HAEMATOLOGICAL MALIGNANCIES: AN OVERVIEW OF CLASSIFICATION AND DRUG THERAPY

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Abstract: The highly complex, multistep and genetic events that characterise the process of carcinogenesis promote transformations in various types of cancer including haematological malignancies. Haematological malignancies being heterogeneous affect the blood, bone marrow and lymphatic systems with the propensity of transformation from one subtype to another. This has made haematological malignancies classification a task that must be approached holistically such that trends in this disease entity are harnessed through research, publications and clinical investigation update to produce a standard document for World Health Organisation (WHO) as a guideline for haematological malignancies classification. The plethora of antineoplastic agents are available and far from being exhausted as more are continually being developed and undergoing clinical trials to affirm their use in haematological malignancies. This review attempts to discuss haematological malignancies classification, some classes of chemotherapy drugs having different mechanisms of action, degree of therapeutics value or activity, specificity or variation and their use for the treatment of different subtypes of haematological malignancies.

Keywords: Haematological malignancies, Cancer, Chemotherapy, Classification, Transformation and WHO.

INTRODUCTION

Haematological malignancies are a diverse group of cancers that vary in occurrence, prognosis and aetiology. Haematological malignancies (HMs) affect the blood, bone marrow and lymphatic systems. They are divided according to the organs that appeared to be most involved, rather than the cell populations of origin involving haematopoiesis as shown in (Fig1). Haematological malignancies account for about 9% of all cancer types in most developed countries of the world and it affect all ages. In Europe, haematological malignancies represent about 45% of all cancers in children and 7% in the elderly with occurrence of 30% and 8% death rate respectively (Gavin *et al.,* 2015).

They are conventionally grouped as leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma and myeloma (Jemal *et al.,* 2010). Poor understanding of the natural history of these diseases in conjunction with methods for diagnosis and prognosis prediction that are non-rapid and advanced have led to poor HM classification (Annan *et al.,* 2014). In addition, variations of HM definition, diagnostic and registration criteria among other factors that exist across countries or regions over time has complicated the classification system and incidence (Carli *et al.,* 2010).

Rapid genetic changes take place that lead to occurrence of malignant transformation in single cell from origin population in bone marrow, thymus or the lymphoid system, result to more transformed or aggressive different tumour type in haematological malignancies (Lin and Aplan,2004). This is major a difficulty in the understanding the pathophysiology of haematological malignancies having overall effect on classification system. For example, transformation of myelodysplastic syndrome to acute myeloid leukemia. Because of transformations, haematological malignancies are dependent on combining several technologies, including morphology, immunophenotyping, cytogenetics and molecular genetics correlated clinical details and classification according to the current WHO guideline, which is useful for epidemiologic and public health purposes.

The proper classification of haematological malignancies is pivotal to the right intervention or treatment that the disease required. The treatment of haematological malignancies involves a holistic or comprehensive approach.

Most malignancies are managed with the regime of chemotherapy among other interventions. This review attempt to give an overview of haematological malignancies classification trend and some specific class of drug therapy used for the treatment of haematological malignancies.

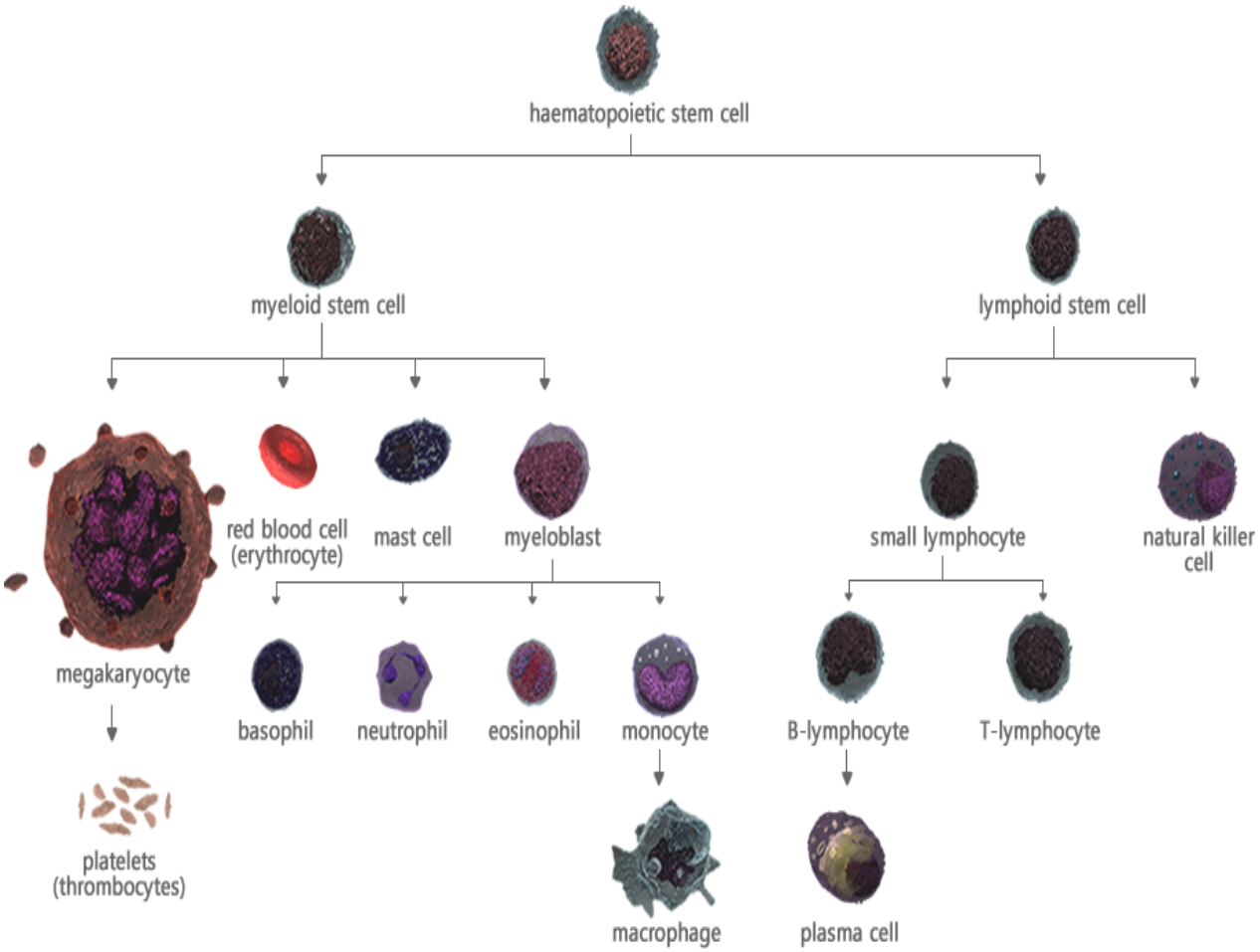

Fig 1. Haematopoiesis (detailed)

Sources: www.hmrn.org/about/classification

TREND IN HAEMATOLOGICAL MALIGNACIES (HM)

Over the years, attempts have been made to classify HM appropriately by experts; oncologists, pathologists, haematologist, researchers and other health professionals. The nature of this type of malignancy differs from others, and as such one gold standard classification could not be achieved giving rise to herculean task for cancer registries, particularly in multiple tumours of HM. Haematological malignancies with such tumours may advance or transform in diseased conditions. This genetic change or alteration could possibly have resulted to individual replicas and become very aggressive, transforming into different tumour types. (Lin and Aplan, 2004). Poor diagnosis rate of 5 % to 15% of Haematological malignancies have been reported (Arber *et al.,* 2016). This resulted in major clinical implication whereby patient suffers from such error undetected in the course of treatment.

An approach that will from onset give a correct diagnosis is strongly suggested through several independent fact-finding modalities. Accurate diagnosis using technology that combines morphology, immune phenotyping, cytogenetics and molecular genetics correlated clinical details are important to meeting the WHO guidelines. Swerdlow *et al.,* (2016) affirmed that combining these aforementioned technologies are essential as it integrates all modern diagnostic test, and reveal clinical information relating to specimen analysis and diagnosis thus helping

professionals in health delivery system. In classifying HM, the natural history of these diseases as well as rapid advances in methods for diagnosis and prognosis prediction is very essential, however, classification of HM is an onerous task that has been ongoing over the years because of the heterogeneous nature of the disease, an update is constantly done from time to time to meet the World Health Organisation standard or guidelines.

The Society for Hematopathology and the European Association for Hematopathology together with The World Health Organization (WHO) has been involved in the classification of HM through scientific information and publications. These published data during the course of years vary as it gives more information on numerous advances resulting from the etiology of HM. The clinical advisory committee (CAC) consists of numerous numbers of pathologists, hematologists, oncologists and geneticists from different parts of the world assembled to propose and update HM classification over a periodic year's interval. This integrates clinical features, morphology, immunophenotyping, cytogenetics, and molecular genetics to define disease entities of clinical significance as the basis of its classification.

The WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues remains the standard blueprint reflecting the consensus opinion of experts that identifies diagnostic criteria for previously described neoplasms and also introduced newly recognized disease entities. Vardiman *et al.,* (2009) in the 4th edition in 2008 published data on HM classification asserted that, for the first time a paradigm shifts from previous schemes or classification where genetic information was incorporated with morphologic, cytochemical, immunophenotypic, and clinical information into diagnostic algorithms for the myeloid neoplasms.

The 4th edition of the WHO classification incorporates new information that has emerged from scientific and clinical studies in years' intervals since the publication of the 3rd edition in 2001.This describes the new criteria for already known neoplasm as well as illuminating and fine-tuning the defining criteria for others. This also adds somewhat to entities that are defined principally by genetic features and that are recently characterized.

The 4th edition attempts to provide an up-to-date classification system that is based on recently published, peer-reviewed data, however, since its publication new information has emerged that eventually lead to our ability to recognize new diseases and change criteria for the diseases already described which call for continuous classification's review and update. The 3rd edition in 2001 WHO classification was improved upon because of rapidly emerging genetic and biologic information in disease entities. The guiding principle introduced in the Revised European-American Lymphoma REAL classification 1994 (Harris *et al.,* 1994) and 2001 WHO Classification 3rd edition (Jaffe *et al.,* 2001) remains; that is, entities are defined by a combination of clinical, morphology, immunophenotype and genotype.

In 1995 through 1997, The Society for Hematopathology and the European Association of Hematopathologists have undertaken as a joint project on the development of a classification of haematological neoplasms for the World Health Organization (WHO). Haris *et al.,* 1994) reported the forecast on the classification haematological malignancies stratifying across neoplasms, primarily according to lineage myeloid neoplasms, lymphoid neoplasms, mast cell disorders and histiocytic neoplasms. The WHO project is updated and revised with additional input from experts in order to broaden the consensus and extend the principles of the disease's definition.

The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues was updated in 2008. The unique identifiable biomarkers associated with some myeloid neoplasms and acute leukemias are largely derived from gene expression analysis and next-generation sequencing (Arber *et al.,* 2016). This has been able to reveal numerous advances in these diseases as shown in Table 1. which lists the major subtypes of myeloid neoplasms and acute leukemias according to the update on the 2016 WHO classification. The 2016 edition represents a revision of the prior classification rather than an entirely new classification and attempts to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since the last edition. Data evaluation is important, the data obtained from clinical trials and laboratory investigations are frequently reviewed, updated, and tested. The consensus from such is used for producing WHO documents. This promotes collaboration and cooperation among haematologists, pathologists, clinicians and clinical scientists of all nationalities, a model that must continue in future for the benefit of patients with Haematological Malignancies and health care system.

Table 1. Update on WHO classification of myeloid neoplasms and acute leukemia

WHO myeloid neoplasm and acute leukemia classification
Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia (CNL)
Polycythemia vera (PV)
Primary myelofibrosis (PMF)
PMF, prefibrotic/early stage
PMF, overt fibrotic stage
Essential thrombocythemia (ET)
Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA, PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: Myeloid/lymphoid neoplasms with *PCM1-JAK2*
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), BCR-ABL1^{-}
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
MDS-RS and single lineage dysplasia
MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood
Myeloid neoplasms with germ line predisposition
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*

Table 1 continued

WHO myeloid neoplasm and acute leukemia classification
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*

Provisional entity: AML with mutated *RUNX1*
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloproliferative neoplasms (MPN)
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
MPAL with t(v;11q23.3); *KMT2A* rearranged
MPAL, B/myeloid, NOS
MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

CHEMOTHERAPY AND HAEMATOLOGICAL MALIGNANCIES

Chemotherapy in cancer treatment is a critical regime where chemicals are used in destroying or killing aggressive diving cells and normal cells. Although other forms of cancer treatments or management are available like surgery, radiotherapy. Chemotherapy largely remains a way to go in ameliorating cancer as there are armamentariums of anti-cancer agents which rapidly grew due to discovery of many of these anti-cancer agents. Cancer chemotherapy drugs are said to be toxic and hence able to cause the death of dividing cells. These actions occur via different mechanisms depending on the class to such the anti-cancer agent belongs.

Many of these agents clearly interfere biological processes necessary for cell division specifically the synthesis of DNA or RNA underpinning the mechanism and some other mechanisms of action as represented in Table 2 according to class. Anticancer drugs can be used alone or in combination with others to achieve more therapeutic

efficacy. Combination therapy usually aims to delay or prevent drug resistance, a situation whereby the response to treatment occurs but over time the disease process recurs and drugs originally used and agents not previously employed become ineffective. Chemotherapy may be administered prior to surgery (neoadjuvant) to facilitate resection and prevent metastasis or after surgical debunking (adjuvant) to reduce the risk of distant relapse. With the ever-increasing and rapid development of active cytotoxic and biological agents, the expectation is that the list of cancers effectively treated and cured using combined modalities will continue to expand. The treatment of hematologic malignancies with the use of chemotherapy drugs have been a forerunner to the medical management of neoplastic disorders. Many classes of anticancer drugs and drugs exist which are used in the management of haematological malignancies and are not limited to the drugs shown in the table below.

TABLE 2: Drugs used in the treatment of Heamatological Malignancies with associated mechanisms of action

Classification	Mechanism of Action	Example
Antitumour	Interact directly with DNA in the nucleus of cells, interfering with cell survival	Bleomycin (Blenoxane) Daunorubicin (Cerubidine) Idarubicin (Idamycin) Doxorubicin (Adriamycin) Mixoxantrone (Novantrone)
Antimetabolites	Block cell's ability to form RNA or DNA, preventing cell growth and accelerating cell death	Cladribine (Leustatin) Cytarabine (Ctytarabine) Fludarabine (Fludara) Hydroxyurea (Hydrea) 6-Mercaptopurine Methotrexate
Immunomodulators	The exact mechanism of action is unclear; immune, cytotoxic and antiangiogenic effect	Interferon (Roferon) Pegylated interferon (PEG IFN) Thalidomide (Thalomid) Lenalidomide (Revlimind)
Histone deacetylase inhibitors	Modulate chromatin structure and gene expression; induce cell growth arrest, cell differentiation and death of leukemia cells	Vorinostat (Zolinza)
Glucocorticoids	Cytotoxic activity against lymphoma and leukemia cells	Dexamethasone (Decadron) Methylprednisolone (Medrol Prednisone (Deltasone)
Bisphosphonates	Block the reabsorption of bone in myeloma and have direct effects on myeloma cells	Pamidronate (Aredia) Zoledronic acid (Zometa)
Plant alkaloids	Act on certain proteins(enzymes) in the cell nucleus that normally repair injury to DNA (DNA-repair enzyme inhibitors)	Etoposide (Etopophos)
	Impair structures in the cell that are required for cells to divide into two daughter cells (block mitosis)	Vinblastine (Velban) Vincristine (Oncovin) Paclitaxel (Taxol)
Alkylating agents	Alter DNA and enhance cell death	Bendamusine (Treanda) Busulfan (Myleran) Carboplatin (Paraplatin) Carmustine (BCNU)

		Chlorambucil (Leukeran) Cisplatin(Platinol) Cyclophosphamide (Cytoxan) Dacarbazine (DTIC-Dome) Ifosfamide (Ifex) Lomustine (CCNU) Mechlorethamine (nitrogen mustard) Melphalan (Alkeran) Procarbazine (Matulan
Proteasome inhibitors	Act on the breakdown of proteins in the proteasome, a key cell function; used for multiple myeloma	Bortezomib (Velcade)
Monoclonal antibodies	Target specific antigens on cancer cells	Rituximab (Rituxan) Tositumomab (Bexxar) Ofatumumab(Arzerra)
Tyrosine kinase inhibitors	Block specific mutant proteins that initiate malignant cell transformation	Imatinib mesylate (Gleevec) Dasatinib (Sprycel) Nilotinib (Tasigna)

*Combinations of these drugs and drug groups are used to treat hematologic malignancies. This table does not include every approved drug or drug under study in clinical trials.
Note. Based on information from Lichtman, 2008 with slight modification for the purpose of this publication.

Alkylating agents and haematological malignancies

They are anticancer drugs that play significant roles in the treatment of several types of cancers (Chaney and Sancar, 1996). Its uses are still relevant now, being among the earliest class of drugs used in cancer treatment. This class of drugs could be monofunctional methylating agents (e.g., temozolomide [TMZ], *N*-methyl-*N*_-nitro-*N*-nitrosoguanidine [MNNG], and dacarbazine), bifunctional alkylating agents such as nitrogen mustards (e.g., chlorambucil and cyclophosphamide), or chloroethylating agents (e.g., nimustine [ACNU], carmustine [BCNU], lomustine [CCNU], and fotemustine) (kondo *et al.,* 2010). Monofunctional means that react with only one DNA strand while bifunctional indicates that they react with an atom on each of the two DNA strands to crosslink the strands covalently. Alkylating agents act by three different mechanisms leading to the disruption of DNA function and ultimately cell death. The use of these class drugs is not new in the management of haematological malignancies, some drugs within these classes are preferred over one another because of systemic toxicity and drug resistance.

Many of the alkylating agents that have been used to specifically treat haematological malignancies are not limited to the following Ifosfamide, melphalan, procarbazine and cisplatin. Ifosfamide has a broad spectrum of activity and as such used in treating different cancer including the treatment of hematological malignancies, mainly non-Hodgkin lymphomas (NHL) and Hodgkin's disease (HD). Right from the onset of its discovery, King and Younes, (2000) reported Ifosfamide's administration as a single agent in relapsed or refractory NHL, showing a satisfactory response rate with major responses (complete and partial remissions, CR and PR) ranging from 28 to 47%.

Antimetabolites and haematological malignancies

Antimetabolites are analogs of natural metabolites that interfere with the normal metabolic processes within cells, targeting RNA and DNA synthesis, and therefore are considered the first generation of targeted drugs. Thiopurines formed the foundation for the development of purine analogs, 5-fluorouracil (5FU) was the first pyrimidine analog while aminopterin and methotrexate are the parent folate analogs of antimetabolites (DeVita and Chu, 2008). Antimetabolites are broadly used for the treatment of many types of cancers including solid tumours and other ailments psoriasis (McDonald, 1981), rheumatoid arthritis (Hoffmeister, 1983) and infections Pneumocystis carinii viral infections in patients with acquired immune deficiency syndrome (Allegra *et al.,* 1987)

Specifically, inhibition of DNA and RNA synthesis is an effective anticancer treatment strategy employed to combat the aberrant proliferation nature of cancer cells compared with normal cells. The use of antimetabolites over the years dates back more than six decades ago, having discovered that aminopterin could cause remission of leukaemia (Farber *et al.,* 1948) and that the unraveling of cellular-level processes has increased in recent years which gives credence to the identification and emergence of potential new target.

Conventional antimetabolites are important in indolent lymphoid malignancies as most cells in these disorders are in the resting phase. New antimetabolite drugs are developed, and a purine analog 2-chlorodeoxyadenosine (2-CdA) has been used in vivo with an outstanding clinical effect observed in hairy cell leukemia having complete remissions of 85% and partial remissions of 12% from a single course of therapy (Saven and Piro, 1994). Interestingly, there were variations for other indolent lymphoid malignancies, alkylator-refractory chronic lymphocytic leukemia achieved a response of 44% (4% complete responses and 40% partial responses) and 54% scored as the non-response sustaining reduction in their peripheral lymphocytosis. Furthermore, chronic lymphocytic leukemia had an 85% response rate (25% complete responses, 60% partial responses) and previously treated low-grade lymphoma achieved an overall response rate of 43% (Saven and Piro, 1994). 2-Chlorodeoxyadenosine is a newer purine analog with potent activity in the treatment of indolent lymphoproliferative diseases and illustrates the model for rational drug development.

Clofarabine is a new-generation nucleoside analog similar to fludarabine and cladribine has been synthesized to constitute a favourable pharmacokinetic profile. These properties not only allow the inhibition of DNA polymerases and DNA synthesis but also bring about strong inhibitions of ribonucleotide reductase (RnR), an enzyme involved in regulating intracellular deoxynucleotide pools and has a high affinity to the enzyme deoxycytidine kinase (dCyd) the rate-limiting step in nucleoside phosphorylation. *In vitro,* study revealed clofarabine as a potent inhibitor of the L1210 mouse leukemia and K562 chronic myeloid leukemia (CML) blast cell lines that depressed deoxyadenosine triphosphate (TP), deoxycytidine TP, and deoxyguanine TP but not deoxythymidine TP pools upon exposure of 0.1 M, 1.0M or 10 M of the drug after 4 hours (Kantarjian *et al.,* 2003). The synergy between cytarabine and clofarabine has been demonstrated *in vitro* (Cooper, et al 2005), besides having antileukemic activity the activity of clofarabine and cytarabine may be enhanced in leukemic cells by a biochemical synergy between these two agents. The clinical trials of the effect of Clofarabine on haematological malignancies, acute myeloid, leukemia AML, acute lymphoblastic leukemia ALL and myelodysplastic syndrome MDS (Jeha *et al.,* 2004, Kantarjian *et al.,* 2003) have been reported.

Anti-tumour and haematological malignancies

Antitumour antibiotics are naturally derived heterogeneous group of antineoplastic agents that originated from fermentation products of microbial cultures and remains a mainstay in the chemotherapy regime (Newman, 2003). Anthracyclins, bleomycins, actinomycin D, and mitomycins are a few anticancer antibiotics used in therapy. All members of this group were isolated from various *Streptomyces* species, however, some can be semi-synthesized. The mechanism of action of various classes of anti-tumour antibiotics differs from one another. While the bleomycin mechanism is via selective oxidative cleavage of DNA and RNA in the presence of oxygen that is metal-dependent (Hetcht, 2000), mitomycins (MTMs) potent antitumor quinones rather form covalent linkages with DNA functioning as alkylating agents (Sastry *et al.,* 1995) that preferentially proceeds in the absence of oxygen (Sartorelli *et al.,* 1994). Anthracycline originally derived from Streptomyces in the 1960s (Brockmann, 1963) are aromatic polyketides that display the widest spectrum of antitumor activity against human cancers (Myers *et al.,* 1988) such as solid tumors and leukemia, daunomycin has been used primarily to treat adult myelogenous leukemia. (Carrion *et al.,* 2000). DNA intercalation of anthracyclines leads to changes in chromatin supercoiling that eventually result in chromatin aggregation (Rabbani *et al.,* 1999), conformational change in the structure of chromatin hinders metabolic processes of DNA, a significant role that induces programmed cell death.

Acute myelogenous leukaemia, multiple myeloma and non-Hodgkin's lymphoma responded positively to idarubicin, a 4-dimethoxy-anthracycline treatment, a congener of daunorubicin (Lipp and Bokemeyer 1999) while mitoxantrone is an effective and better-tolerated alternative to the anthracyclines in most haematological malignancies because the component of low toxicity regimen stabilises the disease in a significant proportion of patients with poor prognosis (Faulds *et al.,* 1991).

Plant Alkaloids and haematological malignancies

Secondary metabolites are mostly small organic molecules from organisms and are simply classified into three main groups namely terpenoids, phenolics and alkaloids. They are synthesized via mevalonic acid, shikimate and other pathways (Kabera *et al.,* 2014)**.** Vinca alkaloid occurs naturally and it is extracted from the leaves of *Catharanthus roseus* (L.) G.Don (formerly *Vinca rosea* L.). Vinca alkaloids often referred to as vinblastine has the capacity to bind tubulin, blocking the process of mitosis and causing metaphase arrest (Cutts, 1961). The antineoplastic activity was carried out in vivo using mice engrafted with L1210 and P1534 leukemia cells and Ehrlich ascites tumor cells (Cutt *et al.,* 1960). Vinblastine is used mainly against acute lymphoblastic leukemia in pediatric oncology practice in combination therapy resulting in a survival rate 80% (Evans *et al.,* 1963) and also in the treatment of lymphomas, Hodgkin's disease, rhabdomyosarcoma, neuroblastoma, and nephroblastoma (Almagro, *et al.,* 2015). Vindesine and vinorelbine are congeners of vinblastine with current or potential use in treating hematological malignancies. Podophyllotoxin is a lignin isolated initially from *Podophyllum peltatum* (American mandrake; Berberidaceae) and can also be obtained from Indian podophyllum, *Podophyllum emodi* (Canal *et al.,* 2000). Etoposide and teniposide are semi-synthetic derivatives of Podophyllotoxin causing topoisomerase-mediated re-annealing of single- and double-strand DNA breaks in S and G2 phases of the cell cycle (Van *et al.,* 1988) and as such referred to as topoisomerase II inhibitors. This action ultimately inhibits the accumulation of DNA damage and induces potent caspase-dependent apoptosis. Etoposide and teniposide were used in 1970 in clinical studies for the treatment of acute myeloid leukemia, Hodgkin's disease and non-Hodgkin's lymphoma (Hande, 1998). Etoposide is effective for different types of leukemias and lymphomas, whereas teniposide attenuates hematological malignancies in single or in combination chemotherapy (Lee and Xiao, 2005). Other natural plants product such as noscapine, bruceantin, combretastatins, honokiol and silvestrol have been reported both in in vitro and in vivo studies for the treatment of different types of haematological malignancies (David *et al.,* 2010).

Monoclonal antibodies (Mab) **and haematological malignancies**

They are identical antibodies that are derived from one type of immune cell that give rise to clones from each single parent cell. They are highly specific in nature, a quality that confers revolutionary applications in targeted therapy and other diagnostic applications. Monoclonal antibodies are designed to target and modulate specific immune pathways while MAb-based therapies may use different mechanisms of action that differ from that of cytotoxic drugs. Possible actions could be by either acting through the activation of host defense molecules or sending apoptotic or growth inhibitory signals. Specifically, three classes of these MAB-based therapies have been identified and used in clinical trials in the treatment of hematologic malignancies. They show promising results as they possibly elicit mechanism actions whereby the antibody delivers sterilizing radiation to the tumour in radioactive immunotherapy, preferentially delivers a potent cytotoxic drug to the tumour (reduced systemic toxicity normally compared to conventional drug therapy), directly induces apoptosis and indirectly activate host defence mechanism against tumour activity.

Monoclonal antibodies (MAbs) are a widespread and great tool for biomedical science because of proven their efficacy in various pathological conditions including malignant and benign hematologic disorders. Rituximab was the first recombinant chimeric anti-CD20 MAbs approved in 1997 by the Food and Drug Administration for the treatment of B-cell malignancies relapsed/refractory B cell non-Hodgkin lymphoma (NHL). Since then several other such approved antibodies are in use, alemtuzumab (Campath-1H), a humanized rat antibody to CD52 for the treatment of refractory chronic lymphocytic leukemia, and gemtuzumab ozogamicin (Mylotarg), a calicheamicin-conjugated humanized mouse anti-CD33 MAb for therapy of drug-refractory acute myeloid leukemia (Sievers, 2000) and anti-CD80 galiximab to treat relapsed or refractory follicular lymphoma (Leonard *et al.,* 2007) just to mention a few. Rituximab has also demonstrated activity against B-CLL and for some hairy cell leukaemia (Thomas *et al.,* 2005) whereas its combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) to treat both newly diagnosed relapsed/refractory low-grade NHL patients recorded an overall response rate of 95% (Vose *et al.,* 2000). MAbs as a single agent have been a potent therapy and their synergism is pronounced in combination therapy, these have impacted significantly in the treatment of an array of cancers and specifically those that of haematological prototypes or origins.

Proteasome inhibitor and haematological malignancies

Cell survival, cell signaling and cell cycle progression are cellular processes mediated by large multimeric protein complex proteasomes that degrade unneeded or damaged proteins (Huber and Groll, 2012). This ubiquitin–protein complex or system maintains protein homeostasis in eukaryotic cells by allowing them to degrade unassembled, damaged and misfolded which is more in tumour cells compared with a normal cell. This system also directs the degradation of short-lived proteins that play a major role in cell cycle regulation, transcription regulation, apoptosis, antigen processing, chemotaxis, angiogenesis, and cell adhesion (Adams, 2002). The proteasome is thus an essential component of cellular metabolism, and, as such, a novel and appealing target for cancer treatment. Human diseases often occur from defects in various components of the ubiquitin-proteasome pathway. For example, Malignant cells are highly dependent on increased protein production and degradation, suggesting that they would be sensitive to proteasome inhibition (Mitsiades, 2006).

Proteasome inhibition results in changes in a large number of substrates, which translates into the disruption of a variety of pathways and checkpoints that leads to cell apoptosis (Mack *et al.,* 2003). This preferentially leads to cell cycle arrest at the G1/S boundary in normal cells (Hideshima *et al.,* 2001) whereas in transformed or malignant cells it induces apoptosis (Adams, 2001). Proteasome inhibitors, bortezomib and carfilzomib have been demonstrated to be a potent therapeutic strategy in several hematologic malignancies for a couple of years now. This has made it a mainstay therapy in lymphoid malignancies, multiple myeloma and mantle cell lymphoma. Bortezomib is the first of its class of proteasome inhibitors tested in humans that showed promising activity in several tumour types, particularly in hematologic malignancies in phase I studies (Andre and Frederic, 2004). Investigational study of bortezomib in patients with relapsed or refractory acute myeloid leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome (Cortes *et al.,* 2002) was conducted in phase one clinical trial as well as the in vitro study. Bortezomib is said to induce apoptosis more efficiently in leukemic cells in combination with other agents and it sensitizes myeloid leukemia cells to TRAIL-mediated apoptosis by reducing the level of FLICE-inhibitory protein (c-FLIP) (Sayer *et al.,* 2003). Previous studies by Masdehors *et al.,* reported apoptosis induction in the lymphocytes of CLL patients but does not occur in normal lymphocytes as a result of treatment with proteasome inhibitors. This did not change the levels of expression of the proapoptotic Bcl-2 family proteins, Bax and Bid, in CLL cells before the onset of apoptosis rather a caspase-independent conformational change of Bax occurs that results in mitochondria perturbation, as evidenced by loss of the mitochondrial membrane potential and cytochrome-c release (Dewson *et al.,* 2003). Proteasome inhibitors such as bortezomib and others remain promising new agents for the treatment of hematologic malignancies.

Immunomodulators and haematological malignancies

Immunomodulatory drugs (IMiDs) are key therapeutically and are analog prototype compounds of thalidomide that are recently recognized as cereblon (CRBN) binding drugs (Fuchs, 2017). IMiDs include thalidomide, lenalidomide, pomalidomide, CC-122, CC-220, CC-885 and CC-90009 till date. IMiDs do have immune-modulation, anti-angiogenic, anti-inflammatory and anti-proliferative effects. In the backdrop of novel drugs, immunomodulating drugs (IMiDs) represent now a real opportunity to ameliorate prognosis in haematological malignancies.

Lenalidomide is an oral immunomodulatory drug with pleiotropic mechanisms of action that potentially add to immunochemotherapy. Its antineoplastic effects include direct antineoplastic activity, immunologic effects mediated by inhibition of tumor cell proliferation and angiogenesis, and stimulation of cytotoxicity mediated by T cells and NK cells (Zhang *et al.,* 2009). Lenalidomide is used in the treatment of DLBCL and other myelodysplasic syndromes showing antitumoral properties via anti-angiogenesis, immune modulation and direct tumor cell toxicities mechanisms (Bartlett *et al.,* 2004). This single-agent use displays durable responses in relapsed/refractory non-Hodgkin lymphoma, and combination with rituximab and other agents leads to improved responses at first line and in relapsed/refractory DLBCL and other diseases (Zinzani, *et al.,* 2011). Lenalidomide has enhanced or synergistic activity with other agents, including rituximab, dexamethasone, bortezomib, and B-cell receptor pathway inhibitors, reflecting its unique mechanisms of action as clinical results highlight the potential activity for lenalidomide-based combinations (Gribben *et al.,* 2015).

Pomalidomide is a potent immunomodulatory drug that has shown striking effects on multiple myeloma (MM) cells and the bone marrow microenvironment (Galustian *et al.,* 2009). Preliminary clinical data indicates its activity against resistance to lenalidomide and bortezomib in relapsed and/or refractory multiple myeloma (RRMM) patients (Lacy,

2011). Generally speaking, IMiDs have a major role to play in the treatment of certain hematologic malignancies, including multiple myeloma, non-Hodgkin's lymphoma, CLL and others. Combining it with other agents resort to new standard approaches to a variety of hematologic neoplasms treatment that has been developed over the years.

Histone deacetylase inhibitors and haematological malignancies

The histone deacetylase (HDAC) enzymes are a multi-class, multi-member family that affect chromatin conformation via the deacetylation of ε-N-acetyl lysine amino acids on histone proteins (Sengupta, 2004). Histones are a family of proteins that interact with DNA resulting in DNA being wound around a histone octameric core within a nucleosome. Histone deacetylases (HDACs) critically regulate gene expression by determining the acetylation status of histones. Studies have increasingly focused on the activities of HDACs as they are involved in inducing numerous biological effects such as cell apoptosis, senescence, differentiation, and angiogenesis. Immunogenicity is correspondingly regulated on immunoreceptors of Nk cell by ligand expression of HDACs (Kato *et al.,* 2007).

The 11 known HDACs are divided into three classes (I, II, and IV) (West and Johnstone, 2014). Each class is characterised by different subcellular locations, substrate specificity, and enzymatic activity. Class I HDACs (1, 2, 3, and 8) are generally located in the nucleus that regulates gene expression by subtype HDAC 1, 2, 3 while class II HDACs (4, 5, 6, 7, 9, and 10) shuttle between the nucleus and the cytoplasm; their substrates of HDAC6 are uniquely involved in cell signaling pathways and protein stability enhancement through interaction with tubulin and HSP90 and the class IV HDAC with subtype (11) (Sadoul K, Khochbi, 2016). Abnormal HDAC expression observed in several kinds of human tumours of colorectal, liver, breast, and lung cancers including haematological malignancies has led to HDACs as proposed as a potential target for cancer treatment (Imai *et al.,* 2016) hence the development of HDAC inhibitors.

Vorinostat a histone deacetylase inhibitor has been reported used in different clinical phases of trials in the treatment of various haematological malignancies. There were reported hematologic responses in refractory cutaneous T-cell lymphoma CTCL (Marks *et al.,* 2007) relapsed diffuse large B-cell lymphoma (DLBCL), (Crump *et al.,* 2008), indolent non-Hodgkin's lymphoma (Kirschbaum *et al.,* 2007), acute myeloid leukemia (AML) myelodysplastic syndrome (MDS), chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia and chronic myeloid (Manero,2008).

It uses is not limited to the treatment of haematological malignancies alone, solid tumours, including platinum-resistant epithelial ovarian cancer, primary peritoneal carcinoma, and non-small cell lung carcinoma (NSCLC) are treated with vorinostat alone and in combination carboplatin and paclitaxel achieving a considerable partial response in clinical studies (Ramalingam *et al.,* 2007). Other histone deacetylase inhibitors valproic acid, panobinostat, entinostat and romidepsin have been reportedly used in different phases of clinical trials and approved by the Food and Drug Administration (FDA) while others are under clinical investigation for the treatment of many types of haematological malignancies and solid tumours (Federico and Bagella, 2011) HDAC inhibitors represent a promising new group of anticancer agents and full understanding of mechanism requires more attention to take advantage of in the biological and therapeutic effect or benefits of these drugs.

Glucocorticoid and haematological malignancies

Over the past centuries, the use of glucocorticoids (GCs) in clinical oncology especially hematology-related cancers has been a mainstay. This could be attributed to their pro-apoptotic action in treating various haematological disorders and their ability to attenuate side effects produced by chemotherapy or radiotherapy even in non-hematologic cancer types.

Glucocorticoids are a class of steroid hormones or cholesterol-derived hormones secreted by the adrenal glands (Kadmiel and Cidlowski, 2013). They are responsible for various physiologic systemic functions in immune responses, metabolism, cell growth, development, reproduction and stress-related homeostasis in humans (Nicolaides *et al.,* 2010). These actions or functions are mediated through the glucocorticoid receptor (GR), a member of the nuclear receptor superfamily of transcription factors (Schoneveld *et al.,* 2004). The exogenously administered GCs into systemic circulation include dexamethasone, prednisolone, triamcinolone and prednisone, by

clinicians for a variety of benign and malignant diseases (Azher *et al.,* 2016). They are obtained from cholic acid in plants or cattle that are further processed into oral, injectable, or topical agents (George, 2015). Cortisol is the most commonly produced endogenous GC in the body.

Since 1944, cortisone has been found to affect the volume, structure and function of lymphoid tissue a reflection of the tumour regression in a murine model (Heilman and Kenda,1944). More studies have been done afterward to confirm the use of GCs which are widely used in the treatment of haematological malignancies (Livingston, 1970). In hematologic malignancies, pathways involved in GC-induced apoptosis include the transactivation of Bim, a BH-3-only protein and apoptosis-inducing member of the Bcl-2 family, and inhibition of the pro-survival transcription factors, AP-1 and NF-kB (Frankfurt and Rosen, 2004). This mechanism of GC-induced apoptosis is complex and involves multiple signaling pathways (Herr *et al.,* 2004). Glucocorticoids are used as single-agent therapy to produce temporary responses in patients with non-Hodgkin lymphoma; they are therefore included in virtually every complex regimen used for the treatment of non-Hodgkin lymphoma. Prednisone is the most commonly used steroid in the treatment of Non-Hodgkin lymphoma as dexamethasone has been used in other hematologic malignancies. While both drugs are being used for Non-Hodgkin lymphomas, particularly, pediatric acute lymphoblastic leukemia (ALL) dexamethasone results in lower incidences of relapse, particularly in the central nervous system, as compared to prednisone or prednisolone, but is associated with increased toxicity (Bostrom *et al.,* 2003). This is contradictory to results obtained in studies of acute lymphoblastic leukemia in adults (Labar *et al.,* 2010). One of the fundamentals of combination therapy was exploited with the use as part of chemotherapy combination regimens because the toxicity of GCs, such as prednisone, did not significantly overlap with that of other compounds, such as alkylating agents or anti-metabolites (Livingston, 1970). A gold standard therapy was established CHOP (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) for diffuse large B cell lymphoma in which prednisone 100 mg daily was given on days one through five of each chemotherapy cycle (Fisher *et al.,* 1993). Dexamethasone has also been incorporated in salvage regimens that combine cytarabine and cisplatin (DHAP) or gemcitabine and cisplatin (GDP) (Hagberg and Gisselbrecht, 2006).

Rajkumar, et al studies in multiple myeloma, revealed the result of low and high dose dexamethasone over a 28-day cycle, as an improved overall survival rate and decreased incidence of deep vein thrombosis, infection, hyperglycemia and grade 3 or 4 non-hematologic toxicity in the low dose dexamethasone arm was obtained (Rajkumar *et al.,* 2010). Currently, the role of GCs in the treatment of NHL is unclear because the optimal dose and optimal duration of GC use, and the risk of GC-induced hyperglycemia or diabetes, are limited and require refined definitions.

Bisphosphonates and haematological malignancies

Bisphosphonates (BP) are chemically stable analogs of inorganic pyrophosphate that have high bone affinity, increase bone mass, bone mineralization, bone mineral density, and resistance and reduce the risk of bone fracture. They are the only pharmacological agents currently recommended for the treatment and prevention of myeloma bone disease (MBD) which remains the standard care. BPs can prevent the increase in bone resorption associated with experimental tumors, particularly those that localize in or metastasize to bone (Martodam *et al.,* 1983). Results from clinical studies reveal the capacity of BPs to not only reduce metastases in bone but also reduce the overall tumor burden (Sasaki *et al.,* 1995). This can be attributed to modification in the release growth factors that likely alter tumour cell growth when reabsorption takes place in the bone (Mundy, 1998). Consequently, BPs change cell attachment and bring about apoptosis directly (Clezardin *et al.,* 2005)

In haematological malignancy, more than 80% of patients with Multiple myeloma MM display evidence of myeloma bone disease (MBD), characterised by the formation of osteolytic lesions throughout the axial and appendicular skeleton (Coleman, 1997). This disease is a result of MM plasma cells-mediated activation of osteoclast activity and suppression of osteoblast activity. This increases the risk of skeletal-related events such as pathologic fracture, spinal cord compression and hypercalcemia. In myeloma, BPs significantly reduced the incidence events (Pavlakis *et al.,* 2005) and also a therapeutic efficacy in breast cancer metastases, and in metastatic prostate cancer, lung cancer, renal cell carcinoma, and other solid tumors (Smith, 2005). The BPs potency and affinity for hydroxyapatite depend on the composition of the two side chains coupled to the central carbon atom of the nucleus. All BPs have the same core phosphate-carbon-phosphate backbone (Russell, 2006). There are possibilities of mechanisms of action

variations that are dependent on their structure that result in either metabolism of bisphosphonates to a cytotoxic analog of ATP or inhibition of enzymes of the mevalonate pathway (Lukman *et al.,* 1998).

Some evidence suggests that bisphosphonates may improve survival in some patients with multiple myeloma, in addition to treating osteolytic bone disease. Although bisphosphonate clodronate had a small effect, pamidronate and the more potent bisphosphonate considerably inhibit myeloma cell proliferation and induce apoptosis (Shipman *et al.,* 1997). Bisphosphonates can be used with other chemotherapy and are clearly effective in managing, preventing and treating the bone disease associated with multiple myeloma increasing survival in some patients with multiple myeloma.

In conclusion, haematological malignancies constitute major health issues in patients owing to transformation from one subtype to another and the proliferation and aggressive nature arising from different sites. Many drugs have been developed with different mechanisms for treatment, with many more drugs used in clinical trials and also with drug repurposing the intervention that will be potent and has fewer side effects compared with the known or conventional anti-cancer drugs.

REFERENCES

1. Adams J. (2001) Proteasome inhibition in cancer: development of PS-341. *Semin Oncol* 28:613-619.
2. Adams J. (2002). Proteasome inhibitors as new anticancer drugs. *Curr Opin Oncol* 14:628-634
3. Alan Saven, MD; Lawrence D. Piro (1994). 2-Chlorodeoxyadenosine: A Newer Purine Analog Active in the Treatment of Indolent Lymphoid Malignancies *Ann Intern Med.* 120(9):784-791
4. Allegra CJ, Chabner BA, Tuazon CU, Ogata-Arakaki D, Baird B, Drake JC. Simmonds JT, Lack EE. Shelhamer JH, Balis F, Walker R, Kovacs JA. Lane HC and Masur H *et al.,* (1987). Trimetrexate for the treatment of Pneiumocystis corinii pneumonia in patients with acquired immunodeficiency syndrome. *N Entgl J Med* 117: 978-985
5. Almagro, L.; Fernández-Pérez, F.; Pedreño, M.A (2015). Indole alkaloids from Catharanthus roseus:
6. Andre Goy, Frederic Gilles (2004). Update on the Proteasome Inhibitor Bortezomib in Hematologic Malignancies *Clinical Lymphoma,* Vol. 4, No. 4, 230-237
7. Anna Gavin, Brian Rous, Rafael Marcos-Gragera, Richard Middleton, Eva Steliarova-Foucher, Marc Maynadie, Roberto Zanetti, Otto Visser *et al.,* (2015) Towards optimal clinical and epidemiological registration of haematological malignancies: Guidelines for recording progressions, transformations and multiple diagnoses *European Journal of Cancer* 51 1109–1122
8. Arber DA, Orazi A, Hasserjian R, et al. (2016). The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 127:2391.
9. Azher S, Azami O, Amato C, McCullough M, Celentano A, Cirillo N *et al.,* (2016). The Non- Conventional Effects of Glucocorticoids in Cancer. *J Cell Physiol.* 231: 2368-2373.
10. Bartlett J. B, Dredge K, and Dalgleish, A. G, (2004). "The evolution of thalidomide and its IMiD derivatives as anticancer agents"*Nature Reviews Cancer*, vol. 4, no. 4, pp. 314–322.
11. Bostrom BC, Sensel MR, Sather HN, Gaynon PS, La MK, Johnston K, Erdmann GR. *et al.,* (2003). Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood.* 101: 3809-3817.
12. Brockmann, H. (1963). Anthracyclinones and Anthracyclines. (Rhodomycinone, Pyrromycinone and Their Glycosides). *Fortschritte der Chemie organischer Naturstoffe*, **21**, 121-182.
13. Chaney S. G, and Sancar A, (1996). "DNA repair: enzymatic mechanisms and relevance to drug response," *Journal of the National Cancer Institute*, vol. 88, no. 19, pp. 1346–1360.
14. Canel C, Moraes RM, Dayan FE, Ferreira D (2000). Podophyllotoxin. *Phytochemistry* 54:115–120. [PubMed: 10872202]
15. Carli PM, Delafosse P, Duchenet V, et al. Guide de recommandations pou l'enregistrement des hémopathies malignes par les registres de cancer. Paris, France: INVS and FRANCIM; 2005.
16. Carrion C, de Madariaga MA, Domingo JC. (2004). In vitro cytotoxic study of immune liposomal doxorubicin targeted to human CD34(þ) leukemic cells. *Life Sci* 75:313–328.
17. Clezardin, P., F.H.Ebetino and P.G. Fournier. (2005). Bisphosphonates and cancer induced bone disease: beyond their antiresorptive activity *Cancer Res.* **65:** 4971–4974.

18. Coleman RE. (1997). Skeletal complications of malignancy. *Cancer;* 80: 1588–94.

19. Cooper T, Agus M, Nowak B, Gandhi V *et al.,* (2004). Biochemical modulation of cytarabine triphosphate by clofarabine. *Cancer Chemother Pharmacol.* 2005; 55:361–368.
20. Cortes J, Elihu Estey E, Giles F, *et al.,* (2002). Phase I study of bortezomib (PS-341, VELCADETM), a proteasome inhibitor, in patients with refractory or relapsed acute leukemias and myelodysplastic syndromes. *Blood* 100(suppl):560a.
21. Crump M, Coiffier B, Jacobsen E. D. *et al.,* (2008) "Phase II trial of oral vorinostat (suberoylanilide hydroxamic acid) in relapsed diffuse Large-B-cell lymphoma," *Annals of Oncology*, vol. 19, no. 5, pp. 964–969
22. Daniel A. Arber, Attilio Orazi, Robert Hasserjian, J¨urgen Thiele, Michael J. Borowitz, Michelle M. Le Beau, Clara D. Bloomfield, Mario Cazzola, and James W. Vardiman *et al.,* (2016) The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia *blood* 27, 28
23. Cutts JH. (1961). The effect of vincaleukoblastine on dividing cells *in vivo*. *Cancer Res;* 21:168–172.
24. David M. Lucas, Patrick C. Still, Lynette Bueno Pérez, Michael R. Grever, and A. Douglas Kinghorn (2010) Potential of Plant-Derived Natural Products in the Treatment of Leukemia and Lymphoma *Curr Drug Targets*. 11(7): 812–822
25. DeVita, V.T. Jr; Chu, E (2008) A history of cancer chemotherapy. *Cancer Res.* 68(21), 8643–8653.
26. Dewson G, Snowden RT, Almond JB, *et al.,* (2003). Conformational change and mitochondrial translocation of Bax accompany proteasome inhibitor induced apoptosis of chronic lymphocytic leukemic cells. *Oncogene* 22:2643-2654.
27. Early Breast Cancer Trialists' Collaborative Group (1992) Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet*, 339: 71-85.
28. Evans, A.E.; Farber, S.; Brunet, S.; Mariano, P.J. (1963). Vincristine in the treatment of acute leukaemia in children. *Cancer* 16, 1302–1306.
29. Farber S. Diamond LK. Mercer RD. Sylvester RF and Wolff JA (1948) Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). *N Entgl J Med* 238: 787-793
30. Faulds, D., Balfour, J.A., Chrisp, P. *et al.,* (1991) *Drugs* 41: 400
31. Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, *et al.,* (1993) Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med.* 328: 1002-1006.
32. Frankfurt O, and Rosen ST (2004). Mechanisms of glucocorticoid-induced apoptosis in hematologic malignancies: updates. *Curr Opin Oncol.* 16: 553-563.
33. Fuchs O (2017). Immunomodulatory drugs and their therapeutic effect in hematological malignancies through cereblon *Hematol Med Oncol,* Volume 2(3): 1-8
34. Galustian C, Meyer B, Labarthe MC, *et al.,* (2009) The anti-cancer agents lenalidomide and pomalidomide inhibit the proliferation and function of T regulatory cells. *Cancer Immunol Immunother* 58: 1033–45.
35. Garcia-Manero G, Yang H, Bueso-Ramos C. *et al.,* (2008) "Phase 1 study of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid [SAHA]) in patients with advanced leukemias and myelodysplastic syndromes," *Blood*, vol. 111, no. 3, pp. 1060–1066.
36. George P. Chrousos. Basic & Clinical Pharmacology Adrenocorticosteroids & Adrenocortical Antagonists. New York, NY: McGraw-Hill; 2015.
37. Gribben, J. G., Fowler, N., & Morschhauser, F. (2015). Mechanisms of action of lenalidomide in B-cell non-Hodgkin lymphoma. *Journal of Clinical Oncology*, *33*(25), 2803.
38. Hagberg H, Gisselbrecht C. Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. *Ann Oncol.* 2006.
39. Hande KR. (1998). Etoposide: four decades of development of a topoisomerase II inhibitor. *Eur J Cancer* 34:1514–1521. [PubMed: 9893622]
40. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JKC, Cleary M *et al.,* (1994). A revised European–American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 84; 1361–92

41. Harris NL, Jaffe ES, Stein H, *et al.,* (1994). A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood.* 84:1361-1392.
42. Hecht, S. M. (2000) *J. Nat. Prod. 63*, 158.
43. Heilman FR, and Kendall EC (1944). The influence of 11-dehydro-17- hydroxycorticosterone (compound E) on the growth of malignant tumor in the mouse. *Endocrinology*. 34: 416 - 426.
44. Herr I, Gassler N, Friess H, Büchler MW *et al.,* (2007). Regulation of differential pro- and anti-apoptotic signaling by glucocorticoids. *Apoptosis*. 12: 271-291.
45. Hideshima T, Richardson P, Chauhan D, ***et al.,*** (2001). The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res* 61:3071-3076
46. Hoffmeister, R. T. (1983). Methotrexate therapy in rheumatoid arthritis: 15-year experience. *The American journal of medicine*, *75*(6), 69-73.
47. Huber EM, and Groll M (2012). Inhibitors for the immuno- and constitutive proteasome: current and future trends in drug development. *Angew Chem Int Ed Engl* 51: 8708–8720.
48. Jaffe ES, Harris NL, Stein H, Vardiman J. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001.
49. Jaffe, E. S., Harris, N. L., Stein, H., & Vardiman, J. W. (2001). Tumours of haematopoietic and lymphoid tissues, WHO Classification of Tumours. *WHO, Geneva*.
50. James W. Vardiman, Ju¨ergen Thiele, Daniel A. Arber, Richard D. Brunning, Michael J. Borowitz, Anna Porwit, Nancy Lee Harris, Michelle M. Le Beau, Eva Hellstro¨m-Lindberg, Ayalew Tefferi, and Clara D. Bloomfield *et al.,* (2016). The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes journal *The Blood* 114(5) 937-952
51. Jeha S, Gandhi V, Chan KW, *et al.,* (2004). Clofarabine, a novel nucleoside analog, is active in pediatric patients with advanced leukemias. *Blood.* 103:784–789.
52. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. *CA Cancer J Clin* 60: 277–300
53. Kabera, J.N.; Semana, E.; Mussa, A.R.; He, X. (2014). Plant secondary metabolites: Biosynthesis, classification, function and pharmacological properties. *J. Pharm. Pharmacol.* 2, 377–392
54. Kadmiel M, and Cidlowski J.A. (2013). Glucocorticoid receptor signaling in health and disease, *Trends Pharmacol. Sci.* 34 518–530.
55. Kantarjian HM, Gandhi V, Kozuch P, *et al.,* (2003). Phase I clinical and pharmacology study of clofarabine in patients with solid and hematologic cancers. *J Clin Oncol.* 21:1167– 1173.
56. Kato N, Tanaka J, Sugita J *et al.,* (2007) Regulation of the expression of MHC class I-related chain A, B (MICA, MICB) via chromatin remodelling and its impact on the susceptibility of leukemic cells to the cytotoxicity of NKG2Dexpressing cells. *Leukemia* 21: 2103–8.
57. Khadem, S and Marles, R.J. (2011). Chromone and flavonoid alkaloids: Occurrence and bioactivity. *Molecules 17*, 191–206.
58. King K, and Younes A (2000). Ifosfamide- and paclitaxel based treatment of relapsed and refractory lymphoma. *Semin Oncol* 27(suppl 1):14–22.
59. Kirschbaum M, Zain J, Popplewell L. *et al.,* (2007) "Phase 2 study of suberoylanilide hydroxamic acid (SAHA) in relapsed or refractory indolent non-Hodgkin's lymphoma: A California Cancer Consortium study," *Journal of Clinical Oncology*, vol. 25.
60. Labar B, Suciu S, Willemze R, Muus P, Marie JP, Fillet G, *et al.,* (2010). Dexamethasone compared to prednisolone for adults with acute lymphoblastic leukemia or lymphoblastic lymphoma: final results of the ALL-4 randomized, phase III trial of the EORTC Leukemia Group. Haematologica. 95: 1489-1495.
61. Lacy MQ, Allred JB, Gertz MA, *et al.,* (2011) Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of two dosing strategies in dual-refractory disease. *Blood* 118:2970–5.
62. Lauren R. Teras, Carol E. DeSantis, James R. Cerhan, Lindsay M. Morton, Ahmedin Jemal, Christopher R. Flowers, *et al.,* (2016). 2016 US Lymphoid Malignancy Statistics by World Health Organization Subtypes *Ca Cancer J Clin* 66:443–459
63. Lee, K-H.; Xiao, Z. Anticancer Agents from Natural Products. Cragg, GM.; Kingston, DGI.; Newman, DJ., editors. Boca Raton, FL: CRC/Taylor & Francis; 2005. p. 71-87
64. Leonard JP, Friedberg JW, Younes A, Fisher D, Gordon LI, Moore J, *et al.,* (2007). A phase I/II study of galiximab (an anti-CD80 monoclonal antibody) in combination with rituximab for relapsed or refractory, follicular lymphoma. *Ann Oncol.* 18(7):1216-23.

65. Lichtman, M.A. (2008). Battling the hematological malignancies: The 200 years' war. *Oncologist, 13,* 126–138. doi:10.1634/theoncologist.2007-0228
66. Lin YW, and Aplan PD. (2004). Leukemic transformation. *Cancer Biol Ther3*(1):13–20.
67. Lipp HP, Bokemeyer C. Anthracyclines and other intercalating agents. In: Lipp HP, editor. Anticancer drug toxicity: prevention, management and clinical pharmacokinetics. Marcel Dekker, New York, 1999: 81–113.
68. Livingston RB. Single Agents in Cancer Chemotherapy: Springer US; 1970.
69. Luckman SP, Hughes DE, Coxon FP, Russell RGG, Rogers MJ *et al.,* (1998). Nitrogen-containing bisphosphonates inhibit the mevalonate pathway and prevent post-translational prenylation of GTP-binding proteins, including Ras. *J Bone Miner Res* 13: 581-589.Mack PC, Davies AM, Lara PN, *et al.,* (2003). Integration of the proteasome inhibitor PS-341 (Velcade) into the therapeutic approach to lung cancer. *Lung Cancer* 41(suppl 1):S89-96.
70. Mario Federico and Luigi Bagella (2011) Histone Deacetylase Inhibitors in the Treatment of HematologicalMalignancies and Solid Tumors *Journal of Biomedicine and Biotechnology* Volume 2011, Article ID 475641, 12 pages doi:10.1155/2011/475641
71. Marks P. A. and Breslow R. (2007) "Dimethyl sulfoxide to vorinostat: development of this histone deacetylase inhibitor as an anticancer drug," *Nature Biotechnology*, vol. 25, no. 1, pp. 84– 90.
72. Martodam, R.R., K.S. Thornton, D.A. Sica, *et al.* (1983). The effects of dichloromethylene diphosphonate on hypercalcemia and other parameters of the humoral hypercalcemia of malignancy in the rat Leydig cell tumor. *Calcif. Tissue Int.* **35:** 512–519.
73. Masdehors P, Merle-Beral H, Magdelenat H, *et al.,* (2000). Ubiquitin-proteasome system and increased sensitivity of B-CLL lymphocytes to apoptotic death activation. *Leuk Lymphoma* 38:499-504.
74. McDonald CJ (1981) The uses of systemic chemotherapeutic agents in psoriasis. *Pharmnacol TImer* 14: 1-24
75. Mitsiades CS, Mitsiades N, Hideshima T, Richardson PG, Anderson KC *et al.,* (2006). Proteasome inhibition as a new therapeutic principle in hematological malignancies. Curr Drug Targets 7: 1341–1347
76. Mundy, G.R. (1998). Bisphosphonates as anticancer drugs. *N. Engl. J. Med.* **339:** 398–400.
77. Myers CE, Mimnaugh EG, Yeh GC, Sinha BK. (1988). Biochemical mechanisms of tumor cell kill by the anthracyclines. In: Lown J.W, editor. Anthracycline and Anthracenedione-based anticancer agents. pp 527–569, Amsterdam: Elsevier
78. Natsuko Kondo,1 Akihisa Takahashi,2 Koji Ono,1 and Takeo Ohnishi *et al.,* (2010). DNA Damage Induced by Alkylating Agents and Repair Pathways Journal of Nucleic Acids Volume 2010, Article ID 543531, 7 pages
79. Newman, D. J.; Cragg, G. M.; Snader, K. M (2003) *J. Nat. Prod. 66*, 1022.
80. Nicolaides NC, Galata Z, Kino T, Chrousos GP, Charmandari E *et al.,* (2010) The human glucocorticoid receptor: molecular basis of biologic function. *Steroids*. 75: 1-12.
81. Pavlakis, N., R. Schmidt & M. Stockler. 2005. Bisphosphonates for breast cancer. Cochrane Database Syst Rev. CD003474.
82. Rabbani A, Iskandar M, Ausio´ J. (1999). Daunomycin induced unfolding and aggregation of chromatin. *J Biol Chem* 274:18401–18406.
83. Rajkumar SV, Jacobus S, Callander NS, Fonseca R, Vesole DH, Williams ME, *et al.,* (2010). Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet oncol.* 11: 29-37.
84. Ramalingam S. S, Parise R. A, Ramananthan R. K. *et al.,* (2007) "Phase I and pharmacokinetic study of vorinostat, a histone deacetylase inhibitor, in combination with carboplatin and paclitaxel for advanced solid malignancies," *Clinical Cancer Research*, vol. 13, no. 12, pp. 3605–3610.
85. Ravandi F, O'Brien S. (2006). Alemtuzumab in CLL and other lymphoid neoplasms. *Cancer Invest*. 24(7):718-25
86. Russell RG (2006). Bisphosphonates: from bench to bedside. *Ann N Y Acad Sci* 1068: 367-401
87. Sadoul K, Khochbin S (2016). The growing landscape of tubulin acetylation: lysine 40 and many more. *Biochem J* 473: 1859–68.
88. Sartorelli, A. C.; Hodnick, W. F.; Belcourt, M. F.; Tomasz, M., Haffty, B.; Fischer, J. J.; Rockwell, S. (1994) *Oncol. Res. 6*, 501.
89. Sasaki, A., B.F. Boyce, B. Story, *et al.* (1995) Bisphosphonate risedronate reduces metastatic human breast cancer burden in bone in nude mice. *Cancer Res.* **55:** 3551–3557.
90. Sastry, M.; Fiala, R.; Lipman, R.; Tomasz, M.; Patel, D. J (1995) *J. Mol. Biol. 247*, 338.

91. Sayers TJ, Brooks AD, Koh CY, *et al.,* (2003). The proteasome inhibitor PS-341 sensitizes neoplastic cells to TRAIL-mediated apoptosis by reducing levels of c-FLIP. *Blood* 102:303-310.
92. Schoneveld, O.J, Gaemers, I.C and Lamers, W.H, (2004). Mechanisms of glucocorticoid signalling, *Biochim. Biophys. Acta* 1680 114–128.
93. Sengupta N, and Seto E, (2004). Regulation of histone deacetylase activities. *J. Cell Biochem. 93*, 57-67.
94. Shipman CM, Rogers MJ, Apperley JF, Russell RGG, Croucher PI *et al.,* (1997). Bisphosphonates induce apoptosis in human myeloma cell lines: a novel anti-tumour activity. *Br J Haematol* 98: 665- 672.
95. Sievers EL, (2000). Targeted therapy of acute myeloid leukemia with monoclonal antibodies and immunoconjugates. *Cancer Chemother Pharmacol.* 46: S18-S22.
96. Smith, M.R. (2005) Zoledronic acid to prevent skeletal complications in cancer: corroborating the evidence. *Cancer Treat. Rev.* **31**(Suppl 3): 19–25.
97. Thomas DA, Ravandi F, Kantarjian H, *et al.,* (2006). Monoclonal antibody therapy for hairy cell leukemia. *Hematology/oncology clinics of North America*. 20(5):1125-36.
98. Van Maanen JMS, Retèl J, de Vries J, Pinedo HM (1988). Mechanism of action of the antitumor drug
99. Vose JM, Link BK, Grossbard ML, *et al.,* (2001). Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 19:389-397
100. West AC, Johnstone RW (2014). New and emerging HDAC inhibitors for cancer treatment. *J Clin Invest* 124: 30–9.
101. Yoichi Imai, Yoshiro Maru and Junji Tanaka (2016). Action mechanisms of histone deacetylase inhibitors in the treatment of hematological malignancies *Cancer Sci* 107 (2016) 1543–1549.
102. Zhang L, Qian Z, Cai Z, *et al.,* (2009) Synergistic antitumor effects of lenalidomide and rituximab on mantle cell lymphoma in vitro and in vivo. *Am J Hematol* 84:553-559
103. Zinzani, P. L. C. Pellegrini, L. Gandolfi *et al.,* "Combination of lenalidomide and rituximab in elderly patients with relapsed or refractory diffuse large B-cell lymphoma: a phase 2 trial," *Clinical Lymphoma,Myeloma and Leukemia*, vol. 11, no. 6, pp. 462–466,