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Recent avenues of chemotherapeutic research

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Chemotherapy of malignancies is now a fifty year old discipline in the complex therapeutic management of cancer patients. In the history of chemotherapy four periods can be distinguished; each of different goal which have various objectives (Table 1).

The approach to drug selection gradually has been changing, as demonstrated in Table 2.

The recent period, based on findings obtained by the methods used in molecular biology can be termed the "molecular period". The main new research categories are: (a) new molecular targets in antitumour drug therapy, (b) synthesis of new drugs exhibiting inhibitory activity against these molecular targets, (c) new concepts emerging from the molecular experimental data.

The molecular targets most frequently investigated are listed in Table 3.

Anticancer drugs are either derivatives of the effective antitumour agents already widely used in the treatment of malignancies, or they are completely new drugs with an original molecular structure. Drug analogues are usually less toxic than the parent molecules or have a broader spectrum of antitumour activity.

Table 1
Objectives of cancer chemotherapy

Period	Objective
Empirical	Antitumour effect; induction of remission, prolongation of survival, tolerable toxicity
Rational	Curative effect on chemosensitive tumours, decreased toxicity
Complex	Curative effect together with surgery and radiotherapy, less toxic drugs
Molecular	Chemotherapy of new molecular targets, quality of life research

Table 2
Drug selection approaches in cancer chemotherapy

Period	Models used
Empirical	Transplantable rodent tumours, tissue cultures
Rational	Nude mice, athymic rodents, other xenograft systems
Complex	Human tumour cell lines, transgenic mice
Molecular	Inhibition of molecular targets (e.g. gene expression, enzyme systems)

Abbreviations: MDR, multidrug resistance; CB 3717, Chester Beatty 3717; 2-CDA, 2-chloroideoxyadenosine; m-AMSA, m-Amsacrin; ADM, adriamycine.

Table 3
New molecular targets

Type	Therapeutic approach	Example
Genetic alteration due to endogenous (hereditary) factors	Reconstitution of normal human genome: gene therapy, chemoprevention	Retinoblastoma, various pediatric tumours, familial cancers: breast, colon, ovary, etc., various preblastomatoses
Altered		
– oncogene expression	$MDR_{1,2,3}$ inhibition topoisomerase I–II inhibition	Sporins, dipins camptothecin derivatives
– enzyme activity	DNA repair enzyme enhancement	DNA ligase activators
Changes in		
– cell cycle	antimitotics	taxanes, new vinca analogues
– apoptosis	increase of apoptosis	apoptosis inducers
– cell surface contact	synthesis of antiadhesion molecules	antimetastatic therapy

The most important analogues recently developed are enumerated in Table 4.

The drugs with a new molecular structure are either rationally designed and proved to be preclinically effective against various tumour models closely associated with human malignancies or they are randomly found to be candidates for serving as antitumour agents, after appropriate screening and testing.

Table 5 demonstrates a list of selected (investigated) drugs categorized according to their probable mechanism of action.

Based on numerous observations published in the literature new concepts have emerged in different research communities. These working theories prompted investigators to verify them in patient treatment. Table 6 gives a short list of those research trends which have the greatest influence on current clinical activities.

Induction of differentiation means any of the procedures aimed at inducing and enhancing DNA repair in tumor cells (towards normality). This is the basis of the idea of chemoprevention. The agents which are capable to initiate "redifferentiation" are naturally occurring substances or chemically synthetized products. Table 7 summarizes the compounds that have been investigated clinically.

Table 4
Antitumour drug analogues currently studied

Group	Drugs
Platinum derivatives	Carboplatin, Iproplatin, Ormaplatin, Loboplatin, Oxoplatin, Cycloplatin
Anthracyclines	Epirubicin, Idarubicin, Pirarubicin, Detorubicin
Vinca alcaloids	Vindesine, Vinorelbine, Vinsolidine
Nitrosoureas	Tauromustine, Fotemustine
Oxazaphosphorines	Ifosfamid, Trophosphamid, Maphosphamid
Antifolates	Trimetrexate, Pyritrexim, 10-ethyl-5-deaza-aminopterin, CB 3717
Cytidines	Azacytidine, 5-deazauridine
Uridines	5-azacytosin-arabinoside
Thymidines	azathymidine
Adenosines	ara-A, 2-fluoro-ara-AMP, 2-CDA, 2-deoxycoformycin
Purines	Tiazofurine
Retinoids	9,13-*trans*-retinoic acid, etretinate, fenretinid

Table 5
The investigated antitumour agents

Mechanism of action	Drugs
Inhibition of the synthesis of	
– DNA	Caracemide
– RNA	echinomycin
– Protein	homoharringtonin, didemnin B
– Polyamines	deoxyspergualin
– Growth factors	suramine
Topoisomerase inhibitors	Camptothecin, topotecan, irinotecan, G-hydroxyellipticin, mAMSA, anthracendiols, anthrapyrazoles, merbaron
MDR reverting agents	Verapamil, nifedipin, nimodipin, niguldipin, dexniguldipin, trifluoroperazin, cyclosporin A, staurosporin
Tubulin stabilizers	Taxans: taxol, taxotere
Membrane-active lipophilic agents	Phosphocholines: edelphosin, ilphosin
Differentiation inducers	HMBA[a], phorbol derivatives
Chemopreventive agents	DFMO[b], MAP[c], finasterid
Heavy metal complexes	Ti, Ru, Mo-derivatives

[a]HMBA, hexamethylenebisacetamid; [b]DFMO, diphenylmethylornithine; [c]MAP, methylacetylputrescine

Induction of apoptosis is an another approach to cancer treatment. Any substance which may induce death in a tumour cell could be considered a potential anticancer agent. Therefore, the enzyme system regulating the cell cycle is also of paramount importance. If any inhibition of a recycling enzyme activity occurs it may lead to cell death (e.g. certain hormones, Bryostatin, etc.).

Since the cell surface of a malignant cell is considerably altered, restitution of the normal fibronectin, laminin, cadherrin content is also essential. Drugs or monoclonal antibodies may restore the cell to cell contact. This might be the future approach to a successful "antimetastatic" therapy.

Table 6
New concepts in drug therapy

Induction of differentiation (chemoprevention)
Enhancement of apoptosis
Inhibition of MDR
Potentiation of drug effect
Supportive drugs, megatherapy
Neoadjuvant therapy

The drug resistance of tumour cell is a major obstacle to the success of cytostatic treatment. Although many mechanisms of drug resistance exist, there is a clear evidence that approximately 60%–65% of the resistance phenomena is due to a 170 kDa glycoprotein found in the tumour cell membrane inhibiting access of any drug to the nucleus. It has been demonstrated that this type of resistance is caused by the activity of the $MDR_{1, 2, 3}$ gene producing large amounts of glycoprotein, its gene product. Any substance which is capable to inhibit the activity of this gene might be a potentially beneficial drug for the cancer patient by overcoming MDR. Table 8 lists the MDR reverting agents clinically tested.

The agents which potentiate the drug effect are presently clinically tested or used widely in treatment of several malignant tumours (colorectal, gastric, head and neck, breast cancer, etc.). Their use is based on the principle that while the amount of a target enzyme may be raised by a non-cytostatic drug, the consecutively administered cytostatic substance may hit an elevated enzyme level, and in consequence the antitumour effect could be greater. The following agents can be cited:

– Leucovorin,
– Thymidine,

Table 7
The differentiation inducing agents

Agent	Type of investigation	
	chemoprevention	therapy
Retinoids		
– 9,13 *trans*-retionic acid – fenretinid	oral leukoplakia other preblastomatoses	
Tamoxifen	preventing relapse and second neoplasm in breast cancer	
Cyclosporin A		M_3 acute leukemia
Tiazofurin		CML, blastic stage
Finasterid	prostate cancer	
DFMO, MAP*	under trial	
HMBA**		lung cancer (too toxic)

*DFMO = diphenylmethylornithine; MAP = methylacetylputrescine; CML = chronic myelogenous leukemia; **HMBA = hexamethylenebisacetamid

Table 8
MDR reverting agents

Group	Agent
Calcium channel blokers	Verapamil, Nifedipin, Nitrendipin, Nimodipin, Guldipin, Dexniguldipin
Sporins	Staurosporin
Topo-inhibitors	Camptothecin analogues
Antimitotics	Etoposide, Tenoposide
Anthracyclines	ADM derivatives

– Azathymidine,
– Diripyridamol,
– Acivicin.

Despite encouraging clinical data it is still unclear whether a cost/benefit analysis would favour the use of these drugs. So far, prolongation of survival seems to be limited and associated with increased toxicity. Nevertheless, new drugs and dose schedules are being developed.

Adjuvant therapy was initiated in a postoperative form more than 20 years ago. Various retrospective metaanalytic studies showed recently its value especially in "high risk" breast cancer. The preoperative form is called neoadjuvant treatment. This combined form of chemotherapy and surgery is still at the stage of exploration. Several data prove that this is the choice treatment in osteogenic sarcomas of the extremities. More long-term observations are needed in the case of head and neck and upper gastrointestinal-tract cancer. New drugs, however, have never been tested either in postoperative or preoperative setting. This might constitute a new research trend for further exploration.

In the "molecular period" of anticancer drug research not only new targets and compounds became available but also supportive drugs to mitigate and avoid the toxicity of the antitumour substances. Various cytokines are capable of preventing or shortening the duration of cytopenias, antiserotonins reduce nausea and vomiting. Broad spectrum antibiotics may maintain sterility in an immune-suppressed patient. There are new drugs with potential activity against cardiotoxicity and studies are in progress in relation to other types of toxicity.

One may conclude that recent avenues of the antitumour drug research are broad enough to increase our hope in the possibility of achieving a successful cancer therapy.