Cancer chemotherapy

Cancer is a disease characterized by a shift in the control mechanisms that govern cell survival, proliferation, and differentiation. Cells that have undergone neoplastic transformation usually express cell surface antigens that may be of normal fetal type, may display other signs of apparent immaturity, and may exhibit qualitative or quantitative chromosomal abnormalities, including various translocations and the appearance of amplified gene sequences.

Such cells proliferate excessively and form local tumors that can compress or invade adjacent normal structures. A small subpopulation of cells within the tumor can be described as tumor stem cells.

They retain the ability to undergo repeated cycles of proliferation as well as to migrate to distant sites in the body to colonize various organs in the process called metastasis. Such tumor stem cells thus can express clonogenic or colony-forming capability.

Tumor stem cells are characterized by chromosome abnormalities reflecting their genetic instability, which leads to progressive selection of subclones that can survive more readily in the multicellular environment of the host. Quantitative abnormalities in various metabolic pathways and cellular components accompany this neoplastic progression. The invasive and metastatic processes as well as a series of metabolic abnormalities resulting from the cancer cause illness and eventual death of the patient unless the neoplasm can be eradicated with treatment.

Cancer Therapeutic Modalities

Cancer chemotherapy, as currently employed, can be curative in certain disseminated neoplasms that have undergone either gross or microscopic spread by the time of diagnosis.

These cancers include germ cell cancer, non-Hodgkin's lymphoma, Hodgkin's disease, and choriocarcinoma as well as childhood cancers such as acute lymphoblastic leukemia, Burkitt's lymphoma, Wilms' tumor, and embryonal rhabdomyosarcoma. In an increasing number of cancers, the use of chemotherapy combined with radiation therapy followed by surgery can increase the cure rate; these include locally advanced bladder cancer, breast cancer, esophageal cancer, head and neck cancer, rectal cancer, and osteogenic sarcoma.

In patients with widespread disseminated disease, chemotherapy provides only palliative rather than curative therapy at present. Effective palliation results in temporary improvement of the symptoms and signs of cancer and enhancement in the overall quality of life.

In the past decade, advances in cancer chemotherapy have also begun to provide evidence that chemical control of neoplasia may become a reality for many forms of cancer. This will probably be achieved through a combined-modality approach in which optimal combinations of surgery, radiotherapy, and chemotherapy.

Combinations of agents with differing toxicities and mechanisms of action are often employed to overcome the limited log kill of individual anticancer drugs. If drugs display nonoverlapping

toxicities, they can be used at almost full dosage, and at least additive cytotoxic effects can be achieved with combination chemotherapy; furthermore, subclones resistant to only one of the agents can potentially be eradicated.

Some combinations of anticancer drugs also appear to exert true synergism, wherein the effect of the two drugs is greater than additive.

The efficacy of combination chemotherapy has now been validated in many human cancers, and combination chemotherapy is now the standard approach to curative treatment of testicular cancer and lymphomas and to palliative treatment of many other tumor types.

Cell Cycle Effects of Major Classes of Anticancer Drugs.

Cell Cycle–Specific (CCS) Agents Cell Cycle–Nonspecific (CCNS) Agents

Antimetabolites

Capecitabine
Cladribine
Cytarabine
Fludarabine
5-Fluorouracil (5-FU)
Gemcitabine
6-Mercaptopurine (6-MP)
Methotrexate (MTX)
6-Thioguanine (6-TG)

Antitumor antibiotic

Bleomycin

Epipodophyllotoxins

Etoposide
Teniposide

Taxanes

Albumin-bound paclitaxel
Docetaxel
Paclitaxel

Vinca alkaloids

Vinblastine
Vincristine
Vinorelbine

Platinum analogs

Carboplatin
Cisplatin
Oxiplatin

Camptothecins

Irinotecan
Topotecan

Antitumor antibiotics

Mitomycin
Dactinomycin

Anthracyclines

Daunorubicin
Doxorubicin
Epirubicin
Idarubicin
Mitoxanthrone

Alkylating agents

Busulfan
Carmustine
Cyclophosphamide
Lomustine
Mechlorethamine
Melphalan
Thiotepa

In general, CCS drugs are most effective in hematologic malignancies and in solid tumors in which a relatively large proportion of the cells are proliferating or are in the growth fraction.
CCNS drugs (many of which bind to cellular DNA and damage these macromolecules) are particularly useful in low growth fraction solid tumors as well as in high growth fraction tumors.

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

Resistance to Cytotoxic Drugs

A major problem in cancer chemotherapy is the development of cellular drug resistance. Some tumor types, eg, malignant melanoma, renal cell cancer, and brain cancer, exhibit primary resistance, ie, absence of response on the first exposure, to currently available standard agents.

The presence of inherent drug resistance is thought to be tightly associated with the genomic instability associated with the development of most cancers. Acquired resistance develops in a number of drug-sensitive tumor types.