Treatment – Part One

FCDS Florida Cancer Data System

A Joint Project of the Sylvester Comprehensive Cancer Center and the Florida Department of Health

FLORIDA DEPARTMENT OF HEALTH

NPCR NATIONAL PROGRAM OF CANCER REGISTRIES

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

MILLER SCHOOL OF MEDICINE
UNIVERSITY OF MIAMI

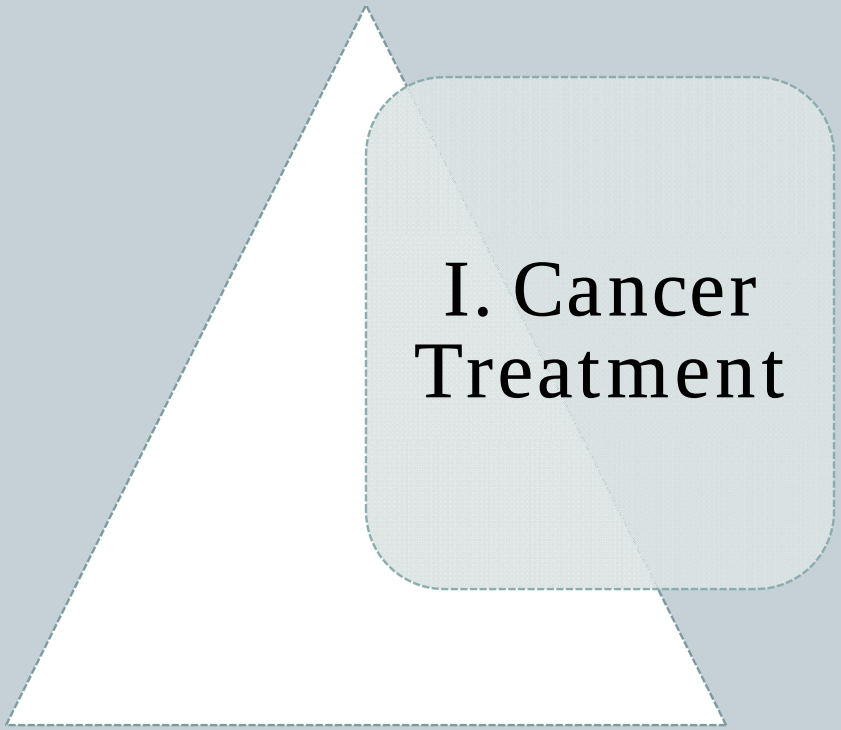
Prerequisites

Completion of FCDS, Introduction to Abstracting module

Learning Objectives

- Recognize cancer treatment modalities
- Acquire a basic understanding of how cancer treatments work and methodologies used in their administration
- Locate cancer treatment information in the medical record
- Identify the coding fields used to abstract cancer treatment information
- Understand how to apply treatment codes to medical record information
- Identify challenging areas in correctly applying treatment codes

Cancer Treatment



Cancer Treatment

Abstracting cancer treatment information, the registrar poses and answers a series of questions for each case:

- Was cancer treatment given to the patient?
- What kind of treatment was given?
- How is the treatment coded?
- Are all the documented procedures and drugs coded as treatment?
- When did treatment start?
- When did treatment end?
- If no treatment was given, why was it not given?
- Is there likely to be other treatment given in another setting outside the hospital?
- How is unknown information coded?
- What text is necessary to support treatment coding?
- Are there “troublesome” data fields to pay attention to in reviewing the abstract?

Was cancer treatment given to the patient?

Cancer treatment is defined in our manuals as any therapy that "modifies, controls, removes, or destroys proliferating cancer cells."

These therapies can be directed against cancer in:

- the primary site-a breast tumor;
- cancer in a regional site-breast tumor extending into the chest wall or cancer cells in axillary nodes;
- or cancer in a metastatic site-breast metastasis to lung.

These therapies can be designed to:

- remove or eradicate the known malignancy-excision of the breast lesion;
- prevent recurrence at the original site of the malignancy-radiation to the tumor bed in the breast;
- prevent the development of metastatic tumors from wandering cells that escaped from the original tumor-systemic chemotherapy or hormonal therapy;
- or relieve symptoms if a “cure” is no longer possible-radiation to a painful bone metastasis from a primary breast cancer.

Physicians develop a treatment plan based on the patient's site and stage of disease, age, health and mental status; the plan may include a single treatment modality or combination of modalities.

The first course of treatment, at time of diagnosis, and the second course at first progression of disease may be intended as curative; later treatments may be described as "salvage" therapy to prolong survival or improve quality of life.

To identify whether cancer treatment is rendered, the registrar must be familiar with cancer treatment procedures and the sources of information located in the medical record and elsewhere.

The agencies which establish standards for collecting cancer information have grouped treatment modalities into seven categories: surgery, radiation, chemotherapy, hormone/steroid therapy, immunotherapy, transplant and endocrine procedures, and other treatment.

New treatments under investigation, such as cancer vaccines and gene therapies, have to date been added to the existing data structure.

Surgery

Surgery is the oldest form of cancer treatment, and until recently the only curative modality.

Surgery may be preventive-prophylactic mastectomy when the second breast may be at high risk for cancer; total colectomy for an inherited familial polyposis syndrome.

Biopsies, or removal of a small piece of tissue or cells from a tumor, are used to diagnose cancer and confirm staging.

Procedures

As treatment, surgical procedures remove or destroy cancers cells through the application of an external force to the malignant lesion.

Surgical procedures may be directed against the tumor in the primary site of cancer, regional lymph nodes, other regional tissues, and sites of distant metastases (usually only for solitary lesions).

Traditionally, surgical procedures have been performed with a scalpel or cutting blade in the hand of a surgeon.

Technology has placed other instruments in the surgeon's hands:

- lasers, focused beams of single-wavelength light which are able to cut and vaporize tissues;
- electrocautery probes, which burn with an electric current;
- grasping and cutting instruments wielded through laparoscopic ports;
- instruments in robotic hands.

Photodynamic therapy is a hybrid type of laser application, considered surgery; a light-sensitive substance is injected intravenously; a laser directed at the malignant tumor activates the chemical that has concentrated within the tumor to release a toxic form of oxygen.

Three types of procedures, all considered surgery, destroy tumor cells by denaturing or altering the structure of cellular proteins.

In cryotherapy, malignant tissue is frozen, generally with liquid nitrogen; argon gas may also be used with greater control of the formation of ice crystals, which damage the cells.

Many types of procedures use heat to destroy malignant tissue;

- heat can be delivered to a local tumor area, using different energy sources such as microwaves, ultrasound, and radiofrequency waves;
- heat can be delivered to regional tissues with perfusion of warmed blood;
- heat can be delivered to the whole body for treatment of metastatic disease with techniques that raise whole body temperature.

With percutaneous ethanol injection (PEI), used in treatment of liver cancers, ethanol is injected into tumor cells, inducing tumor destruction by drawing water out of the cells; acetic acid is used similarly in the treatment of liver cancers.

Tissue Removed

Surgical procedures may be described by the amount of tissue removed.

- An ablation procedure is the local destruction of tumor in place in the body.
- An excision is removal of the tumor from the body.
- A polypectomy is removal of a polyp, generally from the intestinal tract, which harbors a malignancy.
- A partial or complete resection is removal of a wider portion or all of the organ in which the tumor arises.
- A radical resection involves removal of the organ in which the tumor arises plus additional tissue or organs outside the primary organ.

A debulking procedure removes the greatest feasible mass of the tumor, so that adjuvant therapy will be more effective.

Composite resection is terminology used in oral cancers for radical resection of malignancies including removal of underlying bone of the mandible.

The suffix "-ectomy" indicates a surgical procedure which removes tissue or organ:

- mastectomy for removal of breast,
- nephrectomy for removal of kidney,
- colectomy for removal of colon.

The goal of cancer surgery is to achieve clear margins, or a rim of normal tissue around the malignant lesion which is free of cancer cells.

"Microscopic" involvement indicates the presence of tumor cells at the margin or cut edge of a specimen which can only be seen through a microscope.

"Macroscopic" involvement indicates the presence of tumor at the margin or cut edge of a specimen that is visible to the eye.

Surgical Approach

Surgeries may be described by the access to the area where the tissue is removed.

The traditional open procedure involves	• an incision into the body structure, exposure to air and direct surgical access to the tissues or organs to be removed.
An endoscopic procedure, such as endoscopic polypectomy,	• is performed using instruments threaded through an endoscope, or tube inserted into the body.

In minimally invasive surgery, such as laparoscopic and video-assisted thoracoscopic procedures,

- instruments to visualize the operative field and resect tissues or organs are inserted through small surgical openings made into the abdominal/pelvic cavities (laparoscopic) or the chest cavity (thoracoscopic);
- the surgeon wields the instruments while viewing the operative field on a monitoring screen.

With robotic surgery, appropriate for limited, well-defined surgical fields,

- the surgeon sits at a console and manipulates controls;
- the robot at the patient's side translates the surgeon's hand, wrist, and finger movements into movements of miniaturized instruments on multiple robotic arms, the instruments are then inserted into the patient through dime-sized incisions.

Single Port Access surgery (SPA), Natural Orifice Transumbilical Surgery (NOTUS), and Natural Orifice Translumenal Endoscopic Surgery (NOTES) are surgical techniques under investigation to further preserve the integrity of the body and control the impact of invasive procedures on healthy structures.

Transplant

Transplant procedures, another type of surgery,

- involve the removal of a diseased organ and replacement with a donor organ.
- Liver transplants may be used in cancer treatment.

Bone marrow transplants

- are a special type of transplant procedure which are categorized for registry purposes in the hematologic transplant and endocrine surgery group rather than the surgery group.

Reconstruction

Reconstructive surgeries

- rebuild organs or tissues to restore form and/or function impaired by disease or surgery to treat disease.

Reconstruction may be accomplished using

- tissues from other areas of the body-section of small intestine for neobladder; or
- materials foreign to the body-saline implant for breast reconstruction; or
- a combination of tissue and implant.

Reconstructive surgery

- may be done at the time of removal of the organ to be reconstructed, or
- it may be delayed to a later date.

Nodal Procedures

Surgical procedures include removal of node-bearing tissue for staging or prognostic purposes; nodal procedures are coded in registry treatment fields, though they may not be performed with a treatment goal.

The sentinel node biopsy is a specialized procedure, to date used mainly in the diagnosis of melanomas and breast cancers, in which a dye or radioactive material is injected into the main tumor and traced to the first or sentinel node in the lymph drainage system from the tumor.

The node is studied using special stains to reveal the presence of malignant cells, further axillary dissection dependent on sentinel node results.

Sentinel node biopsies represent another step in the development of surgical treatment of breast cancer, from large debilitating procedures to limited surgical approaches combined with other treatment modalities, shown through study to have comparable outcomes in disease control.

Neck dissections for head and neck cancers are undertaken with a goal of cancer control; similarly to the modified surgical procedures for breast cancer, the first radical neck dissection procedures, which included all ipsilateral cervical nodal groups, submandibular gland, spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle, have been modified to remove fewer structures.

A staging laparotomy for lymphoma is another procedure coded as treatment but conducted for staging purposes.

This procedure, rarely performed now, required open exploration of the abdomen, multiple lymph node biopsies, wedge and needle biopsies of the liver, bone marrow biopsy, and splenectomy.

A nodal biopsy for lymphoma is considered a diagnostic procedure if multiple nodes are involved in disease, a treatment procedure if an excisional biopsy of the nodal mass removes all known disease.

Radiation

Radiation destroys cancers by delivering ionizing radiation energy to the cells from high-energy x-rays, gamma rays, electrons, protons, or radioactive isotopes.

The radiation destroys the DNA or genetic material of the cells, so they are unable to divide and reproduce; normal cells in the path of the radiation are also damaged, but they can usually recover their function.

Types of radiation differ in the depth to which they can penetrate into the body and the amount of control over their targeted areas.

Radiation may be delivered with curative intent-to destroy the tumor; prophylatically-to prevent cancer cells from growing in an area; and as palliative care-to shrink a tumor that is causing symptoms.

Tumors vary in their sensitivity to radiation, and in their potential for being cured by radiation.

Source of Radiation

Radiation delivered to a specific region of the body includes:

- a focused beam of photons or charged particles from an outside source-teletherapy;
- a radioactive source implanted within a solid organ-interstitial brachytherapy; and
- a radioactive source inserted into a hollow organ-intracavity brachytherapy.

Beam

Beam radiation is usually given on an outpatient basis on a fractionated schedule, in which small components of the total dose are given at regular intervals.

Beam radiation may be delivered intraoperatively to tumors that cannot be totally excised or that have a high risk of recurrence.

Outside sources of beam radiation include machines which use Cobalt-60 or Cesium-137 as sources of gamma rays; linear accelerators that generate x-rays and electron beams; and cyclotrons that generate proton beams.

X-rays and gamma rays are both forms of electromagnetic radiation; the photon or packet of energy is the elementary particle of these rays.

Electrons and protons are both forms of particle wave radiation; protons can target very high energy to a very small area.

Proton beam therapy is restricted to a very few facilities in the United States.

Traditionally lead blocks have been created and placed into the source machines to shape the beams to the tumor volume, with treatment planning based on two-dimensional models (width and height) of the tumor and blocks exchanged within the machine to vary the dosage delivered to different areas of the body.

Developments in technology have led to enhancements in both treatment planning and radiation delivery.

Three-dimensional conformal radiation therapy uses computer technology to create a treatment plan based on the width, height, and depth of the tumor.

The 3-D model of the tumor is built up from:

- CT (computed tomography), MRI (magnetic resonance imaging),
- PET (positron emission tomography), and
- SPECT (single photon emission computed tomography) images.

The computer shapes multiple single-strength radiation beams to precisely match the contour of the prostate.

Intensity-modulated radiation therapy (IMRT) is a newer type of 3-D conformal radiation therapy that uses a multileaf collimator to continuously shape the radiation beam to the tumor and to modulate the dose of radiation delivered to the tumor and surrounding tissues as the machine is rotated around the patient.

Steroatactic

Stereotactic radiosurgery is a special application of external beam radiation used in the treatment of brain tumors.

Stereotactic radiosurgery uses a large dose of radiation to destroy tumor tissue in the brain.

The patient's head is placed in a special frame attached to the patient's skull, the frame then being used to aim high-dose radiation beams directly at the tumor inside the patient's head.

The radiation can be delivered as:

- a high-energy photon beam from a linear accelerator,
- a gamma ray beam emitted from a cobalt 60 source (gamma knife), or
- a heavy charged particle beam from a proton or helium ion source.

Stereotactic radiotherapy uses the same outside sources of radiation energy to deliver multiple small fractions of radiation to the target tissue instead of one large dose.

Stereotactic radiotherapy is used to treat tumors in the brain as well as other parts of the body.

Brachytherapy

Radioactive materials for brachytherapy are sealed in holders or implants, which may be in the form of thin wires, plastic tubes, ribbons, capsules, or seeds.

With low-dose brachytherapy, radioactive materials are permanently implanted in a solid organ, or inserted into a cavitary organ with an applicator in a monitored hospital environment and held there over a period of days while the radiation dose is delivered.

With high-dose brachytherapy, a single highly radioactive source, Iridium-192, is inserted into treatment catheters or applicators under computer guidance and held at planned positions for planned time periods within the catheters to deliver the treatment dosages; the radioactive source is withdrawn at completion of treatment.

High-dose brachytherapy is delivered in an out-patient setting.

Radioisotopes

Radiation delivered systemically or to the whole body includes radioactive isotopes that are injected intravenously or administered orally in liquid or capsule form.

Radioactive materials used systemically may also be called radiopharmaceuticals.

Radioactive materials for both low-dose brachytherapy and systemic therapy include:

- Iodine-125,
- Iodine-131,
- Strontium-89,
- Strontium-90,
- Phosphorous-32,
- Palladium-103,
- Cesium-131,
- Cesium-137,
- Iridium-192,
- Ruthenium, and
- Cobalt-60.

Radioembolization

In another form of brachytherapy, radioembolization uses radioactive isotopes to block an artery or vein to stop the flow of blood to a tumor, while emitting radiation that helps destroy cancerous cells.

Small radioactive beads or coils may be released through a catheter into a blood vessel feeding the organ or tumor; microspheres of Yttrium-90 are used to treat inoperable liver cancer using this method.

Radioimmunotherapy

Radioimmunotherapy is a new type of delivery system for radioactive isotopes to tumors within the body.

Some tumor cells contain specific antigens that trigger the production of tumor-specific antibodies.

Large quantities of these antibodies can be made in the laboratory and attached to radioactive substances (a process known as radiolabeling).

Once injected into the body, the antibodies seek out cancer cells, which are destroyed by the radiation.

Zevalin is the first radiolabeled antibody approved for use in the United States, in the treatment of non-Hodgkin lymphoma.

Zevalin comes with two types of radiolabeling:

- Indium-111 and
- Yttrium-90.

Bexxar is a second radiolabeled antibody approved for use in the treatment of non-Hodgkin lymphoma, carrying the isotope:

- Iodine-131.

Radiation therapy may be given in conjunction with other types of treatment, surgery or chemotherapy.

Surgery may be used to remove gross tumor, and radiation given to kill microscopic residual tumor cells.

Radiation can also be given before treatment to reduce tumor bulk and to decrease morbidity from a large resection, for a low-lying rectal tumor for example.

Multimodality Treatment

Multiple types of radiation treatment may also be given to a patient, most commonly beam radiation with brachytherapy.

Beam radiation may also be given to different size fields and to different locations covering the primary tumor site and its node-bearing areas.

When multiple modalities are used or multiple fields described, the boost treatment is the treatment given with the smallest focus on the primary tumor site.

Radiosensitizers and Radioprotectants

Two types of drugs that may be given with radiation are ***radiosensitizers*** and ***radioprotectors***.

Radiosensitizers make cancer cells more sensitive to the effects of radiation therapy.

Radiation is often given in conjunction with chemotherapy, and the chemotherapeutic drugs themselves, such as 5-fluorouracil and cisplatin, may have a radiation sensitizing effect.

Whether a drug is considered to have only a radio-sensitizing versus chemotherapeutic effect may be dependent on dose administered, and the registry determines correct coding in consultation with the treating physicians.

Radioprotectants promote the repair of normal cells damaged by radiation therapy.

Amifostine, which helps to reduce dry mouth when the parotid gland is exposed to radiation, is the only drug approved for this use by the FDA.

A radioprotector is not considered a cancer treatment drug.

Chemotherapy

Chemotherapy uses drugs inimical to cell life to inhibit the growth of malignant cells-cytostatic action-or to kill cells-cytotoxicity.

Chemotherapy has traditionally been a systemic treatment attacking cellular DNA, as rapidly dividing cancer cells are most vulnerable to their interference with DNA synthesis and mitosis.

Drugs are given orally or by:

- subcutaneous,
- intramuscular, or
- intravenous injection.

Delivery

Chemotherapy can also be administered as a regional treatment; some drugs will not cross the blood-brain barrier, and are administered intrathecally, directly into the cerebrospinal fluid surrounding the brain and spinal cord.

Chemotherapy agents may be injected into the pleural or pericardial space to control malignant effusions, and into the peritoneal cavity to bring higher doses of drugs to abdominal malignancies.

In chemoembolization, chemotherapy is used as a local agent, with drugs injected directly into the blood supply of a tumor.

Whether given systemically, regionally, or locally, for registry abstracting chemotherapy is a systemic treatment.

Cell Cycle

Traditional chemotherapeutic drugs are classified according to their mechanism of action, and also according to the timing of their action in the cell-division cycle.

The phases of the cell-division cycle include:

- Quiescent,
- Interphase, and
- Metaphase.

Quiescent

- G_0 A resting phase where the cell has left the cycle and has stopped dividing.

Interphase

- G_1 Cells increase in size in Gap 1.
- S Synthesis, DNA replication occurs during this phase.
- G_2 During the gap between DNA synthesis and mitosis, the cell continues to grow.

Metaphase

- M Mitosis, cell growth stops at this stage and cellular energy is focused on the orderly division into two daughter cells.

Alkylating Agents

Alkylating agents attach an alkyl group (univalent radical of carbon and hydrogen atoms arranged in a chain) to DNA, causing cross-linking in the DNA molecule (the same agent links to two positions in the DNA) and abnormal base pairing that interferes with DNA replication; DNA strands may break, and synthesis of enzymes and nucleic acids may be inhibited.

Most agents are not specific to the cell cycle, but rapidly dividing cells may be more sensitive to their effects.

Alkylating agents include:	
Nitrogen mustard and its derivatives:	• mechlorethamine, Melphalan, chlorambucil, and cyclophosphamide;
Ethylenimine derivatives:	• Thio-TEPA;
Alkylsulfonates:	• busulfan;
Nitrosoureas:	• carmustine; and
Trazines:	• DTIC (Dacarbazine) and Temodar.

Alkylating-like Agents

Alkylating-like, platinum-based drugs do not contain an alkyl group but they act in a similar manner, attaching to DNA and inhibiting DNA repair.

These drugs include:

- cisplatin,
- carboplatin, and
- oxaliplatin.

Antimetabolites

Antimetabolites replace structurally similar natural metabolites, altering the function of enzymes required for cell metabolism and protein synthesis.

Their action is most pronounced during the S phase of cell division when DNA, RNA, and protein synthesis occurs.

Antimetabolites include:

Folic acid analogues:	• methotrexate;
Pyrimidine analogues:	• 5-fluorouracil (5-FU); and
Purine analogues:	• mercaptopurine (6-MP).

Folinic acid (leucovorin), not a chemotherapeutic agent, blocks the action of methotrexate on normal cells, and may be referred to as a “rescue” drug.

Anthracyclines

Anthracyclines (antibiotics derived from Streptomyces bacteria) prevent nucleic acid synthesis by intercalation, or the inclusion of molecules between base pairs of DNA or RNA, blocking DNA and RNA transcription.

They inhibit the topoisomerase II enzyme, preventing the relaxing of supercoiled DNA, which also blocks DNA transcription and replication.

They also create iron-mediated free oxygen radicals that damage DNA and cell membranes.

Antitumor antibiotics include:

- Dactinomycin,
- Doxorubicin (Adriamycin), and
- Daunorubicin.

Actinomycin D, Bleomycin, and Mitomycin C are other anti-tumor antibiotics.

Mitotic Inhibitors

Mitotic inhibitors include alkaloids derived from plants; they block cell division by preventing microtubule formation, thus inhibiting mitosis (M phase).

Vinca alkaloids derived from the periwinkle plant include Vinblastine (Velban), Vincristine (Oncovin), Vinorelbine, and Vindesine.

Podophyllotoxins, derived from the Mayapple, include etoposide and teniposide.

They prevent the cell from entering the G1 phase (the start of DNA replication) and the replication of DNA (the S phase).

Taxanes enhance the stability of microtubules, preventing the separation of chromosomes during anaphase (a stage in mitosis) in the cell cycle.

The first taxane was the natural product paclitaxel, known as Taxol and initially derived from the bark of the Pacific Yew tree.

Docetaxel is a semi-synthetic analogue of paclitaxel.

Estramustine is also a mitotic inhibitor.

Topoisomerase Inhibitors

Topoisomerase inhibitors interfere with both transcription and replication of DNA by upsetting proper DNA supercoiling.

Topoisomerases are essential enzymes that maintain the form of DNA.

Drugs in this group include the

- camptothecans,
- irinotecan and
- topotecan.

Hydroxyurea (Hydrea) inhibits enzymes active in the repair of DNA damage.

L-asparaginase is an enzyme used in cancer treatment that catalyzes the breakdown of asparagines into aspartic acid and ammonia; this agent inhibits the growth of tumor cells that are unable to synthesize L-asparaginase, an amino acid necessary for protein synthesis.

Differentiation-Inducing Agents

Differentiation-inducing agents are used to prevent the onset of frank malignancy by inducing less mature progenitor cells or stem cells to differentiate or continue their progression through stages of normal development into tissues with specific characteristics and functions.

Differentiation-inducing agents may control the expression of specific genes to prevent the progression of a premalignant cell to a malignant state, in contrast to cytotoxic chemotherapeutic agents which cause the death of tumor cells.

This group of drugs includes:

- retinoids,
- tretinoin,
- Targretin, and
- arsenic trioxide.

Cytotoxic properties have been recognized in Targretin and arsenic trioxide, and these drugs have been classified as chemotherapy for registry purposes.

Differentiation agents without a cytotoxic effect are not considered chemotherapy.

Combination Regimens

Many traditional chemotherapy drugs are administered in combination regimens, taking advantage of the different mechanisms of drug action during the cell reproduction cycle to:

- increase tumor response rates,
- prevent or delay the development of drug resistance, and
- modulate side effects of therapy.

A treatment cycle is a round of a chemotherapy regimen administered according to a specified schedule, with the first day of treatment noted as Day 1 of Cycle 1.

Cycles have traditionally lasted 21 or 28 days, to give patients time to recover from hematologic toxicities associated with treatment and to allow tumor cells to reenter cell division phases.

However, with support from hematopoietic growth factors to reduce neutropenia, chemotherapy may be given in more intensive regimens.

The hematopoietic growth factors, such as granulocyte colony stimulating factor (GCSM or Neulasta), are not considered chemotherapy.

Multi-drug chemotherapy regimens are named using the first letter of each drug component: CHOP-R, a regimen used in the treatment of lymphoma, contains:

- cyclophosphamide (C),
- doxorubicin hydrochloride (H),
- oncovin (O), prednisone (P, a steroid), and
- rituxan (R).

Leukemia Regimens

Chemotherapy regimens for leukemias usually include an initial induction phase of intensive therapy to induce a complete remission, followed by a second period of intensive consolidation chemotherapy to increase the remission rate or duration.

A final period of less intensive maintenance therapy may be administed over a prolonged time period to delay disease recurrence or relapse.

First, second, or third line salvage chemotherapies, using different drugs, may be attempted to achieve further remissions in patients who have undergone chemotherapy for many types of cancers but have had recurrence of disease.

Multi-Modality Regimens

Chemotherapy is often given as part of a multi-modality therapeutic approach to treating the patient's cancer.

Any type of therapy administered before surgery (including radiation, chemotherapy, hormone therapy) is designated as neoadjuvant treatment.

Any type of therapy administered after surgery is designated as adjuvant treatment.

When neoadjuvant treatment is given, the patient's clinical stage of disease is given priority in reporting; the patient's pathologic extent of disease will also be determined at surgery, as a measure of the effectiveness of the pre-surgical treatment in controlling or shrinking the tumor.

Targeted Drug Therapies – Monoclonal Antibodies

New targeted drug therapies are being developed to attack cancer cells more specifically than traditional chemotherapy drugs.

Two categories of targeted therapies include *monoclonal antibodies* (names ending in "mab") and *tyrosine kinase inhibitors* (names ending in "nib").

Monoclonal antibodies are:

- engineered in the laboratory, to bind to specific antigens on the surfaces of tumor cells;
- they may induce an immunological response against the target cancer cell, or
- be modified to deliver a toxin (chemotherapy), radioisotope (radiation therapy), cytokine (immunotherapy), or other active anti-tumor drug (chemotherapy).

Monoclonal antibodies are described as chimeric or humanized antibodies, depending on the proportion of mouse and human antibodies used in their production.

Trastuzumab (Herceptin), a humanized antibody, is a human epidermal growth factor receptor 2 inhibitor used in the treatment of breast cancer; overexpressed Her2 receptors promote invasion, survival, and angiogenesis of tumor cells and can cause resistance to cancer therapies.

Rituximab (Rituxan), a chimeric antibody, is specific for the CD20 surface marker on B cells; it has a number of effects on B-cells, including inducing apoptosis of the cells.

Gemtuzumab (Mylotarg), a humanized antibody conjugated with a cytotoxic antibiotic calicheamicin, targets an antigen on leukemia cells and is used in the treatment of relapsed acute myeloid leukemia.

Most monoclonal antibodies were initially classified as immunotherapy; however monoclonal antibodies with a specific cytotoxic effect (other than radiation) have been reclassified as chemotherapy.

Tyrosine Kinase Inhibitors

Tyrosine kinases are:

- enzymes grouped into two classes based on their location on cell membranes-receptors, or within the cytoplasm-non-receptors.
- They play critical roles in cell activities including growth, differentiation, metabolism, adhesion, motility, and death.

Many are involved in oncogenesis by gene mutation, chromosome translocation, or over-expression.

Tyrosine kinase inhibitors suppress the activities of these enzymes.

Others

Imatinib mesylate (Gleevec) targets the abnormal bcr-abl protein in chronic myeloid leukemia cells, occupying the tyrosine kinase active site on the protein.

Geftinib (Iressa) is an epidermal growth factor receptor/tyrosine kinase inhibitor approved for the treatment of non-small cell lung cancer.

Erlotinib (Tarceva) is an epidermal growth factor/ tyrosine kinase inhibitor approved for the treatment of pancreatic and non-small cell lung cancer.

Many other tyrosine kinase inhibitors are under development or being studied in clinical trials.

Drugs that inhibit other pathways of cellular activities are also included in the newer targeted therapies.

Thalidomide is an angiogenesis (blood-vessel formation) inhibitor approved for the treatment of multiple myeloma.

Aflibercept is a vascular endothelial growth factor (VEGF) inhibitor in trial for the treatment of ovarian, fallopian tube, and primary peritoneal carcinomas.

The VEGF are signaling proteins involved in the development of new blood vessels in both embryos and adults.

Bortezumib (Velcade) is a proteasome inhibitor (names ending in “mib”).

Proteasomes are enzymes found in cells which play a role in regulating cell function and growth.

The inhibition of these enzymes can lead to death of cancer cells.

SEER has developed and maintains an online database of drug information to identify the type of cancer therapy delivered by a drug and how it should be coded.

The database is updated periodically as new drugs are developed and more information becomes available about the action of the drug on cancer cells.

SEER*Rx is the standard reference for registry coding of drug-related therapies.

For each substance the database includes:

- generic name,
- brand name,
- abbreviations,
- category,
- sub-category,
- NSC number,
- primary cancer sites for use of the drug,
- chemical name, and
- remarks.

(The NSC number is a universally recognized unique identification number that identifies a specific compound throughout the entire lifespan of that specific agent, not just while it is investigational. (The "NSC" refers to the former Cancer Chemotherapy National Service Center with the National Cancer Institute).

New Techniques

New techniques for the administration of chemotherapy are also being developed and studied in clinical trials.

In electrochemotherapy, short and intense electric pulses are delivered through electrodes to increase the permeability of cell membranes, allowing transport of chemotherapy drugs across the membranes into the cytoplasm of tumor cells.

This technique has been used with Bleomycin, a non-permeant drug, and cisplatin, a low-permeant drug.

Nanoparticle albumin-bound, “nab” technology, attaching cytotoxic drugs to albumin, is under development to take advantage of the tumor cell’s preferential pathway for albumin to deliver nutrients across the cell membrane, and the secretion of the SPARC protein (Secreted Protein Acidic and Rich in Cysteine) to concentrate albumin-bound nutrients within the cell.

Bone Marrow Transplants

Bone marrow transplants enable the use of high-intensity doses of chemotherapy in the treatment of certain malignancies, and also the replacement of diseased bone marrow in hematopoietic malignancies.

Chemotherapy is highly toxic to the hematopoietic system, which is continually undergoing cell division and reproduction to maintain red and white blood cell components, and standard chemotherapy regimens are scheduled to allow hematopoietic recovery between drug cycles.

Procedure

In bone marrow transplant procedures, bone marrow or peripheral stem cells (immature cells circulating in the blood stream) are harvested, a “conditioning regimen” of high-dose chemotherapy with or without total body radiation therapy is administered, and the marrow or stem cells are then reintroduced into the patient, where they replace destroyed tissue and resume normal blood cell production.

The procedure has many possible complications and is reserved for life-threatening diseases.

Newer “mini” transplant procedures have been developed to use lower doses of chemotherapy and radiation which do not totally ablate the bone marrow but carry lesser risks for infection and mortality.

The bone marrow or peripheral stem cells may be taken directly from the patient (autologous transplant).

Peripheral stem cells are now used more commonly for autologous transplants; patients may be treated with daily injections of granulocyte colony stimulating factor before stem cell harvest to boost the mobilization of stem cells from the marrow into the peripheral circulation.

HLA Typing/Engraftment

Allogeneic transplants use marrow taken from a matched donor; syngeneic transplants use marrow donations from an identical twin.

Umbilical cord blood is also used as a source of human stem cells.

With allogeneic transplants, donor and transplant recipient are matched on five human leukocyte antigen genes:

- HLA Type I (HLA-A, HLA-B, HLA-C) and
- HLA Type II (HLA-DR, HLA-DQB1).

Mismatch on Type I genes increases the risk of graft rejection; mismatch on Type II genes increases the risk of graft-versus-host disease.

Graft-versus-host disease is an inflammatory disease of allogeneic transplantation, where the engrafted marrow cells attack the recipient's tissues.

Acute GVHD usually occurs within three months after transplantation, involving the skin, intestine, or liver, and is often fatal.

Chronic GVHD is less often fatal, and may present with recurrent infection and symptoms similar to connective tissue autoimmune disorders.

The "graft versus tumor" effect is a beneficial aspect of GVHD, in which the engrafted cells have an immune reaction to the diseased bone marrow of the recipient, thus putting allogeneic transplants into the category of immunotherapy.

Hormone/Steroid Therapy

Steroids are a general class of fat-soluble chemical substances that are structurally related to one another and share the same chemical skeleton.

They are produced naturally in the body and perform many diverse functions.

Cancer therapy interferes with the natural balance between tumors and two types of steroids, hormones and glucocorticosteroids.

The glucocorticosteroids have anti-inflammatory properties, and cancer therapy takes advantage of their effects on white blood cells.

Hormones are messenger substances which help regulate body functions such as growth, metabolism, and reproduction.

Hormonal therapy depends on the responsiveness of certain tumors to hormonal stimulation, generally breast, prostate, and thyroid cancers; tumor growth is suppressed when this stimulation is removed.

Hormone therapy agents include hormone-releasing factors, hormone synthesis inhibitors, anti-hormones, hormones, and hormonal or endocrine surgery.

Synthetic Agonists

Hormone-releasing factors created in the pituitary gland govern the production and/or release of many hormones.

Synthetic drugs which mimic (agonists) the actions of specific hormone-releasing factors are used in the treatment of breast and prostate cancers, by upsetting the natural balance between the releasing factors and their hormones.

Circulating levels of natural estrogens, progestins, and androgens are regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary.

The release of FSH and LH is controlled by gonadotropin-releasing factor (LHRH) from the hypothalamus.

Agonists or mimics of LHRH (leuprolide, goserelin) given at high doses result in the decrease of circulating levels of estrogens, progestins, and androgens, thus removing their stimulus to tumor growth.

Hormone Synthesis Inhibitors

Aminoglutethimide is a hormone synthesis inhibitor.

This drug blocks the action of several enzymes on steroids made by the adrenal gland, resulting in decreased production of adrenal steroids, especially androstenedione which is converted to estrogen, the source of most estrogen in postmenopausal women.

This drug thus helps in the management of estrogen-responsive breast cancer.

Aromatase inhibitors work on another part of the conversion pathway from adrenal steroids to estrogen, by inhibiting the action of the enzyme aromatase, which converts androgens into estrogens by a process called aromatization.

These drugs have become very prominent in the treatment of post-menopausal women to prevent breast cancer recurrence, as the inhibition of the enzyme leads to profound hypoestrogenism.

Antihormones

Antihormones include substances which are designed to fit into hormone receptors on cell surfaces, blocking the natural hormones from attaching to the receptors and delivering their messages to stimulate cellular processes.

Tamoxifen was the first antiestrogen to achieve widespread clinical use in the treatment of breast cancer, belonging to a class of drugs called selective estrogen replacement modulators (SERMS).

Selective estrogen receptor downregulators (SERDS) block estrogen in all tissues of the body.

Faslodex belongs to this group, and is also used in the treatment of breast cancer.

Antiandrogens, flutamide and casodex, attach to androgen receptors of prostate cancer cells and block the actions of testosterone and dihydrotestosterone in stimulating cell growth.

Hormones

Hormonal agents are also used in therapy.

Somatostatin is a hormone which directly inhibits the release of pituitary hormones, suppresses pancreatic function, and inhibits gastrointestinal secretions; given in therapeutic doses, it is effective in treating secretory tumors of the gastrointestinal tract.

Thyroid hormone replacement after thyroidectomy inhibits pituitary production of thyroid stimulating hormone, which could stimulate tumor growth, and is thus considered an anti-cancer therapy as well as therapy for maintaining normal thyroid function.

Corticosteroids have many uses in the supportive care of cancer patients, but they are considered as anti-cancer therapy in the treatment of hematopoietic diseases in controlling the production of white blood cells.

Dexamethasone and prednisone are synthetic glucocorticosteroids often used in supportive care, but also used as cancer treatments, most commonly in multi-agent regimens for lymphomas, leukemias, and myelomas.

Endocrine Surgery

Endocrine surgery manipulates hormone levels by removing hormone-producing organs-ovaries in pre-menopausal women and testes in males.

Endocrine surgery is not commonly used for breast cancer, chemical ovarian ablation with LHRH agonists being an alternative to surgery.

Orchiectomies are more frequently used in the treatment of prostate cancer, as an alternative to long-term hormonal therapy.

Immunotherapy

Immunotherapy enhances the body's own immune mechanisms in the defense against cancer cells.

Immunotherapy drugs, or biologic response modifiers, include agents to stimulate the immune response, immune molecules engineered with recombinant DNA technology, products of immune cells, and immune cells stimulated to act against cancer.

Active immunotherapy attempts to elicit the body's own response to tumor cells; adoptive or passive immunotherapy delivers activated immune cells to the patient.

Active Immunotherapy

Active immunotherapy agents include BCG, Imiquimod, activated dendritic cells, and vaccines.

BCG is a tuberculosis vaccine, prepared from a strain of the attenuated live bovine tuberculosis bacillus.

It is instilled into the bladder to stimulate a generalized immune response, which has been effective in the treatment of superficial bladder cancers.

Imiquimod (Aldara) is a topical cream that elicits an immune response when applied to skin malignancies, the activated immune cells secreting the cytokines interleukin-alpha, interferon-6, and tumor necrosis factor-alpha.

In dendritic cell-based immunotherapy, dendritic cells, which present antigens to the immune system, are harvested from a patient; they are activated with tumor antigens, and then placed back into the patient.

The tumor antigens on the dendritic cells stimulate a lymphocyte response, which is generalized to all tumor cells presenting those antigens.

Experiments with cancer vaccines are ongoing, with attempts to isolate tumor proteins that will stimulate an immune response.

Currently in a phase 2 study for the treatment of small cell lung cancer is an autologous vaccine composed of dendritic cells infected by a virus with a modified p53 tumor suppressor gene, designed to elicit a cytotoxic response of host lymphocytes to p53-positive tumor cells.

Oncophage is a cancer vaccine approved for use in Russia, but in Phase III clinical trials in the United States for use in treatment of melanoma, renal cell cancer, and sarcoma.

Other cancer vaccines are in development, though none have yet been approved for use in the United States.

Adoptive Immunotherapy

In adoptive immunotherapy (also referred to as passive immunotherapy), activated immune cells directed toward a tumor, or products of immune cells, are administered to the patient.

Cytokines are protein molecules produced by lymphoid cells that act as hormones or messengers between immune cells and other cells outside the immune system.

The cytokine Interferon-alpha has been genetically engineered through recombinant DNA technology for use in treatment.

Interferons make tumor cells more vulnerable to the immune system by increasing antigens, blocking the formation of new blood vessels by tumors, and inhibiting DNA and protein synthesis.

Interferons have been used in the treatment of lymphoma and melanoma.

Another cytokine, interleukin-2, IL-2, produced by T lymphocytes,

- stimulates the growth and proliferation of lymphoid cells,
- causes the release of other cytokines, and
- enhances the activity of immune cells transferred into the patient.

IL-2 has been used in treatment of renal cell cancer and melanoma.

Ontak is a fusion protein combining interleukin-2 and the diphtheria toxin, used in the treatment of cutaneous T-cell lymphoma.

In one form of adoptive immunity, used in the treatment of metastatic melanoma, tumor-infiltrating lymphocytes are removed from the patient's tumor, expanded in the laboratory, and reinjected into the patient along with IL-2.

In another approach, a patient's own T cells are exposed to engineered retroviruses with T cell receptors that recognize tumor antigens, expanded in the laboratory, and then reintroduced into the patient.

Cytotoxins produced by the immune system itself are another category of natural agents that may be used against cancer cells.

Tumor necrosis factor (TNF) is a cytotoxin secreted by activated macrophages to selectively kill tumor cells, principally by interfering with their blood supply.

Other Treatment

Other treatment is a miscellaneous category in registry data collection.

It includes treatments that do not fit into the standard categories for the hematopoietic diseases that were made reportable in 2001, experimental treatments or unknown treatments given in double-blind study protocols, and “unproven” treatment regimens rendered by non-medical personnel or outside the standard medical system.

The treatments for the new hematopoietic disorders, myeloproliferative and myelodysplastic syndromes, include phlebotomy (usually for polycythemia vera), transfusions, and aspirin.

Experimental treatments may include gene therapy, studies in which investigators are attempting to directly modify the genetic structure of cells, to alter mutated oncogenic and tumor-suppressor genes that allow the growth of malignant cellular clones.

Drug treatments given to patients in double-blind protocols are unknown until the studies are concluded and the protocol information released; at that time the specific type of treatment they received is available for registry data collection.

"Unproven" treatments include a wide range of alternative therapies sought out by patients.

Care should be taken to distinguish between nutritional support offered in conjunction with cancer treatment and nutritional "cures" used in place of standard treatment.

Alternative pain management methodologies offered by medical personnel, such as acupuncture and massage, are considered palliative care treatments.

Watchful Waiting

Watchful waiting or expectant observation is a treatment decision most often seen with prostate cancer, some chronic hematopoietic malignancies, and benign tumors in the central nervous system.

The decision is made not to treat at diagnosis, but to keep the patient under close observation until the development of further signs or symptoms indicating progression of disease that may start to threaten the patient's quality of life.

The decision for watchful waiting may be accompanied by a plan for active surveillance, specifying the method for tracking progression of disease and the time interval for conducting examinations or diagnostic tests.