Treatment Related Complications in Leukemia

Introduction

Leukemia is a hematological neoplasm of the blood and bone marrow elements. The defining characteristic of leukemia is an overproliferation of the hematopoietic cells—specifically the leukocytes. There are four subdivisions of leukemia based on the type and level of maturity of the leukocytes present in the pathology of the disease. The classification of a leukemia as acute or chronic addresses the maturity level of the cancerous leukocytes, and the classification of a leukemia as myelogenous or lymphocytic references the type of leukocytes involved in the pathology. The acute leukemias (AML and ALL) are characterized by the rapid proliferation of immature myelogenous or lymphocytic cells. The chronic leukemias, on the other hand, are characterized by rapid proliferation of the mature myelogenous or lymphocytic cells.

The distinct pathologies of each leukemia create a challenge in implementing an effective treatment for the disease. In order to ensure efficient eradication of the leukemia, each treatment must be tailored to the specific pathological properties of the leukemic cells present. Thus, the goal of treatment for an individual with leukemia depends on the type of leukemia that is diagnosed. In acute leukemias, the goal is to eradicate the leukemia cells completely and restore normal hematopoiesis. This goal is achieved via the cyclic administration of high doses of anti-leukemia drugs and central nervous system (CNS) prophylaxis to prevent CNS leukemia. In addition, if the patient is a good candidate, bone marrow transplantation may be performed. In chronic leukemias (specifically CML), the goal is not always to cure the disease, but to control the proliferation of the cancerous cells with near restoration of normal hematopoiesis. This goal
is achieved via low dose chemotherapy, bone marrow transplantation, and more recently, targeted molecular therapies such as imatinib (Gleevec).

**General Principles of Chemotherapy**

The treatment of both chronic and acute leukemia involves the use of chemotherapy. Thus, it is important to understand the mechanisms and principles of chemotherapy. The drugs used in chemotherapy are anti-leukemic—they inhibit proliferation and cause the reduction of clonal populations of leukemia cells. The survival of a neoplasm depends on the growth and proliferation of its cells. Chemotherapeutic drugs act by affecting enzymes or substrates related to DNA or RNA synthesis, which are necessary for cell division and growth. Thus, anti-leukemic drugs affect cells that are actively dividing. The effectiveness of chemotherapeutic drugs on clonal populations depends on their ability to interrupt DNA synthesis, or S phase of the cell cycle. This interruption is influenced by several factors. For instance, the greater the proportion of leukemic cells in S phase, the more enhanced is the action of the drug. When a large number of neoplastic cells are present, the proportion of cells not dividing is higher than the proportion of cells that are dividing, which is called a low growth fraction. This means that the fraction of cells that are actually dividing (or are in S phase) in the clonal population is small. Chemotherapy is not as effective on these clonal populations. When a small number of neoplastic cells are present, the fraction of cells that are actually dividing is high in comparison to those not dividing. Chemotherapy is much more effective on these populations of neoplastic cells. This principle is based on the Gompertzian Growth curve, a visual representation of the growth kinetics of cancers. This principle is summarized by Peter Gale, editor of *Leukemia Therapy*, as follows
“Both normal and neoplastic cells divide more rapidly when the population size is small and more slowly when the population is large. Early growth is exponential with a high growth fraction and short doubling time. As population size (density) increases, the doubling time lengthens and the growth fraction decreases….when the tumor is small, a relatively higher proportion of cells are in S phase and synthesize DNA. Large tumors…have few cells in S phase” (Gale 3).

How effectively an anti-leukemic drug eradicates the leukemia cells is also dependent on the repetitions of the administration of the drug. According to Gale, “…drug induced cell kill follows first order reaction kinetics resulting in fractional reduction in the number of malignant cells” (Gale 3). Therefore, chemotherapy regimens must be repeated in order to reduce the fraction of cells still present after the first phase of therapy. Using a combination of anti-leukemic drugs, which are applied in order to take advantage of the different properties of each drug and prevent drug resistance, can also enhance the effectiveness of chemotherapy. This strategy is called combination chemotherapy. For example, in treating AML, cytarabine (a cell cycle phase specific drug) is combined with an anthracycline like doxorubicin (which is cell cycle phase nonspecific). This combination makes use of two drugs that are active as single agents in a tumor and each has different mechanisms of action against DNA replication. Maximum cell kill and minimum resistance are achieved.

Chemotherapy is administered in a set of phases classified based on each phase’s separate goal. It is important to note that the strategy of chemotherapy differs depending on which leukemia is being treated. Edward Henderson, author of Leukemia remarks, “The use of chemotherapy in the treatment of leukemia has evolved remarkably over the past 30 years…However, the therapies for specific leukemias differ markedly, mostly owing to the
differing courses of these diseases” (Henderson 401). Even so, there are some overall similarities shared by all of the chemotherapy regimens regardless of which leukemia to which they are applied.

The first phase of chemotherapy is called induction. Induction is the first line of treatment in acute leukemias and is more specifically termed remission induction therapy. In remission induction therapy, the objective is to return the bone marrow features to normal hematopoietic function. Complete remission is achieved when there are normal numbers of red blood cells, neutrophils, and platelets in the blood. In addition, complete remission is characterized by less than five percent blasts in circulation and normal maturation of bone marrow elements. If complete remission cannot be achieved, then the goal is to reduce the malignant clone and allow for restoration of normal hematopoiesis. In induction, a combination of high dose chemotherapeutic drugs is used in a few cycles administered over a week.

The next phase of chemotherapy is generally called control, consolidation, or intensification therapy. Control or consolidation is administered because even at complete remission, it is statistically probable that up to $10^9$ abnormal blast cells that are morphologically undetectable are still present. Control or consolidation, lasting up to six weeks, involves the continuation of drugs that were used in induction therapy and is used to prevent recurrence of the leukemia. Often, during this phase of treatment, drug resistance may develop. In this case, a new combination of drugs or higher doses of the same drug may be used as an attempt to circumvent the resistance. The alternative strategy in the case of resistance may be to use less toxic combinations or lower doses of drugs.

The final phase of chemotherapy for leukemia is called maintenance. In maintenance therapy, the goal is to reduce further burden of leukemia cells and to maintain remission. This is
achieved via low doses of drugs and by focusing on maintaining an infection-free patient.

Immunity that may have been lost during other phases of therapy is restored in order to aid in preventing infection. The characteristics of each phase of chemotherapy is highly dependent on many variables, including what drugs are in use and the dosage administered to the patient.

**Drugs Used in Chemotherapy**

The drugs used in chemotherapy are classified based on their presumed mechanism of action.

![Image of the figure 5.1: Mechanisms of action of anti-cancer drugs.](image)

**Figure 1** Kenneth Calman. Figure 5.1: Mechanisms of action of anti-cancer drugs. 1980


There are three different general mechanisms of action for chemotherapeutic agents (See Figure 1). Drugs may (1) affect synthesis of nucleic acid precursors, (2) interact with DNA and interrupt transcription or translation, or (3) interact with specific gene products (proteins) and
affect that product’s function or efficiency. Thus, chemotherapeutic agents have an opportunity to act at each stage of the central dogma of gene expression. In addition, drugs are often classified based on where specifically in the cell cycle they mediate their affect. If the drug acts at a specific phase, it is termed cell cycle phase specific. If the drug has no specific cell phase in which it administers its effects, then it is called cell cycle phase nonspecific.

Drugs Used in Chemotherapy

Alkylating agents are used to treat CML and CLL. Their mode of action is to substitute alkyl groups with hydrogen atoms in certain organic compounds. This substitution causes a cross-linking of the DNA that interferes with DNA replication and transcription, thus causing a cytotoxic affect. Alkylating agents are cell cycle phase nonspecific. The most commonly used alkylating agents are chlorambucil, busulfan, and cyclophosphamide. There are five major classes of alkylating agents; the nitrogen mustards, the alkyl sulfonates, the ethylenimine derivatives, the triazine derivatives, and the nitrosoureas. These classifications are based on the chemical structure of each type of alkylating agent. The side effects of alkylating agents are typical for most chemotherapeutic drugs.

Anthracyclines are a natural product of the fungus *Streptomyces* and are used to treat AML and ALL. Their mode of action is to inhibit DNA replication by intercalation of base pairs (where ligands of some appropriate size and structure fit themselves between the base pairs of DNA). These are cell cycle phase nonspecific. The most commonly used anthracyclines are daunorubicin and doxorubicin. At specific high dosages, anthracyclines can cause cardiomyopathic symptoms.

Plant alkaloids are vinca alkaloids extracted from the periwinkle plant. They are used to treat ALL and CLL and act by binding to microtubular proteins and arresting mitosis. These
medications are cell cycle phase specific. The most commonly used are vincristine and vinblastine. Plant alkaloids have some uncommon side effects that are generally associated with autonomic neuropathy. These include symptoms such as depression of the Achilles tendon reflex, paresthesias of the fingers and toes, weakness, and sensory impairment.

The epipodophyllotoxins are semisynthetic derivatives of podophyllotoxins (non alkaloid toxins). They are used to treat AML, CML, and ALL and are sometimes called topoisomerase II inhibitors because they inhibit an enzyme that guides and catalyzes the unknotting of DNA for replication. Thus, epipodophyllotoxins are cell cycle phase specific. The most common epipodophyllotoxins are etoposide and teniposide. Epipodophyllotoxins have the same common side effects as other chemotherapeutic drugs used to treat leukemia, but they also have the uncommon side effects of peripheral neuropathy and radiation recall.

Antimetabolites are analogues of normal compounds that are required for cell function and replication, thus they are usually cell cycle phase specific. They are used to treat ALL or AML depending on the analogue present. Antimetabolites interact with enzymes and damage cells by substitution into intracellular proteins. They may compete with normal metabolites for the catalytic site of an enzyme necessary for replication or cell function, or they may alter the catalytic rate of the enzyme by competing with a normal metabolite that acts at an enzyme regulatory site. The most commonly used antimetabolites are methotrexate, 6-Mercaptopurine, 6-thioguanine, cytarabine, and 5-Azacytidine. Depending on the type of analogue from which they originate, antimetabolites are grouped into three classes: folic acid analogues, purine analogues, and pyrimidine analogues. The side effects of antimetabolites are common to all chemotherapeutic drugs.
Acridine derivatives are heterocyclic organic nitrogen derivatives. They are used to treat AML and ALL. The mode of action for acridine derivatives is to compete with DNA base-pair intercalation by actually inserting into one strand of the DNA double helix and causing the addition of a base in the opposite strand. They are cell cycle phase nonspecific. The most commonly used acridine derivative is AMSA. Acridine derivatives do not have any uncommon side effects in comparison with other chemotherapeutic drugs.

Anthraquinones are aromatic cyclic compounds that are a derivative of anthracene. They are used to treat acute leukemias (ALL and AML). Their mode of action is intercalation of DNA base-pairs and they are cell cycle phase nonspecific. The most commonly used are mitoxantrone (for ALL), and bisantrene (for AML). They have no uncommon side effects in comparison to other chemotherapeutic drugs used to treat leukemia.

Procarbazines are alkylating-like compounds. They are used to treat chronic leukemias, but are usually a second or third line of defense. Procarbazines interfere with biological processes and inhibit DNA, RNA, and protein synthesis; they are cell cycle phase nonspecific. Aside from the typical side effects of chemotherapeutic agents, they also cause disorders of consciousness. These disorders include somnolence, depression, agitation, and psychosis.

Hydroxyurea is an urea analogue used to treat CML, AML, and ALL. Its mode of action is to inhibit ribonucleoside diphosphate reductase (an enzyme essential to DNA synthesis). It is cytotoxic to cells in S phase and is thus cell cycle phase specific. The most commonly used urea analogue is called Hydroxyurea and its side effects are all typical for chemotherapeutic drugs.

L-Asparaginase is an enzyme used to treat ALL. This enzyme destroys extracellular supplies of L-asparagine, which results in the death of cells lacking the enzymes necessary to synthesize L-asparagine. L-Asparaginase is most cytotoxic to cells that are in G1 or S phase, but
is generally labeled as cell cycle phase nonspecific. Due to its low bone marrow and
gastrointestinal toxicity, L-Aspariginase is often used in combination chemotherapy. The most
commonly used L-Aspariginase is called Elspar. Interestingly, L-Asparaginase is associated
with anaphylaxis (an acute systemic allergic reaction), pancreatitis, and decreased clotting
factors.

Adrenocorticoids are found in adrenocorticosteroids. They are used to treat ALL and
CLL and their mechanism of action is not well understood, although they are generally
categorized as cell cycle phase nonspecific. The most commonly used adrenocorticoid is
Prednisone. Some of the side effects of this drug that are often not observed in other
chemotherapeutic agents are sodium and water retention, potassium loss, psychosis, and
exacerbation of diabetes mellitus.

A final drug used to treat leukemia is Gleevec or imatinib. Imatinib is the first line of
therapy for CML. The pathology of CML involves a chimeric kinase protein BCR-ABL, which
activates RAS, MAPK, and PI3K signaling pathways—all of which lead to evasion of apoptosis,
cell proliferation, and to the interruption of cellular adhesion to the bone marrow. Before the
imatinib era, hydroxyurea and an immunotherapy called interferon-α were the typical first line
treatments of CML. These treatments were only mechanisms for control—allogeneic stem cell
transplantation was the only curative treatment. However, allogeneic stem cell transplantation is
only available to about 20%-25% of patients due to age and compatible donor limitations. The
advent of imatinib made the treatment of patients diagnosed with CML who were not candidates
for bone marrow transplantation a possibility.

Imatinib inhibits proliferation of Philadelphia chromosome positive leukemias by
blocking the action of BCR-ABL—the chimeric kinase protein created by the chromosomal
aberration in CML. Imatinib acts as a competitive inhibitor of the ATP binding site of the BCR-ABL tyrosine kinase by binding to and stabilizing its inactive non-adenosine triphosphate (ATP) binding conformation. Imatinib has several pharmacological properties. It inhibits the proliferation and promotes apoptosis in Ph+ CML cells. It also potently inhibits the proliferation of fresh leukemia cells in vitro. In addition to inhibiting the BCR-ABL tyrosine kinase, it also inhibits the receptor tyrosine kinase for platelet derived growth factor and stem cell factor. Finally, imatinib down-regulates telomerase activity and thus, inhibits the proliferation of telomerase-expressing cell lines. In comparison to the previous gold-standard for CML treatment (interferon-α) imatinib is highly effective. In their article “Imatinib: A Review of its Use in Chronic Myeloid Leukemia”, Marit Moen et. al. claim that “In a randomized, nonblind, multicenter phase III trial in patients with newly diagnosed Ph+ chronic-phase CML, imatinib significantly improved the estimated rates of survival with progression and survival without progression to accelerated-phase or blast crisis CML compared with interferon-α” (Moen).

Alternative Therapies: Immunotherapies and Biological Response Modifiers

In addition to chemotherapy, leukemia can be treated by a variety of alternative therapies, including immunotherapy and biological response modifiers. Immunotherapies are generally used to treat acute leukemias. Patients with a large burden of leukemic cells have a small growth fraction, so phase specific and nonspecific cytotoxic drugs are not effective treatments. Theoretically, immunotherapies provide a larger therapeutic margin because they kill only leukemia cells thus, the proportion of pathologically abnormal cells killed increases. However, immunotherapies are only effective on small tumor loads (with large growth fractions) and can prolong, but not induce remission. Immunotherapies include immune stimulation with BCF (bacillus Calmette Guerin), MER (methanol extraction residue), tubercle bacillus, and
levamisole. In addition to these therapies, specific immunization with leukemia cells, cell-free extracts, and cultured cell lines can be attempted.

Biological response therapies are another type of therapy used to treat leukemia. The advent and use of biological response modifiers (BRMs) has been made possible by advances in genetic engineering, cell culturing, and protein and nucleic acid chemistry. BRMs are substances that are produced naturally by the body or can be created in the laboratory that induce or activate natural immunity in the body. One example of a BRM is interferons. Interferons are proteins produced by cells in response to viral infections, double stranded ribonucleic acids, antigens, and mitogens and are categorized by their biochemical properties. Alpha and beta interferons are produced by leukocytes and fibroblasts in response to a virus or double stranded ribonucleic acid and are acid stable compounds. Gamma interferons are produced by T-cells and large granular lymphocytes in response to mitogens or antigens. Interferons have the dual power of direct antiproliferative activity and the ability to activate the immune system. They cause altered expression of cell surface antigens and influence the cellular components of the immune system to activate and respond to abnormal or foreign material. Another example of a biological response modifier is monoclonal antibody treatment, which causes a reduction in leukemia cell count and lymph node size. This treatment is generally attempted for patients with ALL. The patient has his bone marrow removed and treated with anti-ALL monoclonal antibodies. The bone marrow is then engrafted back into the patient.

**Bone Marrow Transplantation**

Bone marrow transplantation (BMT) (also termed engraftment, infusion, rescue, or support), a therapy based on advances in biology, immunity, and genetics, is a common treatment for all four types of leukemia. In 1957, the first successful bone marrow transplants
were performed on patients and in 1959, engraftment was successfully achieved, thus
demonstrating that intravenous infusions of bone marrow can protect against lethal irradiation.
Bone marrow transplantation takes advantage of the properties of stem cells and their plasticity.
Stem cells have high differentiating potential and are able to form many types of tissues in the
body depending on the factors to which they are exposed. In stem cell transplantation (SCT) for
leukemia, stem cells from the bone marrow, peripheral blood, or cord blood are removed from
the patient (or taken from a donor) and given back to the patient after he receives a high dose
treatment of chemotherapeutic drugs or irradiation to ablate the bone marrow. The engrafted
cells restore hematopoietic function so that the irradiation, which causes low immunity, is not
lethal. There are four types of stem cell transplantations classified based on the source of stem
cells used in the graft: allogeneic, autologous, syngenic, and cord blood. In all four cases, the
stem cells are used to reconstitute the patient’s bone marrow, without which the patient is
extremely vulnerable to lethal infections.

In allogeneic BMTs, the stem cells are derived from a donor and not the patient. The
donor must be HLA (human leukocytic antigen) compatible. Human leukocytic antigens are
markers, or proteins, on the surface of all cells, but are at especially high concentrations on the
surface of leukocytes. These special markers play an important role in the specific immune
response of an individual by acting as peptide receptors. An antigen in the body is taken up by
an antigen presenting cell. The antigen is then processed into small peptides and associates with
HLA class I or II molecules (class I present peptides from inside the cell and class II present
peptides from foreign antigens) on the surface of the cell. The antigen can then be presented to
B or T cells. The B and T cells determine if the antigen is self or non-self and then, if it is non-self, initiate an immune response. HLAs are encoded by genes that are closely linked on the
short arm of chromosome 6. There are six loci for these genes. A high degree of polymorphism exists in this region because there are two alleles per each of the six loci, thus, an individual can have up to 12 types of HLAs. Thus, $4 \times 10^{18}$ combinations exist for HLA proteins. Due to this high degree of diversity, each individual has a “fingerprint” that corresponds to their HLA type.

Figure 2 Whittaker J.A., and I.W. Delamore eds. Figure 24.1: The Search for...1987


The optimal donor for an allogeneic BMT is a genotypically HLA-matching sibling (See Figure 2). The limited accessibility to this type of donor has led to interest in other types of donors, including HLA phenotypically matched or partially mismatched family members or HLA-matched unrelated volunteers from the general population. These donor options remain difficult to procure because of HLA-matching obstacles. The editors of Leukaemia, David Whittaker and I.W. Delamore, remark, “The enormous polymorphism of the HLA system remains a formidable barrier currently restricting the availability of HLA-matched unrelated donors to a minority of potential candidates” (Whittaker 568). Still, the use of unrelated donors
remains an often-utilized alternative to sibling donors.

Regardless of the source of the graft, the procedure remains the same in allogeneic bone marrow transplants. In a conventional allogeneic BMT, stem cells from an HLA compatible donor are harvested, stored, and then engrafted into the patient. The stem cells are collected from the donor’s bone marrow or peripheral blood. Peripheral blood stem cells (PBSCs) are becoming the preferable source for stem cells because they are easily collected and rapidly engrafted. The stem cells are preserved by cryopreservation and, meanwhile, the patient receives high doses of chemotherapy and radiation to eradicate any remaining cancer cells in the bone marrow. Finally, the donor’s stem cells are infused into the patient. Thus, there are three phases in an allogeneic BMT. There is a donor matching phase where the cells from the potential donor are tested for compatibility to the patient. Then a conditioning phase, which includes high dose chemotherapy and radiation to eradicate the disease, is administered. Finally, stem cells from the donor are given back to the patient to reconstitute the immune system—a phase called engraftment.

While allogeneic BMTs represent definitive progress in biological and immunological therapies, they are not without disadvantage. These disadvantages include difficulty in finding an appropriate donor, the high treatment related mortality due to toxicity from chemotherapy, and a condition called graft-versus-host disease. Graft-versus-host disease (GVHD) is a complication of allogeneic BMTs that results from incompatible immunities between the donor and the recipient. The engrafted donor cells attack the recipients’ tissues and organs because the engrafted cells target them as foreign. There is both chronic and acute GVHD. Chronic GVHD is one of the most serious complications of allogeneic BMT. The editors of *Leukaemia* explain that “Chronic GVHD is the most serious and common long term complication of
allogeneic hematopoietic stem cell transplantation (HCT)…chronic GVHD remains the major cause of late death despite its association with lower relapse rate” (Whittaker 569).

The advantages of allogeneic BMT are numerous, despite the dangers of chronic GVHD. These advantages include a tumor free graft (because the donor does not have leukemia), undamaged stem cells from the donor, avoidance of secondary AML, and the graft-versus-leukemia (GVL) effect. The GVL effect is a beneficial aspect of GVHD. In fact, patients with chronic GVHD have lower risk of relapse. GVL is a therapeutic immune reaction of the grafted donor cells to the leukemia cells that may still be present in the patient even after chemotherapy. In other words, the lymphocytes of the graft act against the diseased bone marrow of the patient. Thus, GVL is essentially an immunotherapy.

In contrast to allogeneic bone marrow transplantation, autologous bone marrow transplantation (alloBMT) is a therapy that involves harvesting the stem cells from the patient’s marrow, storing them, and returning them to the patient after high doses of chemotherapy (conditioning chemotherapy). There are generally four phases to alloBMTs. The first phase is an induction phase. In this phase, conventional chemotherapy is administered to reduce the disease. Following induction, there is a mobilization or harvesting phase in which growth factors are used to cause the proliferation and mobilization of stem cells from the bone marrow to the bloodstream. This stage is necessary because stem cells are normally at low levels in circulation. Hematopoietic growth factors increase the concentration of stem cells in circulation by a 1000-fold after their administration. The next phase is a conditioning phase, in which high dose therapy (chemotherapy or irradiation) wipes out and conditions the immune system and bone marrow in preparation for the previously harvested stem cells. The final phase of alloBMT is engraftment. This phase involves grafting the stem cells into the patient in order to reconstitute
the immune system after its destruction from conditioning.

Like allogeneic bone marrow transplantation, autologous bone marrow transplantation has disadvantages. The engrafted cells may still be contaminated with disease; and since their source is the patient, there is a high risk of secondary AML. High treatment mortality exists due to increased risk of infection and toxicity. However, because the stem cells come from the patient, there is no risk of chronic GVHD. High dose therapy made possible by previous harvesting may also decrease recurrence of the disease and prolong remission.

Complications Resulting from Treatment

The different forms of leukemia treatment mentioned have the possible disadvantage of creating long-term complications for the surviving patient. One such complication occurs in the prevention of central nervous system leukemia (CNS leukemia). CNS leukemia is the leukemic invasion of the leptomeninges. The leptomeninges are the two innermost layers of tissue that cover the brain and spinal cord. These layers are called the arachnoid and pia mater layers. In its superficial layers, the arachnoid layer houses the blood vessels and passageways for cerebral spinal fluid (CSF). These channels are the principle channels for the intrathecal passage of drugs in CNS leukemia prevention. The arachnoid layer also contains specialized structures called trabeculae. The trabeculae are rod or beam shaped tissues that provide structure and support to the neural matter.

CNS Leukemia

In CNS leukemia, cells follow a predictable course of invasion that corresponds with patterns of lesions and clinical manifestations of the disease. The first sign of CNS leukemia is the presence of leukemic cells in the walls of the veins of the superficial leptomeninges, while the deeper arachnoid layer remains unaffected. The leukemic cells circulating in the blood then
invade the other tissues of the brain. This infiltration causes the destruction of the trabeculae and
the release of cells into the CSF. CNS leukemia can be diagnosed at this stage of leukemic
invasion even without clinical manifestation due to the presence of the leukemia cells in the CSF.
Although they do not yet infiltrate the neural tissues, the leukemia cells pack the arachnoid layers
and extend into the deeper portions of the arachnoid tissue itself. The large cell mass then
destroys a membrane called the pial-glial membrane—a membrane that composes the dual outer
lining of the brain and spinal cord. The leukemia cells then infiltrate the neural tissue.

The predictable course of invasion that the leukemic cells follow indicates five phases of
clinical manifestations in meningeal leukemia. First, the trabeculae are destroyed by infiltrating
cells. There are no clinical signs or symptoms of this phase; however the presence of blasts in
the CSF indicates meningeal leukemia. All the structures entering and leaving the brain must
pass through the leptomeninges and are thus affected by the infiltrating cells. The cranial and
spinal nerves are especially susceptible to the invasion. In addition to directly infiltrating the
nerve fibers, the leukemia cells cause the compression of the spinal nerves and interfere with
blood flow. The result of these structural changes is cranial nerve palsies—the second phase of
meningeal leukemia. Following the compression and interference to blood flow in the vessels of
the arachnoid layer, the flow of CSF is obstructed by the obliteration of the CSF channels
themselves. The destruction of CSF channels occurs when the trabeculae are swollen with
leukemia cells and the channels become so compressed that they self-destroy, which causes
hydrocephalus (an abnormal accumulation of CSF in ventricles or cavities of the brain). A
related blood flow issue occurs in the fourth clinical phase of meningeal leukemia. The
arachnoid tissue occupies a finite space in the brain and when that space is occupied by leukemia
cells, the blood vessels within the arachnoid layer become compressed and blood flow is
restricted, which causes hypoperfusion encephalopathy (decreased blood flow disease of the brain)—the fourth clinical phase of meningeal leukemia. The neurological manifestations of meningeal leukemia occur at this phase. Finally, the last phase is the destruction of the pial-glial membrane. This stage is accompanied by the infiltration of the leukemia cells into the neural tissue (the brain) and usually causes death.

A major limiting factor in the treatment of leukemia is the proliferation of leukemia cells in the CNS. A.M. Mauer et. al., authors of “Central Nervous System Prophylaxis for Therapy of Acute Lymphocytic Leukemia,” explain that until recently, the CNS was a “…sanctuary site protecting the leukemic blast cells present there until drug resistance occurred. This was followed by a CNS, and subsequently, a bone marrow relapse (Mauer et. al. 17). Thus, it is important that CNS leukemia be avoided or treated. In fact, the prevention of CNS leukemia has been effective in reducing relapse in ALL. The prevention of CNS leukemia is called CNS prophylaxis. CNS prophylaxis is achieved by one of two treatment routes—radiation or anti-leukemic drugs. Two methods of radiation are used to irradiate the brain or the spinal cord (or both) including external brain radiation therapy or the instillation of radiocolloids (called intrathecal radiocolloids) into the arachnoid space. The other method of CNS prophylaxis is to inject chemotherapeutic drugs into the spinal canal. An example of this treatment is intrathecal methotrexate—the direct injection of cytotoxic drugs into the spinal cord.

Although CNS prophylaxis is important in preventing relapse in ALL, it is associated with a myriad of complications. These complications are all late consequences of treatment (occurring post-treatment) and may include organ damage, endocrine dysfunction, secondary cancers, CNS dysfunction, and psychosocial disorders that result from structural alternations in the brain. An example of a long term complication that results from CNS prophylaxis is
demyelinating leukoencephalopathy. Demyelinating leukoencephalopathy is a result of alterations in neurovascular permeability to drugs caused by CNS prophylaxis radiation treatment. After radiation, methotrexate is administered, and because the neurovascular permeability is much higher to the cytotoxic drug, the drug is taken up in greater concentrations. This causes damage to the cells that secrete myelin—the substance that insulates the axons of the neuron.

In addition to these physiological issues, there are also behavioral and developmental complications associated with CNS prophylaxis. Studies on these problems, however, are often contentious in their conclusions. The disagreement is caused by empirical issues; the variety in measurement of the neuropsychological defect (the use of IQ tests versus achievement tests to measure disorder, for example), the ambiguity in research design (the establishment of a control group is often difficult if not impossible), and extraneous variables (the severity of illness, school attendance, and age at CNS prophylaxis treatment). However, despite these difficulties, a variety of studies have shown that intellectual performance, growth and development, and structural abnormalities in the brain are all possible results from CNS prophylaxis. A study was performed by JH Rowland and colleagues in 1984 on 104 patient, each receiving one of three different prophylaxis regimens (either intrathecal methotrexate, intrathecal methotrexate plus radiation, or intrathecal methotrexate plus intravenous radiation). The study found that “In contrast to the other two treatment groups, children whose CNS prophylaxis included cranial irradiation attained significantly lower mean Full Scale IQs…, performed more poorly on the Wise Range Achievement Test, a measure of school abilities, and exhibited a greater number of difficulties on a variety of other neuropsychologic measures (Rowland). In addition, in another study performed by G. Paolucci and P.Rosito on 36 patients, it was shown that “Both acute neurologic
toxicity and chronic neurologic dysfunction have been reported” (Paolucci 106) These dysfunctions and abnormalities included leukoencephalopathy accompanied by irritability, confusion, ataxia, slurred speech, dementia, and seizures. The leukoencephalopathy was associated with structural abnormalities such as disseminated cerebral white matter, axonal degeneration, astrocytosis, mineralized grey matter lesions, mineralizing microangiopathy, and dystrophic calcifications. In addition, structural abnormalities were seen in CT scans and were associated with abnormal EEGs, neuropsychological tests, and psychometric tests. In regard to the psychometric tests, Paolucci remarks “Mean scores on the WISC scale in children with ALL and children with solid tumors showed a statistically significant difference between the two groups…with ALL children having the lowest scores…” (Paolucci 108) Despite all of these negative outcomes, CNS prophylaxis is still of utmost importance in preventing relapse in ALL.

**Cardiotoxicity**

Another common complication that arises from the treatment of leukemia is cardiomyopathy—the dysfunction of the heart muscle due to a variety of factors. Childhood cancer survivors often experience some form of cardiomyopathy. Because the cardiomyopathy develops five years from diagnosis or is reoccurring or chronic in nature, this effect is defined as a late effect. The complications associated with cardiomyopathy are dependent on age, gender, race, and the therapy administered. They can be triggered by stress, pregnancy, exertion, growth hormone therapy, or general anesthesia. Cardiotoxicity is one of the most serious chronic complications of treatment for leukemia. In fact, cardiopulmonary diseases caused by this toxicity are the third highest cause of death in cancer survivors. These complications are commonly caused by mediastinal neck radiation or treatment using anthracyclines.
Anthracyclines mediate the generation of free radicals and the cardiac myocytes are particularly susceptible to these free radicals because of the oxidative nature of their metabolism. The attack by the free radicals on the myocytes causes ventricular dysfunction and arrhythmias.

**Multidrug Resistance**

Another complication that often occurs during treatment of leukemia is multidrug resistance. Multidrug resistance is one of the biggest problems that limit the effectiveness of chemotherapeutic drugs. Drug resistant leukemia must be distinguished from unresponsive leukemia. A leukemia is unresponsive, for example, if the drugs administered are phase specific and have been given to the patient at the wrong phase. In contrast, a leukemia is defined as resistant if the activity of standard chemotherapy is less than would be expected for typical populations. Resistance can be intrinsic if the leukemia is resistant at the presentation of the drug, or acquired if it develops over the course of treatment. Resistance occurs because as cancer develops, the damage to the DNA of the leukocytes continues to accrue. This damage results in mutations, which cause changes in genes involved in the sensitivity of a tumor load to certain drugs. In fact, the higher the mutation rates of the leukemic cells, the more likely drug resistance is to develop. This is because the leukemia cells that have developed resistance are selected for by natural selection because the cells that do not develop resistance expire when exposed to the drug. The drug resistant population then expands, relapse occurs, and the initial effective therapeutic treatment is no longer effective. Leukemias in general are initially sensitive to chemotherapeutic drugs, but multidrug resistant leukemia is a complication that often occurs in the treatment of relapsed leukemia. Factors that effect sensitivity and the development of resistance include the growth fraction of the clonal population, the biology of the tumor load, the mechanisms that underlie the drug resistance, and the changes that occur in proteins that initiate
and mediate apoptosis in the leukemia cells.

The cellular mechanisms that define resistance typically involve changes in the expression level or amount of the target protein of the drug. The progression of cancer leads to mutations in genes that code for a target protein of some drug used on the leukemia cells. These mutations cause changes in the target protein’s conformation that make it difficult or impossible for the drug to bind, and binding is thus diminished or inhibited completely. Changes in the amount of target protein are more common than this mechanism. Mutations that result from the progression of cancer cause the amplification or the overexpression of the gene coding for the target protein and result in an increased level of that target protein. Drugs such as antimetabolites, which work to inhibit specific enzymes involved in DNA synthesis, cannot completely inhibit the overproduced enzyme—even at maximum dosages. Resistance can also be initiated by changes in enzyme systems. Certain antimetabolites require activation by specific enzyme systems before they can function. These enzyme systems can be altered so that the antimetabolites cannot be activated.

One of the most common drug resistance mechanisms affects the efflux of drugs into and out of the cell. The efflux of cytotoxic drug waste is carried out by membrane transport proteins that normally efflux potentially harmful compounds. Changes in these transmembrane pumps can lead to decreased intracellular drug concentrations. For example, the expression or activity increase of a protein called P-glycoprotein leads to resistance. This protein is in the ABC-binding cassette protein family and thus, uses ATP to pump drug waste out of the cell. Its overexpression or increased activity leads to it pumping the drug itself out of the cell at a greater rate so that the drug cannot have its normal effect. A clonal population with a high P-glycoprotein expression or expression rate will be resistant to drugs. There are a multitude
of proteins that can be involved in efflux-related resistance. Each protein will pump out specific compounds, and depending on the protein’s structure and specificity, a certain number of structurally related compounds will also be pumped out of the cell. When this occurs, it is called multidrug resistance (MDR). For example, resistance to one P-glycoprotein effluxed drug is associated with resistance to multiple agents including anthracyclines, vinca alkaloids, and epipodophyllotoxins. Another protein associated with this effect is the multidrug resistance protein (MRP). This protein is also part of the ABC-binding cassette family. The mechanism of resistance associated with MRP is similar to the mechanism associated with P-glycoprotein, thus, the MRP is associated with resistance to a whole spectrum of drugs.

On a molecular level, drug resistance is caused by changes in the mechanisms that exist for the repair of damaged DNA. Cytotoxic drugs induce DNA damage to their target cells. Systems exist to repair this damage by arresting the cell cycle or inducing apoptosis (for example, the protein p53 is involved in initiating apoptosis). Tumors that are highly responsive and have low probability of resistance have low mutation rates in these systems, which are therefore active and responsive to damage. However, it is important to note that this correlation is sometimes not so simple. In fact, it has been demonstrated that sensitivity to drugs can be increased by the total loss of systems like p53 because the leukemic cells accrue more damage and become nonfunctional instead of simply arresting and attempting repair. In most cases, any change to DNA repair systems will cause a corresponding change in drug sensitivity.

Repair for damaged DNA involves the removal of the damaged DNA that, if kept in the genome, would give rise to more DNA damage and cause genomic instability. DNA repair involves certain enzymes that have specific catalytic activity targeted at the repair of DNA. Increased activity of these enzymes is associated with resistance to drug agents. For example,
resistance to alkylating agents is associated with the increased activity of DNA repair enzymes called DNA glycosylases. DNA glycosylases recognize DNA damage and initiate base excision repair—where one base pair is removed to repair the DNA. Alkylating agents will add alkyl groups to certain base pairs to induce DNA damage to the genome of the leukocytes. The alkyl group that the alkylating agent adds is removed by glycosylating agents before the “damage” can be recognized and cause cell arrest. In nucleotide excision repair, special enzymes are involved in removing large regions of damage in the DNA sequence. Like base excision repair, the increased activity of the enzymes involved in this repair are, “…implicated in the removal of DNA cross-links formed by alkylating agents and platinum compounds, and…results in decreased drug activity because of increased repair (Henderson 403). Another DNA repair mechanism called DNA mismatch repair is also implicated in drug resistance. DNA mismatch repair is similar to other repair mechanisms in that involves many enzymes that recognize base mismatches in DNA and then initiate repair. If these proteins fail to detect a drug induced mismatch within the DNA sequence, drug activity is decreased because the damage persists causing mutations that lead to drug resistance. Finally, a last mechanism for drug resistance involves changes in the mechanisms that are part of apoptosis. Apoptosis is cell suicide that can be induced by cytotoxic drugs. The cytotoxic drugs initiate cell death or apoptosis via the action of special proteins called caspases. Caspases are activated by a molecule called cytochrome C, which is released from the mitochondria. This release is controlled by proteins such as BAX (which aids this response) and Bcl-2 (which blocks it). Changes in these proteins result in changes in sensitivity. For example, high levels of Bcl-2 are found in clonal populations that have drug resistance.
Secondary Cancer

Another possible complication that may occur in the treatment of leukemia is secondary cancer. The most common of these secondary cancers is secondary acute myelogenous leukemia. JM Rowe, in his keynote address “Therapy of Secondary Leukemia” defines secondary AML as a “…collective term used to describe a group of patients with AML or MDS who have a history of environmental, occupational, or therapeutic exposure to hematotoxins or radiation (JM Rowe). In other words, secondary AML is a leukemia that arises following some disruption to the bone marrow by an external agent. Such agents are often associated with therapy and so secondary AML is often called therapy-related AML (the terms secondary leukemia and therapy-related leukemia are used interchangeably). The term therapy-related AML is a term that implies that the disease does not develop as a primary de novo process, but that it is induced. Therapy-related AML should be distinguished from AML that arises de novo as it is distinct clinically, pathologically, and cytogenetically. AML that results from treatment with alkylating agents is a therapy-related leukemia. Treatment with alkylating agents is associated with changes to chromosome five and seven. Other groups of therapy-related leukemia include AML that results from treatment with topoisomerase inhibitors, which are associated with 11q abnormalities, and a small group of leukemias that follow treatment with miscellaneous therapies, which are associated with t(15;17), inv(16), and t(8;21). Thus, according to Rowe, “…conventionally defined secondary leukemias represent a heterogenous group of diseases with different cytogenetic abnormalities and different prognoses (JM Rowe).

The etiology of therapy-related leukemia is difficult to determine due to the use of a complex combination of drugs in all chemotherapy treatments, variation in the predisposition of the patient for malignancy, and the myriad of other types of exposure the patient might have
received in the course of treatment. However, it is known that drugs that intercalate with DNA (especially alkylating agents) play a major role in the genesis of secondary leukemia and secondary AML is reported as a complication of chemotherapeutic regimens that include epipodophyllotoxons, etoposide, teniposide, or topoisomerase II inhibitors. The abnormalities caused by these drugs include chromosome loss, sequence deletions, and unbalanced translocations. For example, topoisomerase II inhibitors, special agents that are integral to certain chemotherapy regimens, are cytotoxic agents that cause direct DNA damage or cleavage. Topoisomerase II is an enzyme required for the development of sister chromatid exchanges; it controls changes in DNA structure by catalyzing the breaking and rejoining of the phosphodiester backbone of DNA. More specifically, topoisomerase II induces a double strand break while also binding to the 3’ ends of the DNA. This structural change allows the DNA to unwind for replication. Inhibitors of topoisomerase II include intercalating and non-intercalating epipodophyllotoxins. These drugs inhibit the ligase activity of topoisomerase II, which results in protein-associated double stranded DNA breaks as well as sister chromatid exchange. These major chromosomal changes contribute to the development of secondary AML.

It may seem that because secondary AML is pathologically different from de novo AML, its associated treatment strategies would be distinct from those used on de novo AML, but in most respects, the treatments are quite similar. In fact, there is no evidence that suggests that any other therapy would be better or worse than the standard therapy used for de novo AML. The prognosis of the patient depends on clinical, molecular, and cytogenetic factors; however, most patients have a poor prognosis because secondary AML is notoriously drug resistant. It is important to choose a therapy regimen that has few severe myeloablative side effects of post-remission therapy, but still cures the most unfavorable types of secondary AML. These therapies
generally make use of anthracyclines and cytarabines. If the patient is younger, there is the option of allogeneic BMT if an HLA donor match is available. This method is preferred due to the graft-versus-leukemia effect. Older patients do not have access to this method of treatment, so high dose cytarabine with autologous transplant (if it can be tolerated) can be attempted, or as an alternative, immunotherapeutic manipulations may be best tolerated. In most patients with secondary AML, it is not difficult to achieve a response to induction therapy, but it is difficult to maintain the response.

Conclusion

Leukemia is a disease characterized by multiple pathologies and presentations. As such, in the treatment of leukemia, a myriad of different strategies with a variety of goals can be employed. The goal of treatment differs depending on the type of leukemia diagnosed, but overall, the goal is to eradicate malignant cells in order to restore normal hematological function. Chemotherapy, which makes use of the cytotoxic effects of a plethora of drugs to kill leukemia cells, is often used in order to attempt to restore the bone marrow to a functionally normal status. Other treatment routes include immunotherapies, which take advantage of the properties of the immune system to administer effects. There are also biological response modifiers like interferons, which have direct antiproliferative activity. Finally, there is bone marrow transplantation, which uses the plasticity of stem cells to restore bone marrow function and is an important recent strategy to leukemia treatment. The success of all of these treatments varies depending on the degree and type of malignancy present, but all of the treatments may be associated with long-term complications for the patient. These complications manifest in the form of organ or tissue damage, toxicity, behavioral or developmental problems, secondary leukemias, GVHD, or drug resistance. For example, treatment with certain cytotoxic drugs leads
to cardiomyopathy; CNS prophylaxis is linked to alteration in brain structure; and the effects of many chemotherapeutic drugs cause changes in DNA that lead to the development of secondary cancers. In addition, certain types of bone marrow transplants are associated with GVHD—a serious chronic disease that can result in death. There are also long term complications associated with the sensitivity of leukemia to drugs. Drug resistant leukemia, for example, may develop as a result of radiation. All of these complications represent dangerous outcomes for the surviving leukemia patient. Thus, treatment of leukemia, as with many other cancers, represents a challenging balancing act. On the one hand, the goal is to completely eradicate the disease and restore normal bone marrow function, but in doing so, to also minimize the negative long term effects of the treatment so as to ensure the survival of the patient. A thorough understanding of the pathology of leukemia and the full effects of the different treatments is the only method that properly addresses the problem of leukemia treatment.
Work Cited Page


Moen, Marit D; McKeage, Kate; Plosker, Greg L; Siddiqui, M Asif A. “Imatinib: A Review of its Use in Chronic Myeloid Leukaemia.” Drugs. 2007 67(2): 299-320
