, which differentiates to generate the mature bloodforming cells. During this process, lymphocytes (kind of white blood cells) are obtained from the lymphoid line, whereas the myeloid line generates other white blood cells (no lymphocytes), red blood cells and platelets.

Depending on the type of bone marrow cells affected (i.e. myeloid or lymphoid), leukemias are classified in myeloid (or myelogenous) leukemia and lymphocytic (or lymphoblastic) leukemia. The first ones affect to the myeloid progenitor of the bone marrow and the latter to the lymphoid progenitor. Differences between the acute and chronic leukemia are that in acute leukemia, the bone marrow cells cannot mature properly; whereas in chronic leukemia, cells can mature partly but not completely.

Following this classification, leukemias are classified in four main types:

- Acute myeloid (or myelogenous) leukemia (AML)
- Chronic myeloid (or myelogenous) leukemia (CML)
- Acute lymphocytic (or lymphoblastic) leukemia (ALL)
- Chronic lymphocytic (or lymphoblastic) leukemia (CLL)

In myeloid leukemias there is an impaired production of myeloid normal blood cells, which yields a pancytopenia, i.e. reduction of erythrocyte, normal lymphocyte and platelets. Despite on the genetic syndromes, AML is the most common acute leukemia affecting adults and its incidence increases with the population ages.

AML is generally a disease of older people, being the average age of these patients about 66 years. In the United States, there were 14,590 new AML cases in 2012, most of them adults; and 10,370 deaths. This disease is uncommon before the age of 45, being more common among males (risk of 1 in 227) than among females (risk of 1 in 278) [1].

Risks to develop an AML include smoking, certain blood disorders, some genetic syndromes, exposure to certain chemicals (including chemotherapy), and exposure to radiation. The risk is increased by exposure of certain chemicals, such as benzene, and sometimes AML can be a consequence of a certain chemotherapy drugs (such as alkylating agents and platinum agents). Some patients treated with these agents often generate a myelodysplasic syndrome before the AML, which is observed 8 years after chemotherapy. The most common alkylating agents include cyclophosphamide, mechlorethamine, procarbazine, chlorambucil, melphalan, busulfan and carmustine; whereas platinum agents include cisplatin and carboplatin.

Symptoms of AML include weight loss, fatigue, fever, shortness of breath, easy bleeding, increase risk of infection and loss of appetite [2]. Nevertheless, some of these symptoms are also observed in other leukemia. Although several risk factors have been identified, the specific cause is not clear, and this can be difficult to classify AML. In fact, the most commonly used classifications for AML include the older French-American-British (FAB) system [3,4] (Table 1) and the new World Health Organization (WHO) system [5] (Table 2). Both classifications are still used nowadays.

Some genetic syndromes are specially related to AML, in particular those related with chromosomes 8 and 21, as Down syndrome (an extra copy of chromosome 21) or trisomy 8 (an extra copy in chromosome 8). Nevertheless, other genetic mutation present in the birth degenerate also in AML, as happens with Fanconi anemia (chromosome 9), Louis-Barr syndrome (chromosome 11), Blackfan-Diamond syndrome (chromosome 19), Shwachman syndrome (chromosome 7), Li-Fraumeni syndrome (chromosome 17), neurofibromatosis I and Kostmann syndrome. Nevertheless, despite these genetic alterations, AML is the most common acute leukemia affecting adults and its incidence increases with the population ages [6].

Treatment of AML, as in other cancers, is divided in two phases: induction therapy (to achieve a complete remission by reducing the number of leukemic cells) and maintenance therapy (to consolidate and eliminate any residual and to achieve the complete cure). Although both treatments are based in inhibition of cell division or DNA synthesis, induction therapy includes more aggressive treatments, including radiation therapy and chemotherapy. In general, the mechanism of chemotherapy drugs consists in killing cancer or normal cells that divide rapidly, and therefore they include the rapidly dividing bone marrow cells, digestive tract cells and hair follicles. In

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Туре	Name
MO	Minimally differentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia, without maturation
M2	Acutemyeloblastic leukemia, with granulocytic maturation
M3	Promyelocytic, or acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
M4eo	Myelomonocytic together with bone marrow eosinophilia
M5 M5a	Acute monoblastic leukemia
M5b	Acute erythroid leukemia
M6 M6a	Erythroleukemia
M6b	Very rare pure erythroid leukemia
M7	Acute megakaryoblastic leukemia
M8	Acute basophilic leukemia

Table 1: The French-American-British (FAB) classification of AML In the 1970s, a group of French, American, and British experts divided acute myeloid leukemias into eight subtypes (M0-M7). Later, in 1999 [4], a ninth subtype was proposed (M8).

Broad group	Description
AML with certain recurrent genetic abnormalities	AML with a translocation between chromosomes 8 and 21 AML with a translocation or inversion in chromosome 16 AML with changes in chromosome 9 and 11 APL (M3), with translocation between chromosomes 15 and 17
AML with multilineage dysplasia	More than one abnormal myeloid cell type is involved
AML related to a previous chemotherapy or radiation	
AML not otherwise specified (includes cases of AML not in the previous broad groups)	<ul> <li>M0: Undiferentiated AML</li> <li>M1: AML with minimal maturation</li> <li>M2: AML with maturation</li> <li>M4: Acute myelomonocytic leukemia</li> <li>M5: Acute monocytic leukemia</li> <li>M6: Acute erythroid leukemia</li> <li>M7: Acute megakaryoblastic leukemia</li> <li>Acute basophilic leukemia</li> <li>Acute panmyelosis with fibrosis</li> <li>Myeloid sarcoma (also known as granulocytic sarcoma or chloroma)</li> </ul>

Table 2: World Health Organization (WHO) classification of AML

Although FAB classification is still in use, it does not take into account many of the clinical factors that impact diagnosis (outlook). In 2001, the World Health Organization (WHO) published a new system to better classify cases of AML based on patient's outlook.

fact, lateral problems observed in cancer chemotherapy include bone marrow impairs (myelosuppression, including immunosuppression), digestive tract problems (mucositis, or inflammation of the digestive tract) and hair loss (alopecia). In fact, and as a collateral problem, some chemotherapic drugs are able to induce a bone marrow impair and AML. This is the case of some alkylating agents, and for this reason those compounds are not used for AML treatment.

Traditional chemotherapeutics include alkylating agents, antimetabolites (including antifolates or purine and pyrimidine analogues), topoisomerase inhibitors (including some anthracyclines), other plant alkaloids and other tumor agents [7]. All these drugs affect cell division or DNA synthesis. Some new compounds do not directly interfere with DNA, but direct bind to cancer cells or interfere signal transduction. These latter compounds include monoclonal antibodies and tyrosine kinase inhibitors.

The usual treatment of AML includes antimetabolites and anthracyclines, or bone marrow transplantation (for young patients). Nevertheless, in the following, it will be discussed also the effect of other drugs.

## **Nucleotide Analogs**

Anti-metabolites are compounds similar to purines or pyrimidines, which become the building-blocks of DNA. They prevent the normal nucleotides from being incorporated into DNA during the "S" phase (synthesis of DNA) of the cell cycle, stopping normal development and division. They can also affect RNA synthesis. The first nucleotide analogs, acyclovir or ganciclovir, were used as anti-viral. These compounds didn't contain the sugar moiety (Figure 2). In the 1950s, two nucleotides were isolated from the Caribbean sponge *Tethya crypta*, which contained an arabinose sugar rather than a ribose. These compounds led to the synthesis of a new generation of nucleotide analogs [8], which were used as anti-viral but also as anti-cancer drugs [9].

Cytarabine, also known as cytosine arabinoside or AraC is one of these compounds, where the ribose of a cytidine is substituted by an arabinose. AraC is a chemotherapeutic agent used mainly in white blood cells cancers, such as AML and non-Hodgin lymphoma [10]. The mechanism of action of AraC consists in acting as an antimetabolic agent. It is quickly converted by deoxycytidine kinase and other kinases to cytosine arabinoside triphosphate, which damages the cell cycle by stopping it in the "S" phase (synthesis of DNA). It also inhibits both DNA [11] and RNA polymerases and nucleotide reductase, enzymes needed for DNA synthesis.

Another nucleotide analog is vidarabine or AraA. AraA contains the base adenine bound to the sugar arabinose (instead of the ribose). These two arabinose nucleotides are able to cross the blood-brain barrier, and at high concentrations can be toxic for the neuronal system.

The next generation of nucleotide analogs includes a halogen in the C2 position of the base bound to the arabinofuranosyl moiety, thus increasing its stability. Cladribine contains a chloro and fludarabine a fluoro group. Fludarabine is highly effective in the treatment of chronic lymphocytic leukemia, and it has been used together with cytarabine





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and granulocyte coloni-stimulating factor in the treatment of AML [12].

Clofarabine is a rationally designed new-generation of purine nucleoside analog. It was synthesized based on the experience with the earlier deoxyadenosine analogs fludarabine and cladribine, both previously used for the treatment of hematologic malignancies. Its halogenation at the 2-position of adenine made this compound resistant to intracellular degradation through adenosine deaminase. Furthermore, substitution of the fluorine at the C-2'-position of arabinofuranosyl moiety of clofarabine, increases its stability in gastric acid and decreases phosphorolysis by *E. coli* purine nucleoside phosphorylase in the gastrointestinal tract [13-15].

Thus, comparing to fludarabine and cladribine, clofarabine has more bioavailability (more resistance to deamination and phosphorolysis), higher affinity to deoxycytidine kinase, prolonged retention of triphosphate compound in leukemic blasts, and a potent inhibition of DNA synthesis.

In studies with 31 patients adults with AML, patients received clofarabine at an intravenous dose of 40 mg/m<sup>2</sup> daily for 5 days every 3-6 weeks. Of the 31 patients with AML, 13 (42%) achieved a complete remission, and four (13%) a remission with incomplete platelet recovery [16]. In 53 older patients (with a median age of 61 years) with AML, a total of 31 patients (52%) achieved a complete remission and five (8%) a remission with incomplete platelet recovery, and nine patients (15%) died while the study [17,18]. It seems, therefore, that clofarabine is a good compound to treat AML, with more than 50% of remission.

#### Anthracyclines and Topoisomerase II Inhibitors

Topoisomerases are enzymes that maintain the topology of DNA. Inhibitors of topoisomerases interfere with both transcription and replication of DNA. There are two types of topoisomerases, and their inhibitors include irinotecan and topotecan (type I), amsacrine, etoposide, teniposide (type II). Their structure contains a quinolone ring, condensed with another indol or benzene ring.

Daunorubicin or daunomycin (daunomycin cerubidine) is a chemotherapeutic of the anthracycline family (Figure 3). It was initially isolated from *Streptomyces peucetius*. The compound, at a dose is of 90 mg/m<sup>2</sup> per day is used combined with other chemotherapeutic drugs (as AraC), at a dosis of 100 mg/m<sup>2</sup> per day, for treatment of AML. It has been also used to treat neuroblastoma or the blastic phase of chronic myelogenous leukemia. The mechanism of action of daunorubicin consists in an intercalation in DNA and inhibition of DNA transcription [19] by inhibiting topoisomerase II. Administration of daunorubicin should be performed via intravenous infusion, and never intramuscularly or subcutaneously, as it can cause damage to the nervous system and may lead to death [20].

Daunorubicin has been also used as the starting material for semisynthetic drugs such as doxorubicin, epirubicin and idarubicin (Figure 3). Doxorubicin, or hydroxydaunorubicin, is distributed with the names Adriamycin PFS, Adriamycin RDF, or Rubex. This compound is also available encapsulated in liposomes with the names Doxil (USA), Caelyx and Myocet. Epirubicin is commercialized with the nameEllence (US) and Pharmorubicin or Epirubicin Ebewe (elsewhere). Idarubicin, or 4-demethoxydaunorubicin, is distributed with the names Zavedos (UK) and Idamycin (USA), and it is currently combined with cytosine arabinoside (AraC) as a first treatment of AML.

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### Alkaloids preventing microtubule function

These are alkaloids derived from plants, and their action consists in blocking cell division by preventing microtubule function. These compounds are not usually used for AML. The main known alkaloids are vinca alkaloids, Podophyllum alkaloids and taxanes. Vinca alkaloids (vincristine, vinblastine, vinorelbine, vindesine) were obtained from the Madagascar periwinkle (*Catharanthus roseus*, formerly known as *Vinca rosea*).

Other alkaloids derived from the American Mayapple (*Podophyllum peltatum*) or the Himalayan Mayapple (*Podophyllum hexandrum*). These alkaloids include etoposide and tenoposide, and they prevent the cell from entering the "G1" phase (start of DNA replication) and the "S" phase (replication of DNA) of the cell cycle.

Taxanes enhance stability of microtubules, preventing the separation of chromosomes during anaphase. The natural taxane is paclitaxel (known as Taxol), derived from the bark of the Pacific Yew tree. Docetaxel is a semi-synthetic analogue of paclitaxel.

#### Alkylating agents

Some alkylating agents are active as anti-cancer drugs. They stop tumor growth by crosslinking guanine nucleobases in DNA doublehelix strands, directly attacking DNA. This makes the strands unable to uncoil and separate. As it is necessary to separate the strands in DNA replication, the cells can no longer divide. Some examples of alkylating agents include cisplatin and carboplatin, but also mechlorethamine, cyclophosphamide, chlorambucil and ifosfamide [7].

#### Monoclonal antibodies

One possible treatment for cancer involves monoclonal antibodies that bind only to cancer cell-specific antigens and induce an immunological response against the target cancer cell [7]. Gemtuzumab is one of such monoclonal antibodies, which was used from 2000 to 2010 to treat AML. Gemtuzumab is a monoclonal antibody to CD33, a protein expressed in most leukemic blasts cells but also in normal hematopoietic cells. In the United States it was very quickly approved in 2000 by the FDA, in an accelerated-approval process, for patients over 60 years [21]. But after observing a higher mortality of the group taking the monoclonal antibody compared to those not taking the antibody, the product was withdrawn in 2010. Nowadays it is no longer used for AML treatment.

#### Tyrosine kinase inhibitors

Protein kinases are a group of enzymes which transfer the gamma (terminal) phosphate from nucleotide triphosphates (often ATP) to an aminoacid residue (serine, threonine or tyrosine) in a protein substrate side chain, resulting in a conformational change of the protein substrate, thus affecting its function.

BCR-ABL is a constitutively activated tyrosine kinase that is associated with chronic myeloid leukemia [22]. Tyrosine kinase activity is crucial for BCR-ABL, and its inhibition improves cancer symptoms to these patients. Among currently available tyrosin kinase inhibitors to treat chronic myeloid leukemia are imatinib, dasatinib, nilotinib, bosutinib and ponatinib.

## Antioxidants from the diet

There is a strong correlation between diet and cancer, and a large number of studies suggest that a daily intake of fruits and vegetables can reduce the incidence of several types of cancers [23-25]. Fruits and



vegetables contain phytochemicals with specific anti-cancer properties, which have been studied by many researchers. These studies of the anticancer activities of phytochemicals have contributed to the field of chemoprevention, which is defined as the use of naturally occurring agents to inhibit, reverse or retard tumorogenesis [26].

Chemopreventive agents act at different levels, including modulation of hormones, inhibition of oncogene activity, activation of tumor suppressor genes, induction of apoptosis, restoration of immune response, inhibition of angiogenesis, diminution of inflammation and scavenge of reactive oxygen species (ROS) [27]. Depending on their action, chemopreventive agents can be classified into two main categories: blocking and suppressing agents. The former prevent carcinogens from damaged cells enhancing detoxification, modifying carcinogen uptake and metabolism, scavering ROS and other oxidative species, and enhancing DNA repair [27]. The latter inhibit cancer promotion and progression after the formation of neoplastic cells [28].

Quercitin is one of the main flavonoids present in fruits and vegetables, with a daily uptake between 5 mg and 40 mg, which can increase up to 10-fold if the diet includes fruits and vegetables rich in this compound, such as onions, apples and strawberries [29]. The chemopreventive effect of polyphenols has often been associated with their antioxidant activity.

Quercitin is a C6-C3-C6 polyphenol widely present in plant

derived foods and beverages that acts as a powerful antioxidant. After absorption, quercitin is metabolized by conjugation to methyl or sulfate groups or to glucuronic acid [30]. Absorption of quercitin is influenced by gut microflora, and total quercitin derived front the diet is present in the plasma at the nanomolar range (<100 nM) although it can increase to the micromolar range after a 28 days supplementation with 1 g/day (around 1.5  $\mu$ M) [31]. Nevertheless, the International Agency for Research on Cancer (IARC) has stated that quercitin cannot be classifiable as carcinogenic to humans [32]. But the phase I clinical trial in humans recommended a dose of 1.4 g/m<sup>2</sup>, which corresponds to about 2.5 g for a 70 kg individual, administered via intravenous infusion at three-week or weekly intervals. At higher doses, up to 50 mg/kg (about 3.5 g/70 kg), renal toxicity was detected without signs of nephritis or obstructive uropathy [33].

#### Stem cell transplant

Traditional chemotherapeutic agents act by killing cells that divide rapidly, one of the main properties of most cancer cells. In AML combination of nucleotide analogs and anthracyclines seems the best treatment, but for younger it is generally used marrow transplant, if this is possible.

The best postremission therapy for intermediate-risk AML (normal cytogenetics or cytogenetic changes not falling into good-risk or high-risk groups) is less clear and depends on the specific situation, including

the age and overall health of the patient, the patient's personal values, and whether a suitable stem cell donor is available [34].

For patients who are not eligible for a stem cell transplant, immunotherapy with a combination of histamine dihydrochloride (Ceplene) and interleukin 2 (Proleukin) after the completion of consolidation has been shown to reduce the absolute relapse risk by 14%, translating to a 50% increase in the likelihood of maintained remission [35].

#### Conclusions

All FAB subtypes except M3 are usually given induction chemotherapy with cytarabine (AraC) and an anthracycline (most often daunorubicin). This induction chemotherapy regimen is known as "7+3" (or "3+7"), because the cytarabine is given as a continuous intravenous infusion for seven consecutive days while the anthracycline is given for three consecutive days as an intravenous push. Up to 70% of patients will achieve a remission with this protocol [36]. Other alternative induction regimens, including high-dose cytarabine alone or investigational agents, may also be used [37,38]. Because of the toxic effects of therapy, including myelosuppression and an increased risk of infection, induction chemotherapy may not be offered to the very elderly, and the options may include less intense chemotherapy. The M3 subtype of AML is almost universally treated with all-*trans*-retinoic acid in addition to induction chemotherapy, usually an anthracycline [39-41].

The goal of the induction phase is to reach a complete remission. Nevertheless, a complete remission does not mean that the disease has been cured; rather, it signifies no disease can be detected with available diagnostic methods. Even after complete remission is achieved, leukemic cells likely remain in numbers too small to be detected with current diagnostic techniques. If no further postremission or consolidation therapy is given, almost all patients will eventually relapse. Therefore, more therapy is necessary to eliminate nondetectable disease and prevent relapse — that is, to achieve a cure.

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