WHERE THERE IS NO ONCOLOGIST

A MANUAL OF PRACTICAL ONCOLOGY IN RESOURCE-LIMITED SETTINGS

Dr. Brian Camazine, Board member Professionals For Humanity (PROFOH) and President Earthwide Surgical Foundation, Texas United States. He is a Surgeon, certified by American Board of Surgery. Camazine has 30 years of experience as a missionary surgeon in several countries, Guatemala, Nigeria, Bolivia, etc.

Kelechi Eguzo, MD [1]
Chisara Umezurike, MD [1]
Charlotte Jacobs, MD [3]
Brian Camazine, MD [1,2]

[1] Nigerian Christian Hospital
[2] Earthwide Surgical Foundation
[3] Stanford University School of Medicine

Nigerian Christian Hospital-We dress the wound, God heals it.
Aba-Nigeria

Earthwide Surgical Foundation is a 501(c)(3) non-profit organization dedicated to delivering surgical care to the poor of the world by means of manpower, equipment and education.

This book is dedicated to Dr. Henry Farrar-mentor and friend-who started it all.

FORWARD

For several decades, I have been making pilgrimages to the Nigerian Christian Hospital (NCH) on humanitarian surgical trips. As a result of my interest and training in surgical oncology, an increasing number of cancer cases have come under my care. Initially, these were approached largely from the surgical aspects because few patients could afford chemotherapy, and no physician had any specific interest in oncology. I could perform surgery in a few weeks time but was unable to manage chemotherapy from the USA.

Several years ago, a confluence of opportunities arose. I began to take 3-4 trips per year to NCH rather than just one; I formed a collaboration with Dr. Danny Milner, pathologist at Harvard's Brigham and Women's Hospital; and, most importantly, I met a young, ambitious physician, Dr. Kelechi Eguzo. At the time, many of our cancer patients were being referred to teaching hospitals for chemotherapy. I suggested to Dr. Kelechi that we stop this practice and deliver comprehensive oncology care at NCH. Dr. Kelechi took the idea and ran with it. He contacted many international oncologists, studied oncology on the internet and became a self-made oncologist. Thus, the Nigerian Christian Hospital's Oncology Service was born!

Soon, we realized that the knowledge we were acquiring would be helpful for practitioners in resource-limited environments where residency trained oncologists are rare or non-existent. We decided to write a hands-on manual so that a greater spectrum of practitioners could deliver the basics of cancer care. Thus, *Where There is No Oncologist* was born.

We hope this manual will continue to evolve with time and be available to many practitioners.

Brian Camazine, MD
General, Thoracic, and Head and Neck Surgeon
Chief of surgery, Nigerian Christian Hospital
briancamazine@gmail.com

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INTRODUCTION

Cancer is a major health problem in developed countries, and epidemiological evidence shows the emergence of a similar trend in developing countries. Globally the incidence of cancer is rising. In 2007 there were 11 million cancer cases, 7 million cancer deaths and 25 million people living with cancer. This is estimated to increase to 27 million cases, 17 million deaths and 75million people living with cancer in 2050 (1). More than 50% of these cases occur in developing countries where cancer is the second most common cause of death. Cancers are an emerging public health problem in developing countries like Nigeria where they were previously considered rare. The paucity of trained oncologists in Nigeria and other developing countries makes cancer management very challenging.

In Nigeria, there are an estimated 100, 000 new cancer cases annually, but this was estimated by Durosinmi to increase to 500,000 in 2010 (2). Epidemiological data show the most common cancers in Nigeria to be:
Males: Prostate-18.2%, Liver-15.7%, Colorectum-7.8%, Non-Hodgkin's Lymphoma (NHL)-7.4%, Bladder-4.2%
Females: Breast-30.7% Cervix uteri-24.6% Liver-4.6% Colorectum-3.5%, NHL-3.3% (3)

In this book, we shall attempt to highlight the running of the Oncology service at Nigerian Christian Hospital as a model for use in resource-limited settings. Also, we suggest cancer chemotherapy protocols for common cancers, using locally available drugs. In the concluding parts, we address the common challenges of 'circumstantial oncologists' in resource-poor settings.

THE NCH ONCOLOGY SERVICE

Oncology service is very poor in Nigeria, especially in the rural areas. Most trained oncologists are in the Teaching Hospitals and rarely can extend their services to the Secondary health care facilities. Nigerian Christian Hospital (NCH) is located in a rural setting, where it strives to deliver efficient care to the poor.

Most of our patients come from Abia, Akwa Ibom and Rivers States of Nigeria. In the past six years, we have noticed an increase in the number of patients that have cancers. Many of these people present in advanced stages of their diseases and often are not followed up. We have experienced Surgeons and Gynecologists who perform 'cancer surgeries.' Our main limitations were as follows:
1. Lack of a Reliable Pathology Service
2. Lack of a Trained Oncologist for follow up
3. Lack of a guideline/manual for the available physicians

In response to this, first we developed a partnership with Brigham Women's Hospital (USA) for pathology service through Earthwide Surgical Foundation (USA). The specimens we take from patients are sent quarterly to this hospital for diagnosis. Other specimens are sent to nearby laboratories/Teaching Hospitals. Our hospital does not have the manpower or the resources to

start a histopathology section.

Secondly, we networked with oncologists in other regions of the world, especially Canada and the United States of America. With the diagnosis made, we consult with them to plan the best treatment (chemotherapy) protocol for individual patients. This linkage has broadened the expertise of our local doctors in managing various cancers. Also we have networked with other local teaching hospitals (Ahmadu Bello University Teaching Hospital-Zaria, University College Hospital-Ibadan), for radiotherapy treatment. Thus we can make diagnosis, treat the patients (where possible/advisable) or refer them for advanced treatment.

The last limitation has been the lack of a guideline/manual for physicians. Most doctors are 'scared' of attending to cancer patients because they just do not know how to approach the disease. Unlike for malaria and other infectious diseases which are prevalent in Nigeria, there is a paucity of guidelines for cancers. This can be attributed to lack of local research on cancers as well as poor local experience on the management of cancers. In NCH, we have adopted some protocols for the treatment of various cancers. These protocols may not have been developed here but we have found them efficacious. Thus, we are compiling these protocols in a book for other physicians to use. Hopefully, it will help solve the last challenge in our Oncology Service at Nigerian Christian Hospital.

CHAPTER 1. INTRODUCTION TO CANCER

ETIOLOGY OF CANCER

Many agents have been implicated in the etiology of cancers. These include smoking (35%) and dietary factors (50%). Occupational exposure to carcinogens like irradiation and asbestos account for 5%, while the remaining 10% are of unknown etiology but may be linked with viruses, genetic factors and spontaneous mutational events.

The following are dietary substances and their likely cancer sites:

Fat: breast and colon

High total caloric intake: breast, endometrium, prostate, colon and gallbladder

Animal Protein, particularly as red meats: breast, endometrium, and colon

Alcohol, particularly in smokers: oral cavity, pharynx, larynx, esophagus and liver (beer drinking is associated with rectal cancer

Salt-cured, smoked or charred foods: esophagus and stomach

Some dietary elements appear to reduce the risk of cancer, including:

High fiber foods

High content of vegetables, fruits and whole grain cereal

Indole-containing vegetables (cabbage, cauliflower, broccoli)

Beans (especially soybeans and lima beans)

Carcinogenic chemicals, pharmacologic agents, and microbes are implicated in the etiology of cancers in the following sites:

Tobacco Smoke: bronchus, mouth, pharynx, larynx, esophagus, urinary bladder, pancreas

Aflatoxins (from *Aspergillus* containing cereals): liver

Aromatic amines and analine dyes: bladder

Arsenic, soot, tars, and oils: skin, bronchus, lung

Asbestos: bronchus, pleura, peritoneum

Benzene: bone marrow

Betel nut and lime: oral cavity

Bis-(chloromethyl)-ether: lung

Bis-(chloroethyl)-sulfide: respiratory tract

Cadmium: prostate

Chromium compounds and coke ovens: lung

Nickel ores, wood dust: nasal sinuses, lung

Vinyl chloride: liver

Pharmacologic agents implicated in cancer:

Alkylating agents: bone marrow, bladder

Anabolic steroids: liver

Arsenic: skin, stomach

Clornaphezine: bladder

Oral contraceptives: liver, breast

Diethylstilbestrol: vagina

Immunosuppressive drugs: lymphoma
Phenacetin: renal pelvis

Microbial agents associated with cancer:
Clornochis sinensis: bile ducts
Cytomegalovirus: Kaposi's sarcoma, possibly prostate
Epstein-Barr virus: lymphoid tissue (Burkitt's lymphoma in Africa; nasopharynx in Asia)
Hepatitis B and C virus: liver
Human T Cell Lymphotropic virus type 1 (HTLV-1): childhood lymphoblastic leukemia
HTLV-2: lymphoproliferative disorder
HTLV-3 (HIV): related to aggressive B lymphocyte malignancies
Papilloma virus: uterine cervix
Schistosoma haematobium: bladder cancer (in endemic areas)

GUIDELINES ON THE DIAGNOSIS AND MANAGEMENT OF CANCER

An art of medicine is the ability to make decisions in the face of insufficient information. Obtaining sufficient information would alter the host to the point that a different diagnosis and therapy are required.

Histologic proof of malignancy is the cornerstone of diagnosis and treatment. The site that is least risky and most likely to provide the necessary information is biopsied. Specimens should not be routinely placed in formalin. Where lymphoma is suspected or metastasis of unknown primary sites, fixatives such as B5 should be used to permit immunochemistry analysis.

However, it is important to note the shortcomings of pathologic diagnosis. Establishing the type of tumor is not an exact science. This process is prone to error in sampling, processing and interpreting specimens. Histological data, therefore, should be regarded as laboratory tests that must be interpreted as only part of the information about the evolving clinical syndrome. Experts have made the following recommendations (4):

Never confuse the ability to name a tumor with the ability to understand its behavior.

Never accept a histopathology diagnosis as unequivocal.

Review biopsy specimens with the pathologist and communicate important clinical data regarding the patient.

Be sure that the pathologist has reviewed sufficient samples.

When the histological diagnosis and biologic course are not in concert, confirm that the tissue came from your patient and re-review the slides with the pathologist or obtain a second opinion from another pathologist.

Generally in the management of cancers, the following guidelines have been found to be helpful (4):

Provide comprehensive medical care. Treat the whole patient, not just the tumor. Consider every manifestation and ask: "what else besides cancer could cause this," and "what is the likelihood of those possibilities?"

Make decisions without subjecting the patient to every available test. In resource-limited

settings, finance is a big problem. Always weigh the relative risk and benefit of every test.

Prolong life at a functional level tolerable to the patient.

Individualize the goals of therapy for each patient, considering their tolerance of the treatment and toxicity.

Never threaten to desert a patient because the patient requests another opinion or refuses to receive the recommended therapy. The physician, however, must set limits on ill-conceived or dangerous treatment desired by the patient.

There is always a positive role for the physician in the treatment of cancer patients. This role involves aggressive therapy, palliate therapy or psychosocial support.

There are four standard modalities for the treatment of malignancies: surgery; radiotherapy; chemotherapy, including monoclonal antibodies and hormone therapy; and immunotherapy. Depending on the nature of the malignancy, one or more of these treatment modalities may be recommended. This manual will focus on guidelines for cancer chemotherapy--the use of drugs for control and treatment of malignancies.

CHAPTER 2. BASIC PHARMACOLOGY OF CHEMOTHERAPY

One of the most difficult problems with managing cancers in Nigeria and other resource-limited settings is the non-availability of drugs. Most of the drugs are simply non-existent in the country or are extremely expensive. There is the other issue of the quality of the drugs available. It is difficult to find these drugs in hospital pharmacies largely due to economic reasons (low prescription and the drugs could expire in stock). Thus the poor patients most often have to source the drugs in the 'open market', where the quality can be doubtful. The manual includes recommendations based on those agents more readily available in Nigeria.

CELL KINETICS

This refers to the basic understanding of the principles of cellular multiplication and destruction. Chemotherapeutic agents interfere with cell division and affect both normal and neoplastic cells. The schematic summary of cell kinetics is presented below:

Drugs which affect and kill cells at certain points in the cell cycle are said to be cell cycle specific (CCS). Such agents include:
Antimetabolites: Methotrexate, Fluorouracil, mercaptopurine
Vinca Alkaloids: Vincristine, Vinblastine
Podophylline alkaloids: Etoposide, Tenoposide
Bleomycin peptide antibiotics
Other plant **alkaloids**: Paclitaxel (Taxol)

Drugs that destroy cells at any time, irrespective of the cell cycle, are said to be cell cycle non-Specific (CCNS). These include:
Alkylating agents: Cyclophosphamide, busulfan, melphalan, thiotepa
Antibiotics: Dactinomycin, Daunorubicin, Doxorubicin, Mitomycin
Platinum derivatives: Cisplatin, Carboplatin
Nitrosoureas: BCNU, CCNU, methyl-CCNU.

In general CCS drugs have proven most effective in hematologic malignancies and gestational trophoblastic disease. In these cases there are a relatively a large proportion of the cells that are proliferating and have high growth phase. CCNS drugs (many of which bind to DNA and damage these macromolecules) are useful in low growth fraction 'solid tumors' as well as in high growth fraction tumors.

In all instances, effective agents sterilize or inactivate the tumor stem cells, which are only a small fraction of the cells within the tumor. Non-stem cells, those that have irreversibly differentiated, are considered sterile by definition and are not a significant component of the cancer problem.

CLASSIFICATION OF CHEMOTHERAPEUTIC AGENTS

1. **Alkylating agents**
Alkylating agents impair cell function by transferring alkyl groups to amino, carboxyl sulfhydryl or phosphate groups of biologically important molecules. Most importantly, nucleic acids (DNA, RNA) and proteins are alkylated. They are cell-cycle specific. Most alkylating agents are not extensively bound to serum proteins, have a short half-life in the blood, and are excreted in the urine. Tumor resistance to these drugs appears to be related to the capacity of cells to repair nucleic acid damage. Examples of alkylating agents include: Cyclophosphamide, ifosfamide, mechlorethane, melphalan, chorambucil, thiotepa, busulfan and nitrosoureas.

2. **Antimetabolites** (Structural Analogs)
These resemble the natural compounds that are essential for the synthesis of DNA and RNA. Their major effect is in interfering with the building blocks of DNA synthesis. Their activity, therefore, is restricted to the S phase of the cell cycle. Most of these agents (except methotrexate) are metabolized to inactive products. All are excreted by the kidneys.
Examples include: Folic acid antagonists (methotrexate), Purine antagonists (6-mercaptopurine, thioguanine, fludarabine phosphate, cladribine), Pyrimidine antagonists (5-Fluorouracil, Cytarabine, Azacitidine).

3. **Plant Alkaloids:** These include vinca alkaloids, podophyllin alkaloids, campthothecins and taxanes.
Vinca alkaloids are derived from the periwinkle plant-Vinca rosea. They act as spindle poisons during mitosis. They inhibit RNA synthesis during metaphase. Examples include Vinblastine (Velban) and Vincristine (Oncovin). Vinca alkaloids are excreted predominantly in bile.
Podophyllin alkaloids are semi-synthetic derivates of podophyllotoxin, which is extracted from the root of the May apple, *podophyllum pellatum*. They inhibit DNA synthesis. Examples include Etoposide (VP-16) and tenoposide (VM-26). They are excreted in bile and urine.
Campthothecins are natural products that interfere with the activity of topoisomerase I, the enzyme responsible for cutting and replication of single DNA strands. Examples are topotecan and Irinotecan.
Taxanes: Paclitaxel is an alkaloid ester derived from the Pacific yew tree (Taxus brevifolia) and the European Yew, taxus baccata. The drug functions as a mitotic spindle poison. Another example of this group is Docetaxel.

4. **Antibiotics**
Many of these antibiotics bind to DNA through intercalation between specific bases and block the synthesis of new RNA or DNA (or both), cause DNA strand scission and interfere with cell replication.
Examples include anthracyclines (doxorubicin and daunorubicin), dactinomycin, plicamycin, mitomycin and bleomycin.

5. **Metallic Compounds**
Cisplatin (cis-diamminedichloroplatinum) is an organic metal complex. Many platinum analogues of this very important drug have been synthesized. Metallic compounds are thought to act analogously to alkylating agents. They bind DNA through formation of inter strand cross-

links and thereby inhibit DNA synthesis. Carboplatin is one of the platinum analogues of Cisplatin.

6. **Hormonal agents**
Sex hormones and adrenocortical hormones are employed in the management of several types of cancer. Since sex hormones are involved in the stimulation and control of the proliferation and function of certain tissues such as the breasts and prostate gland, cancer arising from these tissues may be inhibited or stimulated by appropriate hormonal agents. The adrenal corticosteroids have been useful in the treatment of hematological cancers as well as advanced breast cancer.
Examples include androgens (fluoxymestrone), antiandrogens (flutamide), estrogens (diethylstilbesterol), antiestrogens (tamoxifen), progestins (megestrol), gonadotrophin releasing hormone analogues (luprolide, goserelin), adrenocorticoids (prednisone), and aromatase inhibitors (anastrozole).

7. **Miscellaneous anti-cancer drugs**
These include
Asparaginase- an enzyme isolated from bacteria
Hydroxyurea- an analogue of urea
Mitoxantrone- an anthracene compound
Mitotane- a DDT congener.

The mechanisms of action for all chemotherapeutic agents are included in Appendix 1 (5).

ADVERSE EFFECTS OF CYTOTOXIC AGENTS

Bone marrow depression
Most cytotoxic drugs have their main action on rapidly dividing cells, which unfortunately includes cells of the bone marrow. The important toxic effect of therapeutic doses of virtually all the alkylating drugs is bone marrow depression and subsequent leucopenia and thrombocytopenia. Severe infections and septicemia may then result. A patient is likely to bleed if the platelet count falls below 20,000/ml and is almost certain to do so if it falls below 10,000/ml. If the leukocyte count is below 1,000/ml, gram-negative septicemia is a danger. The patient may be so immuno-suppressed that he or she shows few signs of it. Treat such a patient as if he had septicemia. If petechial bleeding occurs and/or the platelet count is below 2,500/ml, give 2 units of fresh whole blood. Watch out particularly for bone marrow depression when giving carboplatin, cyclophosphamide, dactinomycin, doxorubicin, etoposide, paclitaxel, and procarbazine..

Gastrointestinal side effects
The gastrointestinal side effects include nausea and vomiting, stomatitis, diarrhea, and constipation. Most alkylating agents (except chlorambucil, thiothepa and busulphan), metallic compounds, plant alkaloids (except vincristine) and cytotoxic antibiotics give rise to nausea and vomiting. Stomatitis and diarrhea are mainly caused by methotrexate, 5-FU and procarbazine. If there is severe nausea and vomiting, stomatitis or diarrhea, there should be reduction of the

dose or delay in the administration of the drug. Vincristine causes constipation, especially in elderly patients, and can result in ileus. Advise patients to keep hydrated and eat foods that soften the stool. Never use a single dose of more than 2 mg in an adult.

Infections
The infections usually follow bone marrow depression. If the temperature of a patient on cytotoxic drugs rises over 38^{o}C for more than 12 hours or the leukocyte count falls below 1,000/ml, start vigorous antibiotic therapy. Gram negative septicemia may be difficult to diagnose in an immune-compromised patient and is often from an opportunistic infection. Stop cytotoxic drugs when septicemia occurs and do not restart until septicemia is controlled.

Alopecia
Many cytotoxic drugs affect the hair follicles and give rise to alopecia. There is almost universal severe or total alopecia at standard dosages of paclitaxel, vincristine, and doxorubicin. Other agents that give rise to alopecia include dactinomycin, cyclophosphamide, etoposide and carboplatin (in high doses). Women undergoing treatment with these agents usually lose their hair two to three weeks after the first treatment. They also lose the eyebrow and pubic hair. This can be emotionally challenging to the women, affecting their self-esteem. They should be properly counseled before starting chemotherapy.

Neurotoxicity
Neurotoxicity consists of areflexia, muscle weakness and peripheral neuritis. A sensory neuropathy (pins and needles progressing to numbness) usually precedes the motor aspect. Use the patient's power to dorsiflex the ankle to monitor neuropathy. Any muscle weakness indicates serious neurotoxicity. If a patient has mild sensory neuropathy (common with vincristine), reduce the dose of the drug. If a patient has severe neuropathy (not uncommon with vincristine) stop the drug. Neurotoxicity is particularly observed with vinca alkaloids (especially vincristine) and Cisplatin. It often reverses spontaneously 4-6 months after the last dose.

Cardiotoxicity
The mechanism of cardiotoxicity appears to involve excessive intracellular production of free radicals within the myocardium. The toxic effects include arrhythmias, chronic cardiomyopathy and eventual cardiac failure. Cardiotoxicity is particularly observed with anthracycline antibiotics such as daunorubicin, doxorubicin (Adriamycin) and idarubicin. It is cumulative and dose dependent. Cardiotoxicity is rarely seen at a doxorubicin cumulative dose below 500mg/m^2 except in elderly patients and with known cardiac disease or prior mediastinal irradiation.

Nephrotoxicity
Cytotoxic drugs can affect the glomerulus, tubules, interstitium or the renal microvasculature with clinical manifestations that range from an asymptomatic elevation of serum urea and creatinine to acute renal failure. Previous renal impairment as well as combination with other nephrotoxic drugs may increase the risk nephrotoxicity in cancer chemotherapy.
Cytotoxic drugs associated with nephrotoxicity include Cisplatin, methotrexate, mitomycin, lomustine, streptozotocin, mithramycin and azacytidine.
Cisplatin, methotrexate and lomustine nephrotoxicities are dose-dependent. Renal toxicity is less

likely when the patient is well hydrated before and after the administration of these agents.

Allergic reactions
These occur most commonly with bleomycin, paclitaxel, etoposide, L-asparaginase, bleomycin, melphalan, and nitrogen mustard. They occasionally occur with doxorubicin, daunorubicin, cyclophosphamide, methotrexate, cisplatin, carboplatin, and procarbazine. Bleomycin and L-asparaginase can cause anaphylaxis.

Other toxicities include, but are not limited to:
Apnea: alkylating agents with succinylcholine

Azospermia: cyclophosphamide, nitrogen mustard, thiotepa, methotrexate

Bone pain: procarbazine (arthralgia), hormonal therapy for breast cancer, leuprolide

Cataracts: busulphan

Conjunctivitis: fluorouracil, methotrexate; drugs associated with stomatitis

Constipation: vincristine, vinblastine, vindesine

Cystitis and hematuria: cyclophosphamide

Disulfiram (Antabuse)-like reaction: procarbazine with alcohol

Drug Interactions:
Alkylating agents with succinlycholine: prolong curariform effect
Cyclophosphamide with allopurinol: increased myelotoxicity
Methotrexate with phenylbutazone, probenecid, salicylates, anti-inflammatory drugs: enhanced methotrexate effect
Mercaptopurine with allopurinol: increased myelotoxicity
Nitrosoureas with cimetidine: increased myelotoxicity
Procarbazine has monoamine oxidase inhibitor activity

Fever: bleomycin, dacarbazine, mithramycin, methotrexate

Fluid retention: corticosteroids, diethylstilbesterol, testosterone derivatives

Gynecomastia: busulfan, diethylstilbesterol, tamoxifen, MOPP combination

Hypercalcemia: hormonal therapy for breast cancer, prostate cancer

Hyperglycemia: L-asparaginase, corticosteroids, cyclophosphamide, vinca alkaloids

Hyperkalemia: chemotherapy for Burkitt's lymphoma

Hypertensive crisis: procarbazine with sympathomimetic amines

Hyperuricemia: mercaptopurine, radiotherapy or chemotherapy for lymphomas and leukemia

Hypocalcemia: mithramycin; rarely with bone healing with hormonal therapy for breast cancer

Hypoglycemia: streptozocin

Hypomagnesemia: cisplatin

Hyponatremia (SIADH): cyclophosphamide, vincristine

Immunosuppression: most drugs

Lacrimation (dacryocystitis, lacrimal duct stenosis): fluorouracil

Liver toxicity:

Moderate or marked: L –asparaginase, 5-azacytidine, mercaptopurine, methotrexate
Mild or rare: cytarabine, chlorambucil, dacarbazine, mithramycin, mitomycin C, nitrosoureas, streptozotocin, thioguanine

Menstrual irregularities: same as azospermia

Muscle cramps: procarbazine, vinblastine, vincristine, etoposide

Muscle lysis: 5-azacytidine

Neoplasia (induction of second malignancy)

Carcinogenic in animals: doxorubicin, nitrosoureas, procarbazine
Leukemia, acute nonlymphocytic: alkylating agents
Squamous cell carcinomas: mercaptopurine
Urinary bladder carcinoma: cyclophosphamide
Vaginal carcinoma: diethylstilbestrol with in-utero exposure

Osteoporosis: corticosteroid, methotrexate (chronic therapy)

Pancreatitis: L-asparaginase

Pulmonary toxicity

Common: bleomycin, busulfan, nitrosoureas
Rare: chlorambucil, cyclophosphamide, melphalan, mitomycin C, methotrexate, procarbazine,

Retroperitoneal fibrosis: busulfan

Skin and nail changes: actinomycin, doxorubicin, bleomycin, busulfan, fluorouracil, methotrexate, vinblastine, cyclophosphamide

Inflammation following subcutaneous infiltration (vesicants): dactinomycin, doxorubicin, daunorubicin, dacarbazine, mithramycin, mitomycin C, nitrosourea, vincristine

Tongue, black hairy: doxorubicin, daunorubicin, fluorouracil

Urine, red: doxorubicin, daunorubicin

COMMON TOXICITIES FOR SPECIFIC AGENTS (6)

Bleomycin: allergic reaction (use 1mg test dose before first dose), pulmonary toxicity (acute pneumonitis, chronic fibrosis-400units lifetime dose for adults), fever, skin toxicity (hyperkeratosis, peeling), mucositis

Carboplatin: hypersensitivity reaction, blood count depression, nausea and vomiting, alopecia,

Cisplatin: blood count depression, nausea and vomiting, tinnitus, hearing loss, peripheral neuropathy (late), renal damage (lessened with proper administration-see below), hypomagnesemia, allergic reaction

Cyclophosphamide (Cytoxan): alopecia, blood count depression, nausea and vomiting, stomatitis, cystitis (keep well hydrated), amenorrhea, sterility, late bladder cancer, SIADH

Dactinomycin (Actinomycin D): local irritant (extravasation), alopecia, blood count depression, nausea and vomiting, stomatitis, diarrhea

Diethylstilbestrol (DES), estradiol: edema, gynecomastia, edema, nausea, hypercalcemia, thrombosis

Doxorubicin (Adriamycin): local irritant (extravasation), alopecia, blood count depression, nausea and vomiting, stomatitis, cardiomyopathy (risk= underlying heart disease and age; keep total lifetime dose below 500mg/m2)

Etoposide (VP-16): blood count depression, allergic reaction, hypotention, fever, alopecia

5-Fluorouracil: alopecia, blood count depression, nausea and vomiting, stomatitis, diarrhea, conjunctivitis, chest pain, hand-foot syndrome, ataxia (rare),

Leuprolide: hot flashes, impotence, gynecomastia, tumor flare

Levamisole: rash, diarrhea, nausea

Megestrol: edema, nausea, rash, hypertension, hot flashes

Methotrexate: blood count depression, stomatitis, acute renal failure

Paclitaxel (Taxol): allergic reaction, alopecia, blood count depression, nausea and vomiting, sensory neuropathy, myalgias, ventricular bradycardia, hypotension

Prednisone: insomnia, dyspepsia, hypertension, edema, euphoria, depression, hyperglycemia, osteoporosis

Procarbazine: blood count depression, nausea, flu-like syndrome, amenorrhea, sterility, hypersensitivity

Tamoxifen: hot flashes, edema, menstrual irregularities, skin rash, hair thinning, thrombosis

Vincristine (Oncovin): local irritant (extravasation), alopecia, sensory and motor neuropathy, constipation, jaw pain, hoarseness, SIADH, sterility, amenorrhea

CHAPTER 3. CHEMOTHERAPY ADMINISTRATION AND DOSE-MODIFICATION

BASICS

Vein Selection: Large veins in the forearm are preferred. Metacarpal veins on the dorsum of the hand are the second choice. If possible, avoid the antecubital fossa and wrist because extravasations in these can result in loss of function. Drugs known to cause discomfort and irritation during administration (dacarbazine and carmustine) should be administered last. If a drug is a potential irritant (vinblastine, vincristine, doxorubicin) and has produced painful phlebitis previously, administer it last and in the opposite arm if possible. Flush canula and tubing with saline or D5W between drugs and after completion of the last drug administered.

Infection: Chemotherapy should not be administered if the patient has an active infection of any type. Exceptions to this rule are highly aggressive but responsive tumors that are curable.

Acute drug toxicity: Generally, chemotherapy should be withheld in patients with evidence of active drug toxicity from previous treatments. In cases of myelosuppression it is advised to delay chemotherapy for 1-2 weeks until blood counts recover. Debilitated patients should be started at reduced doses unless they have rapidly progressing neoplasms that respond well to therapy.

Allergic reaction: Do not re-administer a drug to which a patient has had an allergic reaction.

Alimentary tract toxicity: Drugs that cause stomatitis or diarrhea must not be given until the patient has fully recovered from these symptoms. Doses should be reduced by 25 percent if the patient has had a previous episode of drug-related stomatitis or diarrhea. Each subsequent dose is reduced by 25 percent with recurrence of symptoms.

Abnormal renal function: Drugs that cause renal toxicity (particularly methotrexate, cisplatin and streptozocin) should not be administered unless the creatinine clearance is greater than 50 ml/min (see below for calculation). Other drugs excreted in urine may require dose reduction in the presence of renal dysfunction.

Abnormal liver function: In the presence of hepatic dysfunction, doses of vinca alkaloids (vincristine, vinblastine), anthracyclines (doxorubicin, daunorubicin), cyclophosphamide, dactinomycin, paclitaxel, and etoposide must be reduced.

Myelosuppression: Myelosuppressive drugs generally are not administered to patients with solid tumors and a WBC less than 4000/ml or platelet counts less than 100,000/ml. Increasing the interval between doses is preferable to decreasing the dose.

Nausea/vomiting: Of the drugs listed below, the emetogenic potential is

High: cisplatin, cyclophosphamide, dactinomycin, doxorubicin
Moderate: 5FU, paclitaxel, procarbazine, interferon
Low: methotrexate, vincristine

Antiemetics should be used prior to and after those with moderate to high emetogenic potential:

lorazepam (ativan) 0.5 to 1 mg PO q 4-6 hrs
metoclopramide 20-40 mg PO every 4-6hrs
prochlorperazine (compazine) 5-10 mg PO q 6hrs (If the patient has acute torticollis, stop drug and give benadryl.)
dexamethasone (decadron) 8-12 mg PO daily

ADMINISTRATION AND DOSE-MODIFICATION OF SPECIFIC AGENTS

Calculation of estimated creatinine clearance:

Men: $\frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine} \times 72}$

Women: $\frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{Serum creatinine} \times 72} \times 0.85$

Bleomycin:

Reconstitution: mix in 10ml NS; drug is dosed in units
Administration: premedicate with acetaminophen and diphenhydramine (50mg po); infuse IV over 10 minutes
Dose reduce by 50% if creatinine clearance < 50ml/min; omit if < 30ml/min
Keep total lifetime dose < 400 units

Carboplatin:

Reconstitution: mix with NS for concentration of 10mg/ml
Administration: premedicate with dexamethasone (20mg po) and antiemetic
Infuse IV over 30 min (do not use aluminum needle)

Cisplatin:

Reconstitution: mix in sterile water for concentration of 1mg/ml
Administration: Premedicate with dexamethasone (20mg po) and antiemetics for 3 days

- Prehydrate with 1 liter normal saline (NS) over 2 hrs.
- Do not start cisplatin unless urine output >150cc/hr. If not, continue to hydrate until adequate urine output
- Give mannitol 12.5grams IV in 100cc NS just prior to cisplatin
- Mix cisplatin in 500ml NS and infuse over 2 hrs (do not use aluminum needle)
- Posthydrate with 1 liter NS + 25grams mannitol over 2hrs; then 1 liter NS over 2hrs
- May add KCL to fluid as needed; add 1 gm magnesium sulfate (if available) to each liter to prevent hypomagnesemia

Alternate administration if mannitol not available: 24-hour infusion: use same premedication

- Prehydrate with 1 liter normal saline (NS) over 2 hrs. Do not start cisplatin unless urine output >150cc/hr. If not, continue to hydrate until adequate urine output

- Mix 1/6 of total dose in one liter NS and infuse over 4 hrs; repeat until total dose given over 24hrs (no not use aluminum needles)
- Post-hydration with 1 liter fluid every 12 hrs x 2 liters
- May add KCL to post-hydration fluid as needed; add 1 gm magnesium sulfate (if available) to each liter to prevent hypomagnesemia
- Reduce dose by 50% if CrCl<60ml/min; omit if CrCl <40ml/min;

Cyclophosphamide (Cytoxan):

Reconstitution: reconstitute 500mg vial with 25ml sterile water or normal saline
Administration: premedicate with antiemetics

- Dose <500mg can be given IV push in 100ml normal saline
- Dose > 500mg dilute in 250ml normal saline and infuse over 30-60min
- Reduce by 25% if bilirubin 3-5mg/dl; omit if bilirubin >5mg/dl; reduce by 25% if CrCl <50ml/min; omit if CrCl <10ml/min

Dactinomycin (Actinomycin D):

Reconstitution: reconstitute with sterile water for concentration of 500µg/ml; dilute in NS or D5W for infusion
Administration: premedicate with antiemetics; slow IV push; 10ml flush of saline or D5W before and after infusion
Reduce by 50% if bilirubin>3mg/dl

Doxorubicin (Adriamycin):

Reconstitution: dilute vial with normal saline for final concentration of 2mg/ml
Administration: premedicate with antiemetics; administer slowly into tubing of freely running IV infusion of D5W or saline
Reduce by 50% if bilirubin 1.5-3mg/dl; reduce by 75% if bilirubin >5mg/dl
Keep total life dose < 500mg/m2

Etoposide:

Reconstitution: dilute with 5% dextrose or NS to concentration of 0.2mg/ml
Administration: premedicate with dexamethasone (20 mg po) and antiemetic
Infuse over 1-2 hours; if hypotension, stop until normal BP, then can restart slowly
Reduce by 25% if creatinine clearance <20ml/min; reduce by 50% if bilirubin >1.2 mg/dl, omit if bili >3.0mg/dl

5-Fluorouracil:

Reconstitution: no dilution required
Administration: premedicate with antiemetics. Direct IV push requires no further dilution; for continuous IV over 24 hrs, mix in 1 liter D5W or normal saline

Leuprolide:

Reconstitute with diluents provided. Do not use needles less than 22 gauge. Rotate IM site.

Methotrexate:

Reconstitute: lyophilized powder diluted to 25mg/ml with sterile water or saline

Administration: IV push
Reduce by 25% if bilirubin 3-5mg/dl; omit if bilirubin >5mg/dl; reduce by 50% if CrCl <60ml/min; omit if CrCl< 30ml/min; contraindicated with ascites, effusions or edema

Paclitaxel (Taxol):
Reconstitute: Dilute in 500ml saline for one or 3 hr infusion
Adminstration: Premedicate with dexamethasone (20mg IV or po – or 60-100mg prednisone), diphenhydramine (25-50mgIV or PO), antiemetic--all 30 min to 2 hrs (if PO) prior to chemo.
** High incidence of allergic reaction; must premedicate with steroids.
Reduce by 25% if bilirubin >3mg/dl; omit if bilirubin >5mg/dl

Procarbazine:
Administration: po
Omit if CrCl < 30ml/min

Vincristine (Oncovin):
Administration: Mix in 50 ml saline; inject into tubing of running IV over 15 minutes
Patients need stool softeners or strict dietary management to prevent constipation
Reduce by 50% if bilirubin >1.5 mg/dl; omit if bilirubin >3.5mg/dl

MANAGEMENT OF EXTRAVASATIONS

Extravasation of vesicants is a medical emergency; early detection and prompt appropriate action is required to prevent necrosis and functional loss of the tissue or limb involved.

Vesicant chemotherapies: dactinomycin, doxorubicin, paclitaxel, vincristine

Signs and Symptoms:
An extravasation should be suspected if one or more of the following symptoms have occurred:
The patient complains of burning, stinging, or any discomfort / pain at the injection site. (This should be distinguished from a feeling of cold that may occur with some drugs.)
Observation of swelling, redness, or blistering at the injection site. (This should be distinguished from the 'nettle rash' effect seen with anthracyclines.)

If an extravasation is suspected, take immediate action:
Stop the injection/infusion. Disconnect the intravenous tubing
Withdraw as much of the drug as possible, via existing cannula
Elevate the limb

For dactinomycin and doxorubicin: Elevate the limb. Apply cold pack for 15-20 minutes 3-4 times a day for up to 3 days. Apply hydrocortisone 1% cream as long as redness persists.

For paclitaxel and vincristine: Inject 1500 iu hyaluronidase pincushion s/c injections in 0.1 – 0.2ml volumes around the site. Apply warm pack to remain for 2 - 4 hours.

TUMOR LYSIS SYNDROME

Rapid response to chemotherapy in high-grade, bulky tumors (e.g. Burkitt's lymphoma) can cause tumor lysis with the first treatment. Hallmarks are high potassium, high uric acid, high phosphorous, and low calcium. If untreated it can result in acute renal failure, arrhythmias, seizures and death.

Management:
Begin allopurinol 2-3 days prior to chemotherapy and continue for two weeks.
Rigorous hydration; follow and manage electrolytes for first few days after first treatment

ESSENTIAL TERMINOLOGY AND AIMS OF CHEMOTHERAPY

Induction Chemotherapy. Induction chemotherapy is the use of drugs as an initial therapy, for example in the treatment of acute leukemia to achieve significant cytoreduction (complete remission) of disease as initial therapy.

Consolidation/Intensification chemotherapy. In consolidation/intensification treatment, the same drugs used in induction (consolidation) or drugs that are non-cross resistant to the induction drugs (intensification) are given after remission.

Adjuvant chemotherapy. This is chemotherapy given after the eradication of the primary disease with local treatment (surgical or radiation). Adjuvant chemotherapy is used to treat putative microscopic disease and prevent local or distant relapse.

Neoadjuvant Chemotherapy. This is chemotherapy given before local treatment (surgical or radiation) with the hope of reducing the extent of local treatment or increasing its effectiveness.

Maintenance chemotherapy. Prolonged, often low-dose, outpatient chemotherapy is intended to prolong the duration of remission and achieve cure in patients in remission.

Salvage chemotherapy. This is used to control disease and provide palliation, usually after the failure of other treatments (surgery, radiation, or prior chemotherapy).

Palliative Chemotherapy: This chemotherapy is used for relief of symptoms and to improve quality of life.

Prophylactic Chemotherapy: This involves use of therapy after surgical extirpation when there is no evidence of tumor spread (adjuvant chemotherapy).

Radical Chemotherapy: This is treatment aimed at eliminating known residual disease following incomplete surgery or biopsy.

CHOICE OF CHEMOTHERAPY

Selection of chemotherapeutic agents. Attempts are made to choose drugs that selectively destroy cancer cells and spare normal cells. The scope and indications for treatment must be closely linked with the pathology. In hormonally responsive tumors (breast, prostate), hormonal agents should be considered first as they give longer responses with less toxicity.

Timing: In general, it is preferable to use cytotoxic chemotherapeutic agents in intensive 'pulse' courses every 3-4 weeks rather than to use continuous daily dosage schedules. This allows for maximum effects against neoplastic cell populations with complete hematologic and immunologic recovery between courses. This spares the patient from the being continuously suppressed with cytotoxic therapy.

Note that most cytotoxic drugs have their main action on rapidly dividing cells. This unfortunately includes cells of the bone marrow and the mucosa of the gastrointestinal tract. Cancer cells however divide continuously, whereas marrow cells are quiescent for part of the time. Intermittent doses allow the marrow to recover whilst maintaining antitumor effect; but do not wait so long that the tumor re-grows. A common approach is to give high, intermittent doses and to repeat them every 2, 3, or 4 weeks to allow the marrow recovery.

Drug Combinations: Cytotoxic drugs are used in combination because: They often act synergistically at different stages in the cell cycle or in different ways. Smaller doses can be used, thus limiting individual side effects. The tumor is less likely to develop resistance to combination therapy compared to single therapy. Tumor cells tend to multiply at a constant rate, depending on the proportion of cells dividing. Because of the constant rate of multiplication, a tumor grows exponentially, and its bulk increases more rapidly as it grows. Similarly, chemotherapy kills a constant proportion of dividing cells so that if it is sensitive, the tumor size also reduces exponentially. A large tumor may shrink rapidly at the beginning and then more slowly as it gets smaller. Conversely, combination therapy is more expensive. It may have more toxic effects, although each is less severe. Knowledge of the kinetics of tumor cell proliferation, as well as information on the pharmacology and mechanism of action of cancer chemotherapeutic agents, has become important in designing optimal chemotherapy regimens.

Side effects and toxic effects: All cytotoxic drugs have adverse effects which must be taken into consideration when choosing drugs for cancer chemotherapy. You should be familiar with the side effects of the drugs you intend to give your patient.

Adherence and Follow-up: One has to do his best to see that patients complete their treatment and not abandon it. Either strive to give the patient a complete course or do not initiate chemotherapy; there is no justification for the attitude: "he is hopeless; let's try a little cyclophosphamide…." This calls for adequate treatment preparation.

Administration: Many cytotoxic drugs are irritants. If they extravasate into the tissue they cause large necrotic ulcers. Vincristine, dactinomycin, doxorubicin, etoposide, and nitrogen mustard are best given in free running infusions. Others, like Fluorouracil, may be given bolus intravenously but slowly. Few cytotoxic drugs can be given intramuscularly.

THINGS YOU MUST KNOW BEFORE YOU BEGIN CHEMOTHERAPY

* First treatments are usually more 'likely to succeed' and should never be given in suboptimal doses. Give it all you've got! Second-line treatment is rarely effective.
* Toxic side effects may be unpleasant, if not lethal. It is essential to monitor patients and intervene where necessary.
* It is necessary to objectively assess patients while on therapy. This could be by clinical evaluation or laboratory investigations. Endeavour to examine the patient before each course of chemotherapy to assess clinical response. Also check the blood counts to ensure that the patient is fully recovered from the last chemotherapy. Check the creatinine and/or bilirubin if required for dose reduction (see Dose Modification above).
* It may be dangerous to institute treatment when the patient is almost dying. If a patient dies from complications of cytotoxic drugs, there is an 80% chance that it will be caused by infections, usually septicemia, and 20% chance that the patient will die from intracranial hemorrhage. So always make sure your blood counts are optimal, and give antibiotics where necessary.

HEPATITIS B AND CHEMOTHERAPY

Be aware that chemotherapy can exacerbate Hepatitis B. The majority of cases of HBV reactivation have been reported to occur during or shortly after the withdrawal of chemotherapy (7). The risk of Hepatitis B virus (HBV) reactivation is higher in male sex and lymphoproliferative disorders. It is more commonly caused by regimens containing anthracylines, corticosteroid, cyclophosphamide, fludarabine and vincristine.

It is often necessary to identify and monitor patients who are at risk of having HBV reactivation. It may be helpful to rule out HBV infection before the commencement of chemotherapy, and treat sero-positive cases with Lamivudine. (8)

CHEMOTHERAPY AND HIV PATIENTS

It is important to note that in patients taking anti-retrovirals, caution should be exercised in the use of chemotherapeutic agents. This is largely due to cross side effects and drug interactions. Because traditional cytotoxic chemotherapy regimens are also associated with neutropenia, zidovudine-containing regimens should be avoided and an alternative NRTI (nucleotide reverse transcriptase inhibitors) should be prescribed. If zidovudine use cannot be avoided, less myelosuppressive chemotherapy should be administered or the patient should be closely monitored for neutropenia.

Note that neutropenia in HIV patients can result from the infection, the antiretroviral drugs or cytotoxic agents.

CHAPTER 4. CHEMOTHERAPY PROTOCOLS FOR COMMON CANCERS

In this section, we describe the chemotherapy protocols for common cancers in the developing world. (6, 9) The regimens here described are the same used in Nigerian Christian Hospital, many focused on the cases we have managed here. The suggested protocols are in some cases modified from those currently used in the U.S. because of limitations of available agents. As more chemotherapeutic drugs become available in Nigeria, new protocols will be added.

Chemotherapy doses are usually based on a dose/m2. A body calculator can be found at http://www.medcalc.com/body.html

If a calculator is not available use the nomogram on the next page:
Find the weight in the right column and the height in the left column. Place a straightedge on the nomogram so the weight and height are connected. The point where the straightedge crosses the center column denotes the body's surface in square meters.

Carboplatin dose calculation: Carboplatin is often dosed by area under curve (e.g. AUC 5).

The calculated dose (mg) = AUC x (creatinine clearance +25)

In debilitated patients , if serum creatinine is less than 1.0, use 1.0 in calculating creatinine clearance.

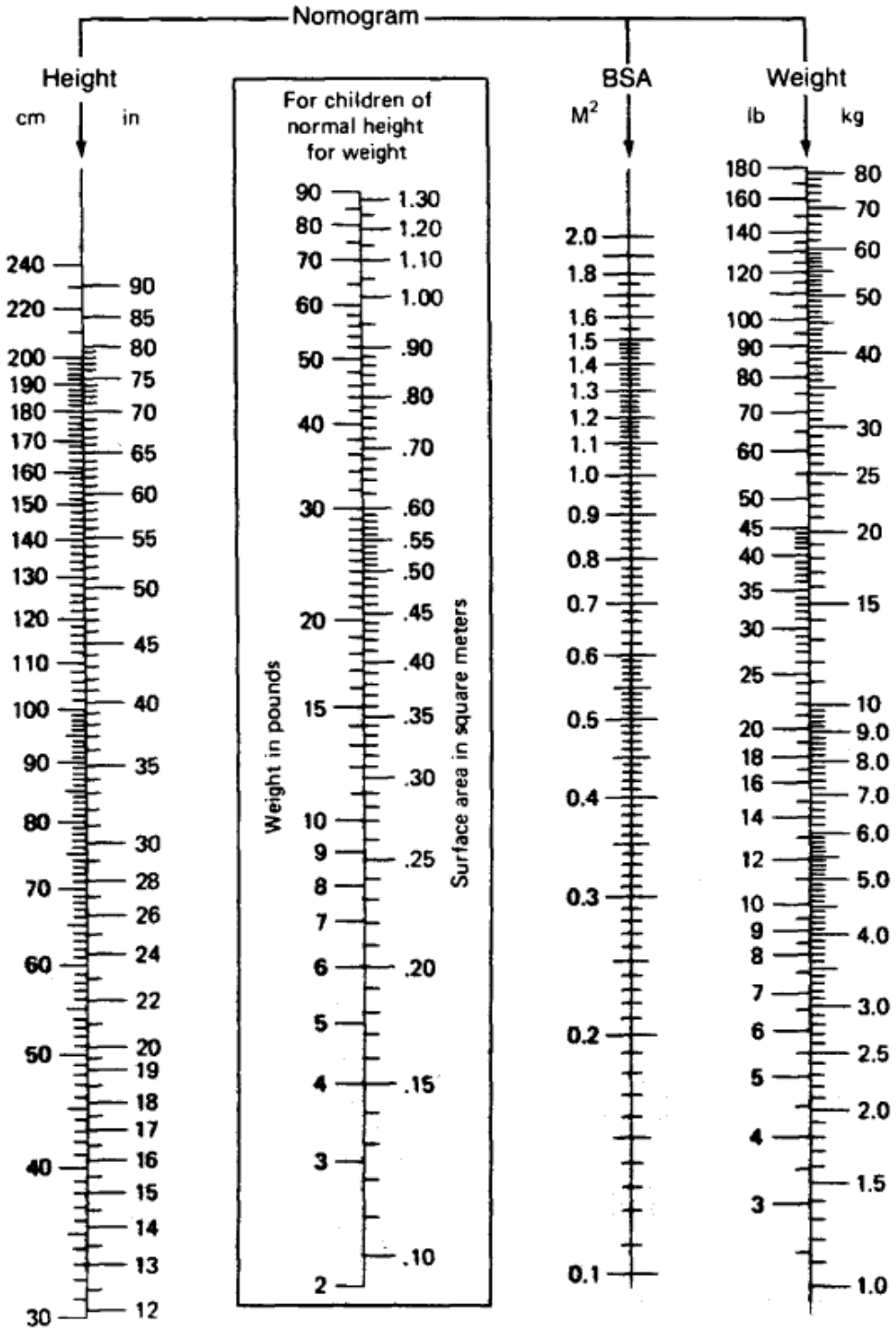

Figure 3–1. West Nomogram (for Estimation of BSA). The BSA is indicated where a straight line connecting the height and weight intersects the BSA column or, if the patient is roughly of normal proportion, from the weight alone (enclosed area). (Nomogram modified from data of E. Boyd by C. D. West; from Vaughan, V. C., and R. J. McKay, eds., *Nelson Textbook of Pediatrics*, 12th ed., Philadelphia: Saunders, 1983.)

Regimen	**Drug Doses**
ANAL CANCER	
5FU/CP (10)	5-Fluorouracil 1000 mg/m2/day continuous infusion x 5days Or 5-Fluorouracil 500 mg/m2 IV push daily x 5 days Cisplatin 100 mg/m2 day 1 Repeat every 21-28 days
BLADDER CANCER – recurrent or metastatic	
CMV (11) Modified	Methotrexate 30 mg/m2 IV days 1, 8 Cisplatin 100mg/m2 IV day 2 (give 12-24 hrs after methotrexate) Vincristine 1 mg/m2 (max of 2mg) IV day 1 Repeat every 21 days
CP (12)	Paclitaxel 175 mg/m2 IV over 3 hrs day 1 Cisplatin 75 mg/m2 IV day 1 Repeat every 21 days
Paclitaxel (13)	Paclitaxel 80mg/m2 IV weekly for 3 weeks Repeat every 4 weeks (one week break)
BREAST CANCER – adjuvant after mastectomy	
For cancer <1cm	
Tamoxifen	Tamoxifen 20 mg PO daily for 5 yrs (ER+ or unknown)
For cancer >1cm or positive axillary nodes:	
CMF (14, 15)	Cyclophosphamide 600 mg/m^2 IV day 1 Methotrexate 40mg/m2 IV day 1 5-Fluorouracil 600 mg/m^2 IV day 1 Repeat every 21 days for 6 cycles After chemo, Tamoxifen – 20 mg PO daily for 5 years (ER+ or unknown)
FAC (15)	5-Fluorouracil 500 mg/m2 IV days 1 & 8 Doxorubicin 50 mg/m^2 IV day 1 Cyclophosphamide 500 mg/m^2 IV day 1 Repeat every 21 days for 6 cycles After chemo, Tamoxifen – 20 mg PO daily for 5 years (ER+ or unknown)

AC (16) Doxorubicin 60 mg/m2 IV day 1
Cyclophosphamide 600 mg/m2 IV day 1
Repeat every 21 days x 4 cycles
After chemo, tamoxifen 20 mg PO daily for 5 years (ER+ or unknown)

BREAST CANCER – locally advanced or inflammatory prior to mastectomy/radiation

AC/Pac (17) Doxorubicin 60 mg/m2 IV day 1
Cyclophosphamide 600 mg/m2 IV day 1
Repeat every 21 days x 4 cycles
Then
Paclitaxel 175 mg/m2 IV over 3hrs day 1
Repeat every 21 days x 4 cycles
Then
Mastectomy or radiation
Followed by tamoxifen 20mg PO daily x5yrs (ER+ or unknown)

BREAST CANCER – metastatic

Hormone – use first for ER+ or unknown if skin/bone disease or cannot tolerate chemotherapy

Premenopausal Oophorectomy **or**
Tamoxifen (18) 20mg PO daily

Postmenopausal Tamoxifen 20 mg PO daily **or**
Megestrol 40mg PO qid **or**
Diethylstilbestrol 15 mg PO daily **or**
Estradiol 10 mg PO tid

Chemotherapy –use first if lung, liver metastasis or hormonal failure

CMF Cyclophosphamide 600 mg/m2 IV day 1
Methotrexate 40 mg/m2 IV day 1
5-Fluorouracil 600 mg/m2 IV day 1
Repeat every 21 days for 6 cycles

Paclitaxel (19) Paclitaxel 80 mg/m2 IV over 1 hr every week
or
Paclitaxel 175mg/m2 IV over 3hrs every 21 days

Doxorubicin Doxorubicin 20 mg/m2 IV weekly
or
Doxorubicin 60mg/m2 IV every 21 days

FAC 5-Fluorouracil 500 mg/m^2 IV days 1 and 8
Doxorubicin 50 mg/m^2 IV day 1
Cyclophosphamide 500 mg/m^2 IV day 1
Repeat cycle every 21-28 days

AC Doxorubicin 60 mg/m2 IV
Cyclophosphamide 600 mg/m2 IV
Repeat every 21 days

BURKITT'S LYMPHOMA (AFRICAN TYPE)

CM (20) Cyclophosphamide 50mg/kg IV day 1
Methotrexate 1mg/kg IV day 1
Repeat every week for 8 courses

CERVICAL CANCER (also used for Mullerian Tumor-Metastatic)

CDF (21) Cisplatin 50-60 mg/m2 IV day 1
Doxorubicin 50 mg/m2 IV day 1
5-flourouracil 500-800 mg/m2 IV day 1
Repeat cycle every 21-28 days

Paclitaxel (22) Paclitaxel 175mg/m2 IV over 3hrs
Repeat every 21 days

CF Cisplatin 90-100 mg/m2 IV day 1
5 Fluorouracil 800-1000 mg /m^2 IV day 1
Repeat cycle every 21-28 days

CC Cisplatin 70-100 mg/m2 IV day 1
Cyclophosphamide 600mg/m2 IV day 1
Repeat cycle every 21-28 days

COLORECTAL CANCER – adjuvant

For stage III colon cancer after resection:

Fluorouracil+
Leucovorin (23) Leucovorin 20 mg/m2 IV push days 1-5
Fluorouracil 425 mg/m2 IV push days 1-5 (immediately after leucovorin)
Repeat every 4-5 weeks for 6 cycles

FLe (24) Fluorouracil 450 mg/m2 IV days 1-5,
Beginning on day 28, 450 mg/m2 weekly
Levamisole 50 mg PO q8h Days 1-3
Repeat every 2 weeks for 1 year

COLORECTAL CANCER – metastatic

Fluorouracil+ Leucovorin (25)
Leucovorin 20 mg/m2 IV days 1-5
Fluorouracil 425 mg/m2 IV days 1-5 (Immediately after leucovorin)
Repeat every 4-5 weeks

Fluorouracil
Fluorouracil 500mg/m2 IV weekly

ENDOMETRIAL CANCER

AP (26)
Doxorubicin 60 mg/m2 IV day 1
Cisplatin 60 mg/m2 IV day 1 (after Doxorubicin)
Repeat every 28 days

AC (27)
Doxorubicin 60 mg/m2 IV day 1
Cyclophosphamide 500mg/m2 IV day
Repeat every 21 days

Dox/Pac (26)
Doxorubicin 50mg/m2 IV day 1
Paclitaxel 150mg/m2 IV over 3 hrs day 1
Repeat every 21 days

Doxorubicin
Doxorubicin 60mg/m2 IV
Repeat every 21 days

Paclitaxel
Paclitaxel 175 mg/m2 IV over 3 hrs
Repeat every 21 days

Hormonal (28)
Megestrol 40 - 160mg PO daily **or**
Depo provera 400mg IM monthly for two years'

FALLOPIAN TUBE CANCER

CP (29)
Paclitaxel 150mg/m2 IV day 1 over 3hours
Carboplatin AUC 5 day 1
(Note that Cisplatin 60mg/m2 IV can be used in place of carboplatin)

GASTRIC CANCER

FAP (30)
5-Fluorouracil 300 mg/m2 IV days 1-5
Doxorubicin 40 mg/m2 IV day 1
Cisplatin 60 mg/m2 IV day 1
Repeat every 5 weeks

CP Cisplatin 100 mg/m2 IV day 1
5- fluorouracil 500 mg/m2 IV days 1-5
Repeat every 28 days

5-FU 5-fluorouracil 500mg/m2 IV days 1-5
Repeat every 28 days

GESTATIONAL TROPHOBLASTIC DISEASE

MA (31, 32) Methotrexate 30-50 mg/m2 IM every week
Actinomycin D 10-13 mcg/kg/day IV days 1-5
Repeat every 2 weeks until Beta HCG is negative
or
Methotrexate 25 mg IV days 1-5
Alternate with Actinomycin D 0.5mg IV days 14-19
Leave 1 week between drugs for one course. Until β hCG is negative.

NOTE: Where β hCG assay is not available, monitor with pregnancy test. If pregnancy test is negative, give one more course and stop.

HEAD AND NECK CANCER (oral cavity, oropharynx, hypopharynx, larynx, nasopharynx)

CP/5FU (33) Cisplatin 100mg/m2 IV day 1
5-fluorouracil 1000 mg/m2 IV over 24 hrs days 1-4
Repeat every 21 days

CP/5FU (alternate) Cisplatin 100mg/m2 IV day 1
5-fluorouracil 500 mg/m2 IV push days 1-5
Repeat every 21 days

Pac/CP (34) Paclitaxel 175 mg/m2 IV over 3 hrs day 1
Cisplatin 75 mg/m2 IV day 2
Repeat every 21 days

Mtx (35) Methotrexate 40mg/m2 IV weekly

Pac (36) Paclitaxel 80 mg/m2 IV weekly

In addition for nasopharynx
Doxorubicin Doxorubicin 60mg/m2 IV
Repeat every 21 days
or
Doxorubicin 20 mg/m2 IV weekly

HEPATOCELLULAR CARCINOMA

Doxorubicin (37)
Doxorubicin 60-75 mg/m2 IV day 1
or
Doxorubicin 20-30mg/m2 IV weekly
Repeat every 21 days

HODGKIN'S DISEASE

CMOPP (38)
Cyclophosphamide 650mg/m2 IV days 1 and 8
Vincristine 1.4mg/m2 (max 2mg) IV days 1 and 8
Procarbazine 100mg/m2 PO days 2-15
Prednisone 40mg/m2 PO days 2-15

KAPOSI'S SARCOMA

Doxorubicin (39)
Doxorubicin 15 mg/m2 IV push
Repeat once every week until 12 doses or 3 months or disease progression
Discontinue if no response after 2 cycles

NON-HODGKINS LYMPHOMA (including Diffuse Large B-Cell Lymphoma)

CHOP (40)
Cyclophosphamide 750 mg/m2 IV day 1
Doxorubicin 50 mg/m2 IV day 1
Vincristine 1.4 mg/m2 IV day 1 (max 2mg)
Prednisone 40 mg/m2 PO days 1-5

CVP (41)
Cyclophosphamide 1000 mg/m2 IV day 1
Vincristine 1.4 mg/m2 IV day 1 (max 2mg)
Prednisone 100 mg/m2/d PO days 1-5

NON-HODGKIN'S LYMPHOMA (low grade, follicular)

CVP (41)
Cyclophosphamide 400 mg/m2 PO days 1-5 or 750 mg/m2 IV day 1
Vincristine 1.4 mg/m2 IV day 1 (max 2mg)
Prednisone 100 mg/m2/d PO days 1-5

Cyclophosphamide
Cyclophosphamide 100 mg/m2 PO daily x 14 days
Repeat every 28 days

OVARIAN – Epithelial cancer
adjuvant after surgical debulking

Cisplatin + Cisplatin 75 mg/m2 day 1
Paclitaxel (42) Paclitaxel 135 mg/m2 IV over 3 hrs day 1
Repeat every 21 days for 4-6 cycles

OVARIAN – Epithelial cancer - recurrent or metastatic

CP (42,43) Cisplatin 100 mg/m2 IV day 1
Cyclophosphamide 600 mg/m2 IV day 1
Repeat every 21 days

Paclitaxel (44) Paclitaxel 135 mg/m2 IV over 3rs
Repeat every 21 days

OVARIAN- Germ cell cancer- adjuvant after surgical debulking.

PEB (45) Cisplatin 20mg/m^2 Days 1-5
Etoposide 100mg/m^2 Days 1-5
Repeat every 21 days.
Bleomycin 30iu IV push weekly (not to exceed 300iu total)

NOTE: Germ cell cancers can cause elevated blood levels of tumor markers such as hCG, alpha-fetoprotein (AFP) and or LDH. If the blood levels of these are elevated before commencement of treatment, they are rechecked during chemo (usually before each cycle). If the chemo is working, the levels will go down to normal. The PEB combination has to given for at least 3 cycles.

PANCREATIC CANCER

5-FU (46) 5-Fluorouracil 425 mg/m2 IV push days 1-5
Repeat every 21 days

PROSTATE CARCINOMA – recurrent or metastatic

Androgen deprivation recommended first:

Orchiectomy or

Leuprolide 7.5mg IM monthly (may have flare of symptoms during first two weeks)
or
Diethylstilbestrol 1-3mg PO daily

Chemotherapy for hormonal failures:

Doxorubicin Doxorubicin 20 mg/m2 IV weekly

CAM
Cyclophosphamide 600 mg/m2 IV day 1
Doxorubicin 40 mg/ m^2 IV day 1
Methotrexate 15 mg/m2 PO Days 9 and 13
Repeat every 21 days

Cisplatin + Doxorubicin
Cisplatin 50-60 mg/m2 IV day 1
Doxorubicin 50-60 mg/ m^2 IV day 2
Repeat every 21 days

CDF (47)
Cyclophosphamide 150 mg/m2 PO days 3-6
Doxorubicin 30 mg/m^2 IV day 1
5-Fluorouracil 400 mg/m2 IV Days 1-8
Repeat every 21 days

SERTOLI-LEYDIG CELL TUMOUR

CAP (48)
Cisplatin 60 mg/m2 IV day 1
Doxorubicin 50 mg/m2 IV day 1
Cyclophosphamide 600 mg/m2 day 1
Repeat every 21-28 days

SARCOMA – adjuvant

After resection for > 5cm high-grade soft tissue sarcoma

AC
Doxorubicin 50-60 mg/m2 IV day 1
Cyclophosphamide 600mg/m2 IV day 1
Repeat every 21 days x 5 cycles

SARCOMA – recurrent or metastatic

Doxorubicin (49)
Doxorubicin 60 mg/m2 IV day 1
or
Doxorubicin 25 mg/m2 IV days 1,2,3
Repeat every 21 days

SARCOMA – OSTEOSARCOMA – adjuvant

6 cycles after resection or 3 cycles before and after resection

Doxorubicin + Cisplatin (50)
Doxorubicin 25mg/m2/day IV days 1, 2, 3
Cisplatin 100mg/m2 IV day 1
Repeat every 21 days

TESTICULAR CANCER

BEP (51)	Bleomycin 30 units IV weekly on days 1, 8, and 15 Etoposide 100 mg/m2 IV on days 1 - 5 Cisplatin 20 mg/m2 IV on days 1 - 5 Repeat every 21 days2
EP(52)	Etoposide 100 mg/m2 IV on days 1 - 5 Cisplatin 20 mg/m2 IV on days 1 - 5 Repeat every 21 days
CP (modified) (53)	Cisplatin 100mg/m2 IV day 1 Paclitaxel 175 mg/m2 IV over 3 hrs day 1 Repeat every 21 days

CHAPTER 5. THE SURGICAL ONCOLOGIST

The practice of surgical oncology is like the second marriage, as described by Samuel Johnson, "*the triumph of hope over experience*". This is especially true in developing countries where patients invariably present to the surgeon with very advanced disease. Despite surgery, chemotherapy and radiation, our patients often succumb to their disease. Sprinkled in these heartrending tales are scattered successes that keep us from despair.

Advanced disease is not the only problem facing the surgical oncologist in developing countries. In the USA, we are used to frozen section turn-around times in minutes and final pathology turn-around times in days. In addition, we are accustomed to accuracy. If local pathologists in the USA cannot get a clear diagnosis, the specimen gets sent via *Fed-Ex* to the Armed Forces Institute of Pathology, MD Anderson or the Mayo Clinic-where some of the most experienced pathologists in the world render a verdict. Developing countries not so lucky; frozen section is rarely available, pathology results take weeks and the results are often inaccurate or incomplete. This is not meant as a criticism of the third world pathologist. There is a tremendous gap between the facilities and equipment available to the pathologist in developing countries and his colleagues in the developed world. This poses a difficult problem for the surgeon. He often has to make decisions based on incomplete or inaccurate information.

Another problem facing the surgical oncologist in developing countries is equipment and facilities. In the USA, the surgical oncologist is used to having whatever he needs for every case, such as electrophysiologic monitoring of the recurrent laryngeal nerve during thyroid surgery, technetium-99 sentinel node biopsy during breast surgery, or surgical staplers during GI surgery. This is rarely the case in the third world. Imagine doing chest surgery with no surgical staplers, no pleurevac and no double lumen endotracheal tube. The patient needs four units of blood but his brother is the only donor. After the patient survives the surgery, he is taken to a ward where he is one of twenty patients taken care of by two nurses. The surgical oncologist in developing countries must be innovative, flexible and skilled in order to compensate for the lack of equipment and facilities.

For decades, I have been making pilgrimages to the Nigerian Christian Hospital on humanitarian surgical trips. I enjoy being innovative, flexible and, of course, skilled but have been frustrated by many of the issues mentioned above. Slowly, over time, we have solved some of these problems. We have a very well organized and equipped operating room that is supplied with critical items such as drains, suture, surgical staplers etc. We have invested in training nurse anesthetists who can manage complex surgeries under difficult situations. We have a program to administer all our own chemotherapy rather than send patients to other centers. We have developed collaboration with the Brigham and Woman's Hospital Department of Pathology wherein they process our surgical specimens. We have made contacts with radiation oncologists and nuclear medicine physicians in Nigeria. All these actions have resulted in an oncology program that can deliver comprehensive care to our oncology patients.

CAMAZINE'S ONCOLOGY RULES

1. Not every cancer needs a definitive diagnosis before treatment (I know this is blasphemy!)
2. Don't be an armchair surgeon
3. When in doubt, get the biopsy gun
4. Be aggressive surgically
5. Don't procrastinate
6. Think of the patient, not the possible outcome
7. It is better to be hoarse than dead
8. It is better to be alive than dead

CASE 1: A patient presents with a large ulcerated, fungating breast mass with axillary nodes. What should you do? It is obvious that the patient has breast cancer so there is no sense wasting time and money-neither of which the patient has. Start neoadjuvant chemotherapy then do a mastectomy. You will get the definitive diagnosis from the mastectomy specimen.

CASE 2: A patient presents with a large breast mass, which has skin retraction, peau d'orange skin changes and axillary nodes. The plan is same as above.

CASE 3: A young adult presents with a non-mobile neck mass and a benign ENT exam. What should you do? Get out the biopsy gun and do a TruCut biopsy. There is a good chance that this is nasopharyngeal cancer and treatment will be non-surgical.

CASE 4: A patient presents with a large parotid mass. What should you do? Perform a parotidectomy, sacrificing any/all branches of the facial nerve that enter the tumor. If nodes become obvious during the surgery, do a radical neck dissection.

CASE 5: A patient presents with a large fungating parotid mass. What should you do? Perform a parotidectomy and radical neck dissection, removing all affected skin and sacrificing any/all branches of the facial nerve that enter the tumor. Be aggressive!

CASE 6: A patient presents with a thyroid mass. What should you do? Perform a total thyroidectomy (on every thyroid surgery). During the dissection, you find that the thyroid tissue on one side is unusually stuck to the trachea and there appears to be tumor at the junction of the recurrent laryngeal nerve and the larynx. What should you do? Sacrifice the nerve-the patient will be fine but hoarse (assuming your other nerve is intact).

CHAPTER 6. PREVENTION OF CANCER

The adage that says that prevention is better than cure is particularly true for cancer. In fact, with regard to cancers, it should be better put that prevention is better than treatment because cure is not common in the management of most advanced cancers.

The anti-cancer drugs described in this manual are largely unavailable and unaffordable in Nigeria due to prevalent poverty and economic deprivation fueled by endemic corruption. For instance, the current cost of one vial of carboplatin is more than the average worker's two months' salary. Moreover, due to lack of medical insurance, most of the patients who undergo chemotherapy in our practice sell all their valuable pieces of property in order to procure the drugs. Their other social responsibilities such the children's education are abandoned to enable them buy their drugs. No wonder then that over 95% of the world's anticancer drugs are sold in the United States of America, Europe and Japan while less than 5% are sold in the rest of the whole world. Sixty-one percent of the world's anticancer drugs are sold in the United States alone. The developing countries where the negligible proportion of the world's anticancer drugs is sold, contribute nearly 70% of the world's cancers. Therefore, it is obvious that the best option for developing countries is prevention.

There are three levels of prevention. Primary prevention refers to measures taken to prevent cancer in otherwise healthy people. Secondary prevention refers to screening which detects either pre-cancer diseases or early stages of cancer. Tertiary prevention refers to measures taken to prevent recurrence of cancer in those who have already survived an episode of the disease.

PRIMARY PREVENTION

Primary prevention can be accomplished by avoiding a carcinogen or altering its metabolism; pursuing lifestyle or dietary practices that modify cancer-causing factors or genetic predispositions. Put differently, primary prevention attempts to avoid the risk factors for cancer. The following are common ways of preventing cancers:

Tobacco: Tobacco damages nearly every organ in the human body and is linked to at least 15 different cancers and costs billions of dollars each year. It accounts for some 30% of all cancer deaths.

There is no doubt tobacco use is increasing in Nigeria and other developing countries. Tobacco use is the single most preventable cause of cancer death worldwide.

Measures that can be adopted to prevent tobacco related deaths include:

- smoking ban in public places
- advertising bans
- health warning labels
- increasing taxation on tobacco companies so as to discourage more production.

This last measure is said to be the single most effective way of reducing tobacco demand.

The professional organizations (such as Nigerian Medical Association) and the media in Nigeria can be in the forefront of bringing to prominence the harmful effect of tobacco and create the necessary public and political support needed to enact laws against tobacco use. In addition, they can create the awareness necessary for people to adopt appropriate life style devoid of tobacco.

Diet: Diet is most closely associated with the development of cancers of the gastrointestinal tract and of cancers that are affected by hormones (breast, endometrium, ovary, and prostate). The National Cancer Institute has advocated a well-rounded diet, similar to that recommended for the prevention of cardiovascular disease. This change would include reducing the intake of fat (to 30% of total calories) and cholesterol; increasing the ratio of polyunsaturated to saturated fats; increasing the consumption of fiber (fruits, vegetables, and whole grain cereal products); increasing the percentage of protein from vegetables (peanuts, beans, peas); reducing the intake of salt; consuming alcohol in moderation.

Infection. Infections are linked to as much as 20% of all cancers in developing countries. They contribute about 10% of all the cancers in developed countries. Infections may cause long-term inflammation, immune-suppression or initiate transformation process in the cells.

Human papilloma virus is thought to be responsible for cancer of the cervix. It is sexually transmitted. Public health measures such as abstinence until marriage and being faithful to one's partner will also check cancer of the cervix. Avoidance of early sexual exposure is particularly important. Vaccination against human papilloma virus has been developed and has become available even in some developing countries.

The hepatitis B and C viruses are associated with cancer of the liver. They are transmitted by sex and blood transfusion, like HIV. Measures adopted in preventing HIV will have positive impact on transmission of hepatitis B and C. Hepatitis B and C vaccines are also available; widespread vaccination with the vaccines will go a long way in preventing cancer of the liver.

Physical inactivity. Physical inactivity is another risk factor for overweight/obesity and cancer. Physical inactivity can therefore combine with unhealthy diets to further increase obesity and cancer risk. All forms of physical activity protect against some cancers, as well as against weight gain, overweight and obesity. Regular physical activity can help one to gain strength, relieve stress, boost self-esteem, reduce anxiety, sleep better and feel more energetic. The WCRF/AICR recommends that physical activity should be made a vital part of everyday life, that people should be moderately physically active, equivalent to brisk walking, for at least 30 minutes every day. Physical activity of longer duration or greater intensity is more beneficial.

SECONDARY PREVENTION

Secondary prevention involves screening populations for early cancer, precursor disease, and predisposition to cancer. When cancers are detected early, treatment is easier, and survival is a lot better. When precursor lesions are detected, they can be completely cured, and cancer can therefore be prevented. The World Health Organization estimates that a third of cancers in the world could be cured if detected early and treated adequately.

Cancer of the Breast

It is estimated that about 1.3 million new cases of breast cancer occur annually. Each year breast cancer constitutes about 22% of all new cancer cases in women. Worldwide, breast cancer is the most frequently diagnosed cancer in women. Women have 1 in 8 lifetime chance of developing

breast cancer. An estimated 465,000 breast cancer deaths occurs annually. It is therefore the leading cause of cancer deaths in women worldwide.

Breast cancer is also the commonest cancer in women of Nigeria and is also the leading cause of cancer death. The factors contributing to the high case-fatality rate for breast cancer in Nigeria include: late presentation with advanced disease with metastasis, refusal of breast surgery, inadequate radiotherapy services, lack of organized screening services and lack of awareness of breast cancer and what can be done to prevent the disease.

Breast Self Examination (BSE)

This is one way women starting from their 20s can keep abreast of their breast health. BSE helps women establish a baseline for what is normal for them. That way something abnormal can be more readily detected and reported quickly to the physician. This examination has to be done regularly every month.

Breast Clinical Examination (CBE)

Women in their 20s and 30s should have clinical breast examination (CBE) as part of a periodic (regular) health exam by a health professional (doctor, nurse, midwife etc) every three years. After age 40, women should have a CBE every year.

Mammograms

A mammogram is a special type of x-ray of the breasts. Screening mammograms are used to look for breast disease in women who are asymptomatic. Mammograms can show tumors long before they are big enough to be detected by BSE and CBE. Mammograms are recommended every year for women who are 40 and above. Such women should continue to have yearly mammograms for as long as they are in good health.

Cervical Cancer

The cervix is the part of the uterus that projects into the upper part of the vagina. By virtue of its projection into the vagina, it is an external organ that can be easily reached and assessed. The aim of a screening test on the cervix is to detect a pre-invasive disease that can be cured in almost 100% of cases.

Pap Smear

The first and the mostly widely used screening method is the Papanicolaou (PAP) smear. It is recommended that pap smear screening should begin within three years of sexual intercourse or by age 21 and then yearly until age 30. After age 30, most women can continue annual testing or can choose to be tested two to three years after three consecutive negative pap tests.

Colorectal Cancer

Colorectal cancer is the third leading cause of death from cancer among women and the fifth cause of cancer mortality among men in Nigeria. This cancer fortunately can be preceded by non-cancerous, pre-malignant lesions commonly referred to as polyps. Screening tests that can detect these pre-cancerous polyps and early stage of the disease will go a long way in reducing mortality from colorectal cancer.

It is recommended that men and women of age 50 and above who are at average risk of developing colorectal cancer should have sigmoidoscopy every 5 years or colonoscopy every 10 years. The colonoscopy is now the gold standard for colorectal cancer screening because it visualizes the entire colon surface and allows for removal of any pre-cancerous polyps at the same time.

Cancer of the Prostate

Prostate cancer is now the commonest cause of cancer death among men in Nigeria. It is also one of the leading causes of cancer deaths in men globally. Early cancer of the prostate usually causes no symptoms and is most often detected by screening tests. Prostate cancer is a slowly growing tumor and is often advanced by the time it becomes symptomatic.

It is therefore recommended that health care professionals offer the prostate specific antigen (PSA) blood test and digital rectal examination (DRE) yearly, beginning at age 50.

CHAPTER 7. FINAL WORDS…

There is no medicine like hope No incentive so great
And no tonic so powerful
As the expectation
Of something better tomorrow
- Orison Swett Marden

There comes a time in practice when one would have to break the news '*…I'm sorry madam but I think you have a cancer'*. Breaking bad news remains an unexplored art in medical practice, but it is an essential skill in managing cancer patients. More worrisome is the fact that the clinician would have to shoulder the responsibility of telling the rest of the family, perhaps more than 10 times, the same bad news. Sometimes, it is necessary to break the news with some bit of hope!

Thus, in this concluding section we would explore practical ways of breaking bad news in oncology practice, especially in places where most people may not be literate enough to understand what you may be talking about. The central theme is to give hope as much as possible, while being open about the diagnosis and prognosis. Here are some practical suggestions.

BREAKING THE NEWS

Breaking bad news is not something that most clinicians and nurses are eager to do. Somebody once said: "Never break bad news...it will only get you in trouble." And stories abound about unskilled physicians blundering their way through an important conversation, sometimes resulting in serious harm to the patient. Many patients with cancer can recall in detail how their diagnosis was disclosed, even if they remember little of the conversation that followed, and they report that physician competence in these situations is critical to establishing trust.

Some physicians contend that breaking bad news is an innate skill, like perfect pitch, that cannot be acquired otherwise. This is incorrect. Physicians who are good at discussing bad news with their patients usually report that breaking bad news is a skill that they have worked hard to learn. Furthermore, studies of physician education demonstrate that communication skills can be learned, and have effects that persist long after the training is finished.

Robert Buckman, in an excellent short manual, has outlined a six step protocol for breaking bad news (54). Given his well thought-out steps, we are quoting directly from his website:

Getting started
"The physical setting ought to be private, with both physician and patient comfortably seated. You should ask the patient who else ought to be present, and let the patient decide. Studies show that different patients have widely varying views on what they would want." You can't be a dictator. You get what you need by polite, quiet insistence. Never give bad news standing up. Never, ever, *ever* give bad news in a hallway. As you're getting in the room, and the chair, people will become alarmed and ask you what has happened. Wait, saying you'd like to talk

about it in private, please. You seat everyone. You take a deep breath, and then you say it. And then, most importantly, you say you're sorry."

Finding out how much the patient knows.
"By asking a question such as, "What have you already been told about your illness?" you can begin to understand what the patient has already been told ('I have lung cancer, and I need surgery'), or how much the patient understood about what's been said ('the doctor said something about a spot on my chest x-ray'), the patients level of technical sophistication ('I've got a T2N0 adenocarcinoma'), and the patient's emotional state ('I've been so worried I might have cancer that I haven't slept for a week')."

Finding out how much the patient wants to know.
"It is useful to ask patients what level of detail you should cover. For instance, you can say, 'Some patients want me to cover every medical detail, but other patients want only the big picture--what would you prefer now?' This establishes that there is no right answer, and that different patients have different styles. Also this question establishes that a patient may ask for something different during the next conversation."

Sharing the information.
"You must keep in mind that only the first few words will be heard. After that, the mind shuts out the rest. "Decide on the agenda before you sit down with the patient, so that you have the relevant information at hand. The topics to consider in planning an agenda are: diagnosis, treatment, prognosis, and support or coping. However, an appropriate agenda will usually focus on one or two topics. For a patient on a medicine service whose biopsy just showed lung cancer, the agenda might be: a) disclose diagnosis of lung cancer; b) discuss the process of workup and formulation of treatment options ('We will have the cancer doctors see you this afternoon to see whether other tests would be helpful to outline your treatment options'). Give the information in small chunks, and be sure to stop between each chunk to ask the patient if he or she understands ('I'm going to stop for a minute to see if you have questions'). Long lectures are overwhelming and confusing. Remember to translate medical terms into English, and don't try to teach pathophysiology." Eventually there will be questions. You answer them with the facts you have, leaving out all interpretation, excuses, religion, or philosophizing."

Responding to the patient's feelings.
"If you don't understand the patient's reaction, you will leave a lot of unfinished business, and you will miss an opportunity to be a caring physician. Learning to identify and acknowledge a patient's reaction is something that definitely improves with experience, if you're attentive, but you can also simply ask ('Could you tell me a bit about what you are feeling?')." When the prognosis is poor, avoid using terms such as "there is nothing more we can do for you", as goals in care will change to good pain control and symptom relief, all of which are possible."

Planning and follow-through.
"At this point you need to synthesize the patient's concerns and the medical issues into a concrete plan that can be carried out in the patient's system of health care. Outline a step-by-step plan, explain it to the patient, and contract about the next step. Patients who have a clear plan for the future are less likely to feel anxious and uncertain. An important part of this is providing

treatment and care options to the patient. Be explicit about your next contact with the patient ('I'll see you in clinic in 2 weeks') or the fact that you won't see the patient ('I'm going to be rotating off service, so you will see Dr. Back in clinic'). Give the patient a phone number or a way to contact the relevant medical caregiver if something arises before the next planned contact."

What if the patient starts to cry while I am talking?
"In general, it is better simply to wait for the person to stop crying. If it seems appropriate, you can acknowledge it ("Let's just take a break now until you're ready to start again") but do not assume you know the reason for the tears (you may want to explore the reasons now or later). Most patients are somewhat embarrassed if they begin to cry and will not continue for long. It is nice to offer tissue paper if they are readily available (something to plan ahead); but try not to act as if tears are an emergency that must be stopped, and don't run out of the room: you want to show that you're willing to deal with anything that comes up." If there is no crying, you let the silence stretch, no matter what else you have to do. You can take these few moments for something this important.

The final thing, and probably the most important, you could offer your patient is hope. Even when people know that the end may not be far away, they prefer to face it on a positive note. It usually is helpful to show empathy to the patient, while 'hoping' for a better tomorrow. Hope is a force that sustains and regenerates your will to live. Even if there is only a remote chance for a successful outcome, hope can still empower the spirit to fight for life. Hope can also motivate people to make positive changes in their lifestyles that engender better health.

Hope is fragile. It can ebb and flow depending on the success or failure of therapy. For newly diagnosed cancer patients and their relatives and friends, hope is usually focused on treatment and the potential for a cure or remission. With advanced cases of cancer, patients and their families frequently hope for pain control, an end to suffering, and a peaceful death. Another form of hope lies in spirituality, including a belief in transcendence, or the continuation of the soul after death.

Hope can be nourished in many ways, including accomplishing a goal, having control over your life, feeling appreciated and useful, experiencing religious faith/spirituality, and spending quality time with family and friends. Recent advances in cancer therapy are also a cause for hope."

Lastly, oncology practice is not an exact science. No matter how hard you work there are times when the patient passes on despite your best effort. This often comes after the patient has taken up your time, mind and energy. A sad fact of life. It could be draining practicing oncology in resource-poor settings. In times like this always remember that you are human. Do not play God! When the end comes, it may help to shrug your shoulders in fulfillment and move on. The next patient needs a clear-thinking oncologist. See you in the next edition.

REFERENCES

1. Omolara KA. Feasible Cancer Control Strategies for Nigeria: Mini-Review, *American Journal of TROPICAL MEDICINE & Public Health* 2011; 1(1):1-10

2. Durosinmi MA. Cancer control in an economically disadvantaged setting; Nigeria. *INCTR Newsletter* 2008; www.inctr.org/publications/2004_v05-n01_s02.shtml. Accessed 19/5/2008

3. Globocan(2008).Country fast stats-Nigeria http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=566 . Accessed 23/5/2011

4. Dennis Albert Casciato and Mary C. Territo, *Manual of Clinical Oncology*, 2th Ed, Philadelphia: Wolters Kluwer Health, 2009

5. Nancy Beaulieu, M. Henry J Durivage, David S. Fisher, and Tish Knobf. *The Cancer Chemotherapy Handbook*, St. Louis: Mosby, 2004

6. Edward Chu and Vincent T. DeVita, Jr. *Physicians' Cancer Chemotherapy Drug Manual*, Sudbury MA: Jones and Bartlett Publishers, 2011

7. Alexopoulou A et al. Hepatitis B virus reactivation in patients receiving chemotherapy for malignancies: Role of precore stop-codon and basic core promoter mutations. *J Viral Hepat* 2006; 13:591-6

8. Saab S et al. Hepatitis B prophylaxis in patients undergoing chemotherapy for lymphoma: a decision analysis model. *Hepatology* 2007; 46:1049-56

9. www.nccn.org

10. Hung A et al. Cisplatin-based combined modality therapy for anal carcinoma. *Cancer* 2003; 97:1195-1202

11. Harker WG et al. Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. *J Clin Oncol* 1985; 3:1463-70

12. Dreicer R et al. Phase II study of cisplatin and paclitaxel in advanced carcinoma of the urothelium. *J Clin Oncol* 2000; 18:1058-61

13. Vaughn D et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. *J Clin Oncol* 2002; 20: 937-40

14. Weiss RB et al. Adjuvant chemotherapy after conservative surgery plus irradiation versus modified radical mastectomy. Analysis of drug dosing and toxicity. *Am J Med* 1987; 83:455-63

15. Martin M et al. Doxorubicin in combination with fluorouracil and cyclophosphamide versus methotrexate in combination with fluorouracil and cyclophosphamide as adjuvant chemotherapy for operable breast cancer: a study by the GEICAM group. *Ann Oncol* 2003;14:833-42.

16. Fisher B et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol* 2000; 8:1483-96

17. Henderson IC et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 2003; 21:976-83

18. Jaiyesimi IA et al. Use of tamoxifen for breast cancer: twenty-eight years later. *J Clin Oncol* 1995; 13:513-29

19. Perez EA et al. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol* 2001; 19:4216-23

20. Beogo R et al. Endemic Burkitt lymphoma of maxillofacial region: results of induction treatment with cyclophosphamide plus methotrexate in West Africa. *Pediatr Blood Cancer* 2011; 56:1068–70
21. Kavanagh JJ et al. Combination chemotherapy for metastatic or recurrent adenocarcinoma of the cervix. *J Clin Oncol* 1987; 10:1621-23
22. Thigpen T et al. The role of paclitaxel in the management of patients with carcinoma of the cervix. *Semin Oncol* 1997; 24:S41-6
23. O'Connell MJ et al. Controlled trial of fluorouracil and low-dose leucovorin given for 6 months as postoperative adjuvant therapy for colon cancer. *J Clin Oncol* 1997; 15:246-50
24. Figer A. Mature results of a prospective randomized trial comparing 5-flourouracil with leucovorin to 5-flourouracil with levamisole as Adjuvant Therapy of Stage II and III Colorectal Cancer. *J Cancer* 2011; 2:177-85
25. Poon MA et al. Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989; 7:1407-18
26. Fiorica JV. Update on the treatment of cervical and uterine carcinoma: focus on topotecan. *Oncologist* 2002; 7 Suppl 5:36-45
27. Thigpen JT, et al. A randomized comparison of doxorubicin alone versus doxorubicin plus cyclophosphamide in the management of advanced or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 1994; 12:1408-14
28. Thigpen JT et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *J Clin Oncol* 1999; 17:1736-44
29. Brown JV et al. Three-hour paclitaxel infusion and carboplatin is an effective outpatient treatment for stage III epithelial ovarian cancer. *Gynecol Oncol* 1998;68:166–8
30. Cullinan SA et al. Controlled evaluation of three drug combination regimens versus fluorouracil alone for the therapy of advanced gastric cancer. North Central Cancer Treatment Group. *J Clin Oncol* 1994; 12:412-16
31. Homesley HD et al. Weekly intramuscular methotrexate for nonmetastatic gestational trophoblastic disease. *Obstet Gynecol* 1988; 72:413- 8
32. Lurain JR. Gestational trophoblastic tumors. *Semin Surg Onco* 1990; 6:347-53
33. Forastiere A et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol* 1992; 10:1245-51
34. Hitt R et al. A phase I/II study of paclitaxel plus cisplatin as first-line therapy for head and neck cancers: preliminary results. *Semin Oncol* 1995; 22:50-4
35. Forastiere A et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol* 1992; 10:1245-51
36. Colevas A et al. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. *J Clin Oncol* 2006; 24:2644-52
37. Venook AP. Treatment of hepatocellular carcinoma: too many options? *J Clin Oncol* 1994; 12:1323-34
38. DeVita VT et al. Combination chemotherapy in the treatment of advanced Hodgkin's disease. *Ann Intern Med* 1970; 73:881-95
39. MA, Krown SE, KP et al. Weekly doxorubicin in the treatment of patients with Kaposi's

sarcoma. AIDS Clinical Trials Group. *J Acquir Immune Defic Syndr* 1993; 6:259-64
40. Mckelvey EM, et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. *Cancer* 1976; 38:1484-93
41. Bangley CM et al. Advanced lymphosarcoma: intensive cyclical combination chemotherapy with cyclophosphamide, vincristine, and prednisone. *Ann Intern Med* 1972; 76:227-34
42. McGuire WP et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996; 334:1-6
43. Swenerton K et al. Cisplatin-cyclophosphamide versus carboplatin-cyclophosphamide in advanced ovarian cancer: a randomized phase III study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1992; 10:718-26
44. McGuire WP et al. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med* 1989; 111:273-9
45. Pectasides D et a. Germ cell tumors of the ovary. *Cancer Treat Rev* 2008;34:427-41
46. DeCaprio JA et al. Fluorouracil and high-dose leucovorin in previously untreated patients with advanced adenocarcinoma of the pancreas: results of a phase II trial. *J Clin Oncol* 1991; 9:2128-33
47. Chelebowski RT et al. Cyclophosphamide (NSC 26271) versus the combination of adriamycin, 5-fluorouracil, and cyclophosphamide in the treatment of metastatic prostatic cancer: a randomized trial. *Cancer*, 1978; 42:2546-52
48. Gershenson DM et al. Treatment of metastatic stromal tumors of the ovary with cisplatin, doxorubicin, and cyclophosphamide. *Obstet Gynecol* 1987;70:765-9
49. Santoro A et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. *J Clin Oncol* 1995; 13:1537-45
50. Souhami RL et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. *Lancet* 1997; 350:911-17
51. Saxman SB et al. Long-term follow-up of a phase III study of three versus four cycles of bleomycin, etoposide, and cisplatin in favorable-prognosis germ-cell tumors: The Indiana University Experience. *J Clin Oncol* 1998;16:702-6
52. Xiao H et al. Long-term follow-up of patients with good-risk germ cell tumors treated with etoposide and cisplatin. *J Clin Oncol* 1997;15:2553-58.
53. Kondagunta et al. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors.*J Clin Oncol* 2005; 23:6549-55
54. Robert Buckman. "Breaking the News"
(http://depts.washington.edu/bioethx/topics/badnws.html)

ABOUT THE AUTHORS

Brian Camazine M.D. is a general, thoracic and head and neck surgeon. In 1985, he made his first humanitarian trip to Nigeria and realized that this was the work he was meant to do. Since 1985, he has made 35 surgical trips to countries including Bolivia, Guatemala, Kenya and Nigeria. In 2004, he formed the Earthwide Surgical Foundation, a 501(c)(3) non-profit organization, dedicated to delivering surgical care to the poor of the world by means of manpower, equipment and education.

Kelechi Eguzo, MD is an attending physician as well as the Medical Administrator at Nigerian Christian Hospital. He has strong interest in Public health, Cancer care and family medicine. Currently, he serves as the Director of Health Transformations International (formerly Hope Advocacy Nigeria), a non-governmental Organization.

Chisara Umezurike, MD
Chisara C Umezurike was born in Mbaise-Nigeria. He obtained Bachelor degrees in Pharmacology and Medicine and Surgery at University of Port Harcourt. He is also a Fellow of the West African College of Surgeons in Obstetrics and Gynecology. He is married to Mrs. Tochi Umezurike (Nee Achinefu) and is blessed with four children. He is currently a Consultant Obstetrician and Gynecologist at Nigerian Christian Hospital Nlagu, Aba. He is also an author of numerous articles in learned peer-review journals.

Charlotte Jacobs MD is an emeritus Professor of Medicine (Oncology) at Stanford University, Stanford, California, where she served as Director of the Clinical Cancer Center, taught oncology, conducted clinical trials, and managed adult cancer patients for over thirty years. She currently treats cancer patients at the Palo Alto Veterans Administration Hospital in Palo Alto, California.

APPENDIX 1

MECHANSIMS OF ACTION (5)

ALKYLATING AGENTS: Mechanism of Action

Drug	Actions
Amsacrine	DNA intercalation, inhibition of topoisomerase II
Busulfan	DNA cross-linking, alkylation of cellular thiols
Carboplatin	DNA cross-linking
Carmustine (BCNU)	DNA cross-linking, inhibition of DNA polymerase, DNA repair, RNA synthesis
Chlorambucil	DNA cross-linking, alkylation of cellular thiols
Cisplatin	DNA cross-linking, intercalation, DNA precursor inhibition, alteration of cellular membranes
Cyclophosphamide	DNA cross-linking
Dacarbazine (DTIC)	DNA methylation, alkylation
Hexamethylmelanine	DNA alkylation, inhibition of DNA and RNA precursor
Ifosfamide	DNA cross-linking and chain scission
Lomustine (CCNU)	DNA cross-linking, inhibition of DNA polymerase, DNA repair, and RNA synthesis
Mechlorethamine	DNA cross-linking
Melphalan	DNA cross-linking, alkylation of cellular thiols
Procarbazine	DNA alkylation, inhibits incorporation of methyl group into RNA
Sreptozocine	DNA cross-linking, inhibits DNA repair enzyme guanine-O^6-methyl transferase
Thiotepa	DNA cross-linking

NATURAL PRODUCTS: Mechanism of Action

Drug	Actions
Asparaginase	Hydrolyzes the amino acid asparagines
Bleomycin	DNA strand scission by free radicals
CPT-11	Inhibition of topoisomerase II
Dactinomycin	DNA Intercalation and adineation, inhibition of topoisomerase II
Daunorubicin	DNA intercalation, preribosomal DNA and RNA inhibition, alteration of cell membranes, free radicals formation
Doxorubicin	Same as Daunorobicin
Etoposide	Inhibition of topoisomerase II
Idarubicin	Same as Daunorubicin
Mitomycin	DNA cross-linking, DNA depolymerization, free radicals formation
Mitoxantrone	DNA intercalation, inhibition of topoisomerase II
Piroxantrone (oxantrazole)	DNA intercalation, inhibition of topoisomerase II
Plicamycin (Mithramycin)	DNA adinaeation and intercalation, osteoclast inhibition
Porfiromycin	Same as Mitomycin
Suramin	Inhibits growth factors (platelet-derived, epidermal, others), inhibits DNA polymerases
Taxol (paclitaxel)	Promotes microtubules assembly, stabilizes tubulin polymers resulting in formation of non-functional microtubules
Taxotere(docetaxel)	Same As Taxol
Teniposide	Same as Etoposide
Topotecan	Inhibition of topoisomerase I
Vinblastine	Tubulin binding (microtubule assembly inhibition and dissolution of mitotic spindle structure)
Vincristine	Same as Vinblastine
Vinorelbine	Tubulin binding (microtubule assembly inhibition and dissolution of mitotic spindle structure)

ANTIMETABOLITES: Mechanism of Action

Azacitidine	Competes for incorporation into nucleic acids, blocking production of cytidine and uridine
2-Chlorodeosyadenosine (2-cda)	Deoxyadenosine analogue that accumulates in cells and blocks

	RNA synthesis
Cytarabine	Competitive inhibition of DNA polymerase, and enzyme involved in conversion of cytidine to deoxycytidine, blocks DNA repair
Edatrexate (10-EDAM)	Inhibits dihydrofolate reductase, thereby halting thymidylate synthesis
Floxuridine	Inhibition of thymidylate synthesis
Fluorouracil (5FU)	Inhibition of thymidylate synthetase, an enzyme involved in conversion of deoxyuridylic acid to thymidylic acid
Hydroxyurea	Inhibition of ribonucleoside reductase (inhibits deoxyribonucleosides), thymidine incorporation into DNA and DNA repair
Mercaptopurine	Competes with ribotides for enzymes responsible for conversion of inoinic acid to adenine and xanthine ribotides (inhibits purine synthesis)
Methotrexate	Inhibits dihydrofolate reductase, thereby halting thymidylate and purine synthesis
	PALA Inhibits aspirate carbamylase, an enzyme that is important in the synthesis of uridine
Pentostatin	Inhibits adenosine deaminase, an enzyme that is important for the metabolism of purine nucleosides,
Thioguanine	Competes with guanine in nucleotide (purine)
Trimetrexate	Same as methotrexate