

Leukemia and Therapy

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Abstract: Problem statement: Leukemia is a cancer which linked intimately with the immune system. It is a group of heterogenous neoplastic disorder of white blood cells characterized by the uncontrolled proliferation and block in differentiation of hematopoietic cells. Generally, leukemia can be classified into myeloid or lymphoid referring to the type of abnormal cell found most in the blood. **Approach:** Many drug discovery researches have utilized the leukemic cell lines to screen for their potential as chemotherapy agents for leukemia. **Results:** The understanding on the types of leukemia and current choice of chemotherapy drugs can help to select the best target cell lines to study and the most suitable chemotherapy drug as positive control. **Conclusion/Recommendations:** This review cover types of leukemia, current option of chemotherapy drugs and some potential cytotoxic and immunomodulatory natural products targeting leukemic cancer cell line.

Key words: Leukemia, therapy, cytotoxic, natural products

INTRODUCTION

Cancer is a heterogeneous group of diseases, characterized by uncontrolled growth of cell population (Gomathi and Thangaraj, 2010). Continuous division of these cells results in the formation and growth of tumors. Tumors are classified with reference to a number of criteria including their behavior, their appearances and their origins (Evans, 1991). Cancer cells escape from many of the normal homeostatic mechanism that control proliferation (Goodman, 2008).

Clinical experience indicates that there are two fundamental types of tumors, benign and malignant, which behave in different ways (Darnell *et al.*, 1986). Benign tumors remain localized and do not spread to different part of body (Evans, 1991). Malignant tumors do not remain localized and encapsulated. They invade surrounding tissues, get into the body's circulating system and set up areas of proliferation away from the site of their original appearance (Darnell *et al.*, 1986).

Most tumors contain alterations in both tumor-suppressor genes and oncogenes, suggesting that the lost of a tumor-suppressor genes function within a cell must be accompanied by the conversion or activation of proto-oncogenes into an oncogene before the cell becomes fully malignant (Becker *et al.*, 2000). Proto-

oncogenes and tumor-suppressor genes encode many kinds of proteins that help control cell growth and proliferation. Mutations in these genes can contribute to the development of cancer (Lodish *et al.*, 2000).

Cancerous tumor is the disease of malignant tumors. Malignant tumors or cancer are aggregates of cells caused by a series of chromosomal changes. Cancer cells often differ from their normal neighbors by a host of specific phenotypic changes, such as rapid division rate, invasion of new cellular territories, high metabolic rate and altered shape. Transformation of normal cells to malignant cells may triggered by several factors including chemical exposure, viruses and radiations. It also can occur deliberately under cellular control during the processes such as meiosis or hypermutation (Alves *et al.*, 2011; Lodish *et al.*, 2000).

Cancers originate within a single cell. Hence, cancers can be classified by the type of cell in which it originates and by the location of the cell as carcinomas, adenocarcinomas, malignant melanoma, sarcomas, leukemias, lymphomas or teratocarcinomas. Carcinomas originate in epithelial cells. Adenocarcinomas originate from glandular epithelial tissue. Malignant melanoma arises in melanocytes, a pigmented epithelial cell. Sarcoma begins in the connective tissue of bone or muscle. Leukemias start in

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the bone marrow stem cells. Lymphoma is a cancer originating in lymphatic tissue. Teratocarcinomas begin within germ cells (Evans, 1991).

Leukemia: Leukemia is a cancer which linked intimately with the immune system. It is a malignant hematopoietic disease characterized by an uncontrolled proliferation and block in differentiation of hematopoietic cells (Lee *et al.*, 2007). These malignant cells can spread to the lymph nodes, spleen, liver and other tissues. Leukemia is broadly classified as acute or chronic referring to the type of cell affected and by the rate of cell growth and of myeloid or lymphoid according to the type of cell that is multiplying abnormally. Acute leukemia signifying rapidly progressing disease with a presence of immature, blast cells, while chronic leukemia, denotes slowly progressing disease with more mature and well-differentiated cells. Some chronic leukemia may transform into an acute phase as “blast crisis” (Leonard, 1998).

The leukemias are classified in accordance with silent pathological features of the abnormal excessive hemopoietic cells (Mughal and Goldman, 2003). They are four major subtypes of leukemia and several rare forms. The acute leukemias are divided into Acute Myeloid Leukemia (AML) and Acute Lymphocytic Leukemia (ALL). The chronic leukemias are divided into Chronic Myeloid Leukemia (CML) and Chronic Lymphocytic Leukemia (CLL). Other, rare types of leukemia include hairy cell leukemia, sezary cell leukemia, plasma cell leukemia, prolymphocytic leukemia and the leukemia phase of lymphoma (Ball and Kagan, 2007). According to Lee *et al.* (2007), leukemia might affect people of all ages.

Type of leukemia:

Acute Myeloid Leukemia (AML): Acute myeloid leukemia or Acute Myelogenous Leukemia (AML) is characterized by the malignant transformation of myeloid stem cells in the bone marrow, which are in capable of normal differentiation and maturation (Mughal and Goldman, 2003). This type of leukemia is also referred to as Acute Nonlymphocytic Leukemia (ANLL) because nonlymphoid cells are affected (Lowenberg *et al.*, 1999). Since the normal hematopoiesis is organized hierarchically, the malignant transformation can occur at several levels. AML may arise in a stem cell capable of differentiating into cells of erythroid, granulocytic, monocytic and megakaryocytic lineages, or in a lineage-restricted stem cell (Mughal and Goldman, 2003). AML is most common between ages 63-65 years among adults (Lowenberg *et al.*, 1999).

Table 1: French-American-British (FAB) classification of Acute Myeloid Leukemia

Designation	Description
M0	Undifferentiated leukemia
M1	Acute myeloblastic leukemia with immature cells
M2	Acute myeloblastic leukemia with some mature cells
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M5	Acute monocytic leukemia
M6	Erythroleukemia (immature red and white blood cells)
M7	Acute megakaryocytic leukemia (immature platelets megakaryocytes)

(Leonard, 1998)

Most patients with AML present with signs and symptoms arising from bone marrow failure and organ infiltration by leukemic cells. Occasionally, patients may present as a consequence of hyperleucostasis. The diagnosis of AML is made when more than 30% of blast cells (myeloblasts) are found in bone marrow or peripheral blood (Mughal and Goldman, 2003). This results in anemia, thrombocytopenia and granulocytopenia with obvious symptoms such as fatigue, fever, dizziness, infection and bleeding. This disease has a very rapid onset. Without treatment, a patient only rarely survives more than 6-12 months (Mattiuzzi *et al.*, 2003).

AML is classically subdivided into subtypes L0 through L7 based on the various degrees of differentiation and the lineage of cell maturation using the French-American-British (FAB) classification (Table 1). M1, M2 and M3 leukemia show predominantly granulocytic differentiation and differ from one another in the extent and nature of granulocytic maturation. M4 shows both granulocytic and monocytic differentiation and M5 shows predominantly monocytic differentiation. They are usually monoblast in M5. M6 shows predominantly erythroblastic differentiation and M7 is associated with leukemic megakaryocytes (Bennett *et al.*, 1985).

Acute Lymphocytic Leukemia (ALL): Acute Lymphocytic Leukemia (ALL) also known as acute lymphoblastic leukemia is a cancer of lymphocytes. It is characterized by abnormalities of lymphoid cell precursors, leading to excessive accumulation of leukemic lymphoblasts in the marrow and other organs, in particular the spleen and liver (Mughal and Goldman, 2003). ALL is the most common cancer in children between the ages of 2 and 3 years (Gustafsson *et al.*, 1998). Approximately 85% of leukemia in children derived from the acute types (Anino *et al.*, 2002; Fitri *et al.*, 2011). Since it affects mainly children, emotion regulation has been identified as one of the key point of consideration during undergoing chemotherapy (Fitri *et al.*, 2011). It also affects adults, mainly those between 30 and 50 years of ages, accounting for 20% of all adult acute

leukemia. The disease is biologically and clinically heterogeneous and the immunophenotypic heterogeneity of ALL gradually emerged with age (Mughal and Goldman, 2003).

The presenting features of ALL are result of the depressed hematopoiesis due to the overgrowth of leukemic cells in the bone marrow. Almost 80% of patients with ALL have lymphadenopathy. The lymph nodes are usually painless and movable, the spleen and liver are also frequently enlarged, with up to 70-75% of patients presenting with hepatomegaly and/or splenomegaly. The most common initial symptoms of ALL are attributable to anemia, neutropenia and thrombocytopenia. They are manifested by fatigue, weakness, fever, weight loss and bleeding (Henderson and Afshani, 1990). Rarely, patients may present with respiratory difficulties as a consequence of a mediastinal mass (Mughal and Goldman, 2003).

ALL is divided into subgroups L1-L3 categorized according to the French-American-British (FAB) Classification based on the appearance of the leukemia or blast cells (Table 2). In the subtype L1, the lymphoblast is relatively small with scanty cytoplasm and inconspicuous nucleoli. The lymphoblast is larger with more abundant cytoplasm in the subtype L2. In the subtype L3, the lymphoblast is mature and resembles the Burkitt's-Like leukemia (Mughal and Goldman, 2003).

Chronic Myeloid Leukemia (CML): Chronic Myeloid Leukemia (CML) is also known as chronic myeloid, chronic myelocytic leukemia or chronic granulocytic leukemia. CML is a clonal disease that results from an acquired genetic change in a pluripotential hemopoietic stem cell (Mughal and Goldman, 2003). CML is a myeloproliferative disorder characterized by a biphasic or triphasic clinical course in which a benign chronic phase is followed by transformation into an accelerated and blastic phase (Faderl *et al.*, 1999). It is characterized by the uncontrolled proliferation of granulocytes and usually accompany with proliferation of erythroid cells and megakaryocytes. This disease occurs mainly in adults and very small numbers of children develop this disease (Mughal and Goldman, 2001; Melo and Chuah, 2007).

Common early symptoms of CML are fatigue, tiring easily, weight loss and a sense of fullness in the upper abdominal from an enlarged spleen, which is the most common finding at diagnosis. The swollen spleen (splenomegaly) may fill most of the abdomen.

Table 2: French-American-British (FAB) classification of acute lymphocytic leukemia

Designation	Description
L1	The lymphoblasts tend to be small, with little cytoplasm and regularly shaped nuclei; they are more mature in appearance than other subtypes
L2	The lymphoblasts appear more immature, varying in size and nuclear shape
L3	The lymphoblasts tend to be large, with abundant cytoplasm and similarly shaped nuclei.

(Leonard, 1998)

Headaches, sweating, fever and bone pain or tenderness also may occur. About 90% of CML patient have a genetic translocation between chromosom 9 and 22 in their leukemic cells called the Philadelphia chromosome (Ph¹) causes uncontrolled reproduction and proliferation of white blood cells and platelets (Leonard, 1998).

In later stages of the disease, however the leukemic cells lose the ability to mature and blast cells begin to build up in the bone marrow and blood. CML has three distinct phases, the chronic phase, the accelerated phase and the blast phase (or crisis). In the chronic phase (the most common at diagnosis), there are few blast cells and promyelocytes in the blood and bone marrow. This phase may last from several months to several years. More blast cells and fewer normal cells are found in the bone marrow and blood in the accelerated phase. In the blast phase, more than 30% of the cells in the blood or bone marrow are blast cells. During blast phase, collections of blast cells may form tumors in the bones or lymph nodes (Leonard, 1998).

Transition from the chronic phase to the accelerated and later the blast phase may occur gradually over a year or more, or it may occur abruptly. This new phase is referred to as "blast crisis". Blast crisis occur an average of 3-5 years after diagnosis and is very similar to aggressive acute leukemia but more difficult to treat (Leonard, 1998).

Chronic Lymphocytic Leukemia (CLL): Chronic Lymphocytic Leukemia (CLL) is also known as chronic lymphatic leukemia. CLL typically consists of clonal expansion of mature, long-lived, functionally deficient B-lymphocytes that express high levels of the anti-apoptotic protein BCL-2 (Hanada *et al.*, 1993). In 95% of cases, CLL is a predominantly malignant clonal disorder of B lymphocytes. The remainder is secondary to a T-cell clone. The neoplastic cell is a hypoproliferative, immunologically incompetent small lymphocyte. There is primary involvement of the bone marrow and secondary release into the peripheral blood. The re-circulating lymphocytes selectively infiltrate the lymph nodes, the spleen and the liver (Pepper *et al.*, 1996).

Table 3: Rai staging system for chronic lymphocytic leukemia

Stage	Description
0	Absolute lymphocytosis
1	Absolute lymphocytosis and lymphadenopathy
2	Absolute lymphocytosis and splenomegaly or hepatomegaly
3	Absolute lymphocytosis and anemia (hemoglobin < 11g dL ⁻¹)
4	Absolute lymphocytosis and thrombocytopenia (platelets < 100 000 µL ⁻¹)

(Mughal and Goldman, 2003)

Table 4: Binet Staging System for Chronic lymphocytic leukemia

Stage	Description
A	Two or fewer lymphoid-bearing areas.
B	Three or more lymphoid-bearing areas.
C	Presence of anemia (hemoglobin < 10g dL ⁻¹) and/or thrombocytopenia (platelets < 100 000 µL ⁻¹)

(Mughal and Goldman, 2003)

It is the most common type of leukemia in the western world, accounting for more than 30% of all leukemias, affects people over age of 40 years, but it almost never affects children (Pepper *et al.*, 1996; Mughal and Goldman, 2001).

CLL is primary a disease of the elderly, with the media age of onset being 65 year. Patients with CLL may have general feeling of ill health, fatigue, lack of energy, fever, loss of appetite, night sweats, lymphadenopathy and infection. Some patients have enlarged lymph nodes in the neck or groin showed sign of splenomegaly, anemia, thrombocytopenia or infection (Leonard, 1998). Immunophenotyping is useful in distinguishing B-from T-cell disorders and from a variety of the related lymphoproliferative disorders such as hairy cell leukemia, prolymphocytic leukemia, lymphoplasmacytoid lymphomas and the leukemic phase of follicular non-Hodgkin's lymphoma (Catovsky *et al.*, 1984).

CLL has no standard staging system. The Rai's staging system (Table 3) and the Binet classification (Table 4) are different from the staging used to evaluate other nonleukemic cancers. These systems are based on cytology. One commonly used system known as Rai's staging system (Rai *et al.*, 1975).

Acute Promyelocytic Leukemia (APL): Acute Promyelocytic Leukemia (APL) is a subtype of acute Myelogenous Leukemia (AML) characterized by proliferating abnormal promyelocytes (Kingsley *et al.*, 1987). It is classified as the M3 variant of AML in the internationally accepted French-American-British (FAB) Classification. APL cells are heavily granulated promyelocytes, often with bundles of Auer rods (Mughal and Goldman, 2003). It also occurs in a variant or microgranular form (Golomb *et al.*, 1987).

APL represents approximately 10-15% of acute myeloid leukemias in adults. The median age is

approximately 40 years, which is considerably younger than the other subtypes of AML (Tallman *et al.*, 2002). Most patients with this disorder present with a hemorrhagic diathesis usually associated with Disseminated Intravascular Coagulation (DIC) (Kingsley *et al.*, 1987). Bleeding is usually in the form of petechiae, which correlate the degree of thrombocytopenia or ecchymoses which generally are caused by DIC commonly seen in patients with APL (Tallman *et al.*, 1997).

The human promyelocytic leukemia cells line (HL-60) is the derivation of the myeloid cell line HL-60 from the leukemic blood cell population of a 36-years old female with Acute Promyelocytic Leukemia (APL) (Gallagher *et al.*, 1979). The HL-60 cell line proliferates continuously in suspension culture with a doubling time of about 36-48 h (Collins *et al.*, 1977).

The cultured HL-60 cells have certain cytologic properties that have been associated with leukemic promyelocytes. These include nuclear/cytoplasmic asynchrony, nuclear bleb formation and heavy azurophilic granulation. The cultured HL-60 cells lack other features that have been described for promyelocytes from some cases of acute promyelocytic leukemia, including morphologically abnormal granules with Auer rod and extensive intracytoplasmic fibril formation and deformation and dilatation of the cisternae of the endoplasmic reticulum (Valdivieso *et al.*, 1975).

These promyelocytes can be induced to differentiate into granulocytes, macrophages or monocytes, eosinophils and basophils by various chemical inducer and culture condition (Matsuhisa and Mori, 1995). Thus, HL-60 cell line provides a unique *in vitro* model system for studying the cellular and molecular events where aqueous environment, suspended and round cells are needed (Ratanachoo *et al.*, 2002).

Leukemia therapy: Cytotoxic drug and their future:

Drug used in the treatment of leukemia represent a wide range of classes with different mode of actions. Until the late 1980s, induction therapy for patients with Acute Promyelocytic Leukemia (APL) was similar to all other patients with Acute Myeloid Leukemia (AML) and included an anthracycline and cytarabine. However, the leukemic cells from patients with APL are peculiarly sensitive to anthracyclines, perhaps because of significantly lower P-glycoprotein (P-gp) expression and other resistance markers in APL cells compared with other subtypes of AML (Lowenberg *et al.*, 2003). Both daunorubicin and idarubicin as single agents induce Complete Remission (CR) in 60-80% of patients (Witz *et al.*, 1998).

Current evidence appears compelling that an anthracycline (daunorubicin or idarubicin) should be included in induction in contrast to cytarabine which probably can be omitted (Tallman *et al.*, 2002). Anthracycline (*doxorubicin, daunorubicin, idarubicin, mitroxantrone*) is a class of antibiotic drugs is regularly used to treat a variety of cancers. Despite their widespread use, their mechanism of action remains unclear. Three postulates exist. Anthracyclines intercalate between DNA base pairs leading to unwinding of the superhelix and interfering with DNA and RNA synthesis, they undergo metabolism to form free radicals and they inhibit topoisomerase II, resulting in DNA strand breakage (Mazzotta *et al.*, 2001).

Note that mitroxantrone is an anthracenedione, an anthracycline-like compound with reduced ability to form free radicals. Daunorubicin, which has a narrower spectrum of utility than doxorubicin, is mainly used in the treatment of acute leukemia. Doxorubicin is used to treat a number of solid tumours as well as multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma and acute lymphocytic leukemia. Idarubicin is used in the treatment of acute myeloid leukemia (Mazzotta *et al.*, 2001).

Anthracyclines are metabolized in the liver and excreted in the bile. Dose reduction for patients with decreased liver function is recommended, especially if hyperbilirubinemia is present. Myelosuppression, mucositis and cardiac toxicity are common toxicities of these drugs. Irreversible cardiac toxicity is thought to occur via drug induced oxidative damage by free radicals. The use of lower doses and dexrazoxane (an iron chelator that blocks generation of free radicals) had been shown to prevent cardiac toxicity without loss of antitumour activity. Mitroxantrone causes less cardiotoxicity, nausea and vomiting (Mazzotta *et al.*, 2001).

A recently study has shown that patients with APL fare just as well without cytarabine as part of their induction or consolidation treatment (Sanz *et al.*, 1999). The introduction of All-Trans Retinoic Acid (ATRA) has prompted several study groups to exploit this peculiar sensitivity to anthracyclines by omitting cytarabine during induction. Nevertheless, the evidence appears compelling that cytarabine can be omitted during induction when an anthracycline is given with ATRA. The European APL Group is currently conducting a trial in which patients presenting with a White Blood Cell (WBC) count of $10,000 \mu\text{L}^{-1}$ or fewer are prospectively and randomly assigned to ATRA and daunorubicin or to ATRA plus daunorubicin and cytarabine (Tallman *et al.*, 2002).

Most patients with acute promyelocytic leukemia can be put in complete clinical remission by daily oral administration of all-trans retinoic acid (tretinoin). Side effects include headache, dry skin, xerostomia and itching. Leukocytosis and transient elevation of liver enzymes are often observed. Up to 40% of patients with APL being treated with ATRA develop a syndrome of fever, respiratory distress, pulmonary infiltrates and effusions. The syndrome is usually reversible with steroid treatment. Because the response to ATRA usually lasts only 3-5 months, with resistance rapidly developing, ATRA is stopped soon after complete remission is achieved and conventional chemotherapy regimens are administered (Warrell *et al.*, 1993).

More recently, there are many types of natural products particularly from plants derived substances possess inhibitory and suppressive effect against leukemic cancer cells. Extracts from plants such as *Elephantopus scaber, Vernonia amygdalina, Zingiber zerumbet, Morinda elliptica, Micromelum minutum, Triticum aestivum* and *Goniothalamus macrophyllus* have showed their cytotoxicity and potential to kill various type of leukemic cancer cells (Ho *et al.*, 2009; Yeap *et al.*, 2010b; 2012; Alitheen *et al.*, 2010; 2011; Al-Qubaisi *et al.*, 2011; Saeed and Elias, 2010; Tan *et al.*, 2009; Faujan *et al.*, 2010). Compounds isolated from these plants were found to contribute to the cytotoxicity against leukemic cancer cell. Process of discovering potential natural compounds antileukemia activity can be shorten using Quantitative Structure Activity Relationship (QSAR) study (Pugazhenthii and Rajagopalan, 2009; Saeed and Elias, 2010). Other than direct cytotoxicity, concept of inhibiting the growth of leukemic cancer cell via modulating the immune system by the immunomodulator agents also receiving inadequate attention. Plant extract such as *Rhaphidophora korthalsii* (Yeap *et al.*, 2011) and compounds isolated from ginger including Zerumbone and Curcumin have found to inhibit leukemic cell lines via stimulation of anticancer cytokines (Yeap *et al.*, 2010a; Gao *et al.*, 2004).

CONCLUSION

Research direction to discover novel chemotherapy agents for leukemia should focus on identifying natural compounds which carry both cytotoxic and immunomodulatory effects while possess low or no toxicity against normal cell.

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