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

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

Table 2

<table>
<thead>
<tr>
<th>Period</th>
<th>Models used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical</td>
<td>Transplantable rodent tumours, tissue cultures</td>
</tr>
<tr>
<td>Rational</td>
<td>Nucle mice, athymic rodents, other xenograft systems</td>
</tr>
<tr>
<td>Complex</td>
<td>Human tumour cell lines, transgenic mice</td>
</tr>
<tr>
<td>Molecular</td>
<td>Inhibition of molecular targets (e.g. gene expression, enzyme systems)</td>
</tr>
</tbody>
</table>

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


<table>
<thead>
<tr>
<th>Type</th>
<th>Therapeutic approach</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic alteration due to endogenous (hereditary) factors</td>
<td>Reconstitution of normal human genome: gene therapy, chemoprevention</td>
<td>Retinoblastoma, various pediatric tumours, familial cancers: breast, colon, ovary, etc., various preblastomatosis</td>
</tr>
<tr>
<td>Altered</td>
<td>MDR1,2,3 inhibition topoisoenzymes I-II inhibition</td>
<td>Sporins, dipirs, camptothecin derivatives</td>
</tr>
<tr>
<td>- oncogene expression</td>
<td>DNA repair enzyme enhancement</td>
<td>DNA ligase activators</td>
</tr>
<tr>
<td>- enzyme activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changes in</td>
<td>antimitotics</td>
<td>taxanes, new vinca analogues</td>
</tr>
<tr>
<td>- cell cycle</td>
<td>increase of apoptosis</td>
<td>apoptosis inducers</td>
</tr>
<tr>
<td>- apoptosis</td>
<td>synthesis of antiadhesion molecules</td>
<td>antimitotic therapy</td>
</tr>
<tr>
<td>- cell surface contact</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The most important analogues recently developed are enumerated in Table 4. The drugs with a new molecular structure are either rationally designed and prove 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 synthesized products. Table 7 summarizes the compounds that have been investigated clinically.

| Table 3 |
| New molecular targets |

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</table>

| Table 4 |
| Antitumour drug analogues currently studied |

<table>
<thead>
<tr>
<th>Group</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum derivatives</td>
<td>Carboplatin, Iproplatin, Ormaplatin, Loboplatin, Oxoplatin, Cycloplatin</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Epirubicin, Idarubicin, Pirarubicin, Detorubicin</td>
</tr>
<tr>
<td>Vinca alcaloids</td>
<td>Vindesine, Vinorelbine, Vinsolidine</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>Tumorustine, Fotemustine</td>
</tr>
<tr>
<td>Oxazaphosphorines</td>
<td>Ifosfamid, Trophosphamid, Maphosphamid</td>
</tr>
<tr>
<td>Antifolates</td>
<td>Trimetrexate, Pyrrotoxim, 10-ethyl-5-deaza-aminopterin, CB 3717</td>
</tr>
<tr>
<td>Cytidines</td>
<td>Azacytidine, 5-deazauridine</td>
</tr>
<tr>
<td>Uridines</td>
<td>5-azacytosin-arabinoside</td>
</tr>
<tr>
<td>Thymidines</td>
<td>azathymidine</td>
</tr>
<tr>
<td>Adenosines</td>
<td>ara-A, 2-fluoro-ara-AMP, 2-CDA, 2-deoxycoformycin</td>
</tr>
<tr>
<td>Purines</td>
<td>Tiazofurine</td>
</tr>
<tr>
<td>Retinoids</td>
<td>9,13-trans-retinoic acid, etretinate, fenretinid</td>
</tr>
</tbody>
</table>
Table 5
The investigated antitumour agents

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of the synthesis of</td>
<td></td>
</tr>
<tr>
<td>- DNA</td>
<td>Caracemide</td>
</tr>
<tr>
<td>- RNA</td>
<td>echinomycin</td>
</tr>
<tr>
<td>- Protein</td>
<td>homoharringtonin, didemnin B</td>
</tr>
<tr>
<td>- Polyamines</td>
<td>deoxyspergualin</td>
</tr>
<tr>
<td>- Growth factors</td>
<td>suramine</td>
</tr>
<tr>
<td>Topoisomerase inhibitors</td>
<td>Camptothecin, topotecan, irinotecan, C-hydroxyellipticin, mAMSA, anthracendiol, anthrapyrazoles, merbaron</td>
</tr>
<tr>
<td>MDR reverting agents</td>
<td>Verapamil, nifedipin, nimodipin, nignudipin, dexignudipin, trifluoroperazin, cyclosporin A, staurosporin</td>
</tr>
<tr>
<td>Tubulin stabilizers</td>
<td>Taxans; taxol, taxotere</td>
</tr>
<tr>
<td>Membrane-active lipophilic agents</td>
<td>Phosphocholines; edelphosin, ilphosin</td>
</tr>
<tr>
<td>Differentiation inducers</td>
<td>HMBA(^a), phorbol derivatives</td>
</tr>
<tr>
<td>Chemopreventive agents</td>
<td>DFMO(^b), MAP(^c), finasterid</td>
</tr>
<tr>
<td>Heavy metal complexes</td>
<td>Ti, Ru, Mo-derivatives</td>
</tr>
</tbody>
</table>

\(^a\)HMBA, hexamethylenetetraamid; \(^b\)DFMO, diphenylmethylenithione; \(^c\)MAP, methylacetylpentacese

Induction of apoptosis is 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 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, cadherinin 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*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type of investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retinoids</strong></td>
<td></td>
</tr>
<tr>
<td>- 9,13 trans-retion-acid</td>
<td>oral leukoplakia</td>
</tr>
<tr>
<td>- fenretinid</td>
<td>other preblastomatoses</td>
</tr>
<tr>
<td><strong>Tamoxifen</strong></td>
<td>preventing relapse and second neoplasm in breast cancer</td>
</tr>
<tr>
<td><strong>Cyclosporin A</strong></td>
<td>M acute leukemia</td>
</tr>
<tr>
<td><strong>Tiazofurin</strong></td>
<td>CML, blastic stage</td>
</tr>
<tr>
<td><strong>Finasterid</strong></td>
<td>prostate cancer</td>
</tr>
<tr>
<td><strong>DFMO, MAP</strong></td>
<td>under trial</td>
</tr>
<tr>
<td><strong>HMBA</strong></td>
<td>lung cancer (too toxic)</td>
</tr>
</tbody>
</table>

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

Table 8
*MDR reverting agents*

<table>
<thead>
<tr>
<th>Group</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>Verapamil, Nifedipin, Nitrendipin, Nimodipin, Guldipin, Dexnigulipin</td>
</tr>
<tr>
<td>Sporins</td>
<td>Staurosperin</td>
</tr>
<tr>
<td>Topo-inhibitors</td>
<td>Camptothecin analogues</td>
</tr>
<tr>
<td>Antimitotics</td>
<td>Etoposide, Tenooside</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>ADM derivatives</td>
</tr>
</tbody>
</table>

- Azathiomydine,
- Diripyradoxol,
- 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.