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Antineoplastic Drugs : Treatment Principles and Toxicity

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Abstract

The therapy of cancer has improved dramatically during the past half century. This improvement can be traced to a number of factors: a better understanding of cancer's cause and natural history, better technologies for early detection and diagnosis, improved control of primary tumors through surgery and radiation therapy and more effective drugs. The evolution of drug therapy for cancer has progressed rapidly from alkylating agents and antimetabolites to natural products, and most recently, molecular targeted drugs such as imatinib and gefitinib. As our understanding of the biology of cancer improves, new targets for therapy are being identified daily.

Keywords: Antineoplastic drugs, Drug classes, Pathophysiology, Treatment, Toxicity

Introduction

Malignancies arise from excessive cellular proliferation and /or insufficient physiological cell death. The optimum management of a particular malignancy often involves multimodality therapy, primarily including surgery, radiation therapy and chemotherapy. Surgery and radiation therapy are used against localized tumors whereas chemotherapy may be used in management of localized tumors and systemically disseminated malignant cells.

General indications for chemotherapy

1. Primary treatment of chemosensitive local or systemic tumors with curative intent eg:- transmissible venereal tumor or palliative intent e.g. hematopoietic malignancies.
2. Adjuvant treatment, usually with palliative intent, directed against microscopic metastatic disease, after removal of primary tumor.
3. Neo-adjuvant treatment, in which the rationale is to reduce the size of primary tumor in order to improve the chances of its eradication by other means such as surgery.

Cytotoxic drug classes

1) Alkylating agents- mechlorethamine, chlorambucil, melphalan, cyclophosphamide, busulfan, procarbazine, thiotepa
2) Tubulin-binding agents–vincristine, vinblastine, etoposide, paclitaxel
3) Anthracycline antibiotics- doxorubicin, mitoxantrone, idarubicin, epirubicin
4) Other antitumor antibiotics-plicamycin, actinomycin D, bleomycin
5) Platinum analogs- cisplatin, carboplatin
6) Antimetabolites- methotrexate, cytosine arabinoside, 5-fluuorouracil
7) Miscellaneous- L-asparaginase, hydroxyurea

All cells, both normal and neoplastic, progress through the cell cycle which consists of five major steps ;

M- the mitotic phase

G_o- the resting phase

G_1-the intermitotic phase (synthesis of cellular components for DNA synthesis)

S- the DNA synthesis phase

G_2-the premitotic interval (synthesis of cellular components for mitosis)

The growth fraction of a tumor is the proportion of tumor cells which are actively replicating, i.e. are within the cell replication cycle. Microscopic tumors are usually in the log phase of growth with a high growth fraction whereas macroscopic tumors are in the plateau phase with low growth fraction.

Most of the chemotherapy drugs are cell-cycle-dependent and will be most effective against tumors with a high growth fraction. Some of the drugs are cell-cycle-dependent and phase-specific (only kill a limited number of cells with any single drug exposure) whereas some are cell-cycle-independent.

e.g. M phase specific–vincristine, vinblastine, paclitaxel

S phase specific – hydroxyl urea, cytosine arabinoside
S phase specific self limiting - 6 - mercaptopurine, methotrexate
Cell-cycle-independent alkylating drugs, antitumor antibiotics cisplatin, Procarbazine

Treatment Principles

Dosing principles: The objective of cytotoxic therapy is to use the dose regimen that combines maximum antitumor effect with minimal normal tissue toxicity. Cytotoxic agents follow a first order kinetics *i.e*. the same proportion of cells in a tumor is killed with each dose. Cytotoxic agents often have a steep dose response curve and should be used at the highest dose possible to achieve highest log cell kill. Agents should be used at the shortest intervals possible to avoid significant tumor cell repopulation. Dose rates are calculated according to body surface area in square meters as this permits better matching of dose the to the animal's capacity to metabolize drug than dosing per unit of body weight. However, it may be appropriate to calculate dose rates according to body weight in Kilograms whereas processes independent of metabolic rate are important for elimination of drugs such as Melphalan.

Cytotoxic agents have a small therapeutic index. The recommended dose rate for some drugs is the maximally tolerated dose rate (MTD). The MTD may be defined as the rate that has been shown to result in mild to moderate but sublethal toxicity in a significant per cent of patients, or serious toxicity to approximately 5% of normal animals of that species.

Drug administration techniques include systemic administration and local drug administration (intracavitary injection of liquid formulations, intratumoral injections of liquid formulations, superficial application of creams and implantations of slow-release solid formulations).

Agent selection: Treatment with multiple drugs is often more effective than single agents and may delay or avert the onset of clinical drug resistance. When using multiple drugs sequentially or in combination, agents used should have activity against specific malignancy and have different or non overlapping dose-limiting toxicities, different mechanism of action and not be subject to predictable cross resistance.

Drug resistance: It may be intrinsic or acquired and can be categorized in three ways

Kinetic resistance: occurs as a result of small growth fraction. Hence a large primary tumor is in the G_o phase – a problem with large primary tumors especially for cell-cycle-phase-specific agents. This may be overcome by reducing the tumor bulk by surgery/ radiotherapy, by using a drug combination including drugs active against cells in G_o phase, or by scheduling drugs to synchronize cell populations and increase cell kill.

Biochemical resistance: Resistance is due to numerous biochemical mechanisms including those leading to decreased drug accumulation, altered drug metabolism, altered drug targets and enhanced nucleic acid repair capacity. e.g. in canine lymphoma, mechanism of resistance is due to increased drug efflux mediated by P-glycoprotein (a membrane transport protein confer multiple drug resistance to different classes anthracycline antibiotics, vinca alkaloids and taxanes).

Pharmacological resistance: It is caused by poor or erratic drug absorption, metabolism or excretion, or drug interactions. Some forms of pharmacological and biochemical resistance may be overcome by increasing the drug dose, providing that the toxicity to the recipient is minimal or non existent at the current dose.

Chemotherapy toxicity

Toxicity is the major factor limiting maximum drug dose rates. Overall prevalence of chemotherapy induced toxicity has been estimated to be 5-40% for veterinary patients. Cytotoxic agents are more harmful to rapidly dividing cells. Clinically significant acute toxicity most commonly affects the bone marrow, gastrointestinal system and CNS.

e.g. 1. nitrogen mustard, melphalan – acute myelosuppression
2. Alkylating agents – oral mucosal ulceration and intestinal denudation
3. Ifosfamide- most neurotoxic – altered mental status, coma, generalized seizures and cerebellar ataxia.

Acute, low-grade, non cumulative, non hematologic toxicities lasting 1-3 days, e.g. inappetence or mild vomiting, do not usually warrant dose modification. More severe toxicity require 25-50% reduction of the dose or discontinuation of the drug. Clinically significant hematologic toxicity usually due to neutropenia or thrombocytopenia warrants reduction of drug doses. Subclinical hemolytic toxicity, manifest as cytopenia on routine blood cell counts, may not require dose requirements. Dysfunction of organs involved in drug metabolism and excretion, principally liver and kidney may warrant drug dose adjustment. Discontinuation of a specific drug should be considered upon the occurrence of a non-dose-related toxicity such as anaphylaxis. Discontinuation should be considered of evidence of chronic/cumulative toxicity is found, e.g. doxorubicin-induced cardio-

toxicity or cisplatin-induced nephrotoxicity. Many drugs cause vesicant (blistering) or irritant tissue damage of extrsvasated e.g. ActinomycinD, BCNU, Doxorubicin, Ethoposide, Vincristine. Cytotoxic agents may impair fertility and breeding of animals undergoing chemotherapy in unwise. Avoid cytotoxic drug administration during proliferative phase of wound healing.

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