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The Selectivity of Effectiveness of Cytostatic Agents

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The clinical benefit of cytostatic agents is based on their effect to suppress the symptoms of the diseases with a maximum of intensity and duration and with an indulgence and rehabilitation of the patients as far as it is possible. A complete destruction of pathological cell proliferations is no essential condition of the therapeutic success, since the tumor disease is less characterized by the single tumor cell but far more by its general clinical picture. In hemoblastoses an overlapping of reactive and neoplastic cell proliferations may be observed to some degree. The application of cytostatic agents for the suppression of immune reactions aims at a temporary decrease of cells competent for antibody formation.

In the present time the clinical application of cytostatic agents encloses a broad spectrum of indications. On the one hand there are generalized metastatic sarcoma and undifferentiated carcinoma, on the other hand are immune reactions, while hemoblastoses are found in the middle of this scale.

If the clinical results are considered, a difference among the applied cytostatic drugs is already observed in malignant tumors. In hemoblastoses and immune reactions it becomes most evident that different diseases can be exclusively influenced in an optimal way only by certain cytostatic drugs as earlier clinical experiences have shown. The attempt to enclose the whole scale of malignancy with a *single* compound may be regarded now as useless. Moreover, one may expect further valuable results from a simultaneous and cyclic concentration of several cytostatic agents on *one* indication.

A selectivity of cytostatic effects is dependent from the chemical nature of the drug, from its mode of action and dosage, from localization and speed of activation and from its metabolism and excretion (Tab. 1). The effectiveness of antitumor drugs does not aim selectively at one certain cell system, but at a variety of special cell functions in different cell systems. It is therefore dependent from momentary functions of the cell. From a biochemically different site of action of alkylating compounds, of antimetabolites, of mitotic inhibitors, and of ionizing radiation also different spectra of cytostatic effects are derived, which are partly overlapping. If the effect on the hemopoiesis is considered, for instance, it can be shown, that folic acid antagonists and cytosine-arabinoside are chiefly affecting the erythropoiesis and the

Tab. 1. The selectivity of the cytostatic action is dependent from

A. The cytostatic agent		
	1. Mode of action:	→special cell systems
		→special functions of different cell systems
	2. Applied dose:	concentration
		time factor
		shock therapy-continuous therapy
		locally applied high concentrations
	3. Speed of activation:	accelerated activation
		retarded activation by changes of solubility or encoding of the molecule
	4. Metabolism and excretion:	chemical nature and concentration of metabolites
		mode of transportation
		mode of excretion
B. The proliferating tissue		
	1. Sensitivity:	special cell output
		dedifferentiation
		multiplying effects by combination of several drugs of different modes of action
		increased temperature
		changes of ionic strength
		increased fibrinolytic activity
	2. Acquired resistance to therapy	
C. The recipient		
	1. Degree of malnutrition	
	2. Integrity of defense mechanisms	
	3. Regenerative capacity of hemopoiesis	
	4. Selective protection of hemopoiesis	

promyelocytes, purine antagonists to myeloblasts and plasma cells, nitrogen mustards the reticulum cells of lymphatic tissues, ethyleneimines the lymphocytes and granulocytes and finally sulfonoxydes the granulocytes.

High doses affect less selectively the total proliferating tissues. By application of multiple single doses the selective action may be controlled to some degree. This may be also possible for the range of side effects. A continuous therapy performed throughout several months also acts differently from an intermittent shock-treatment. A continuous therapy with cyclophosphamide (Endoxan) and azathioprine (imuran) suppresses chiefly the gammaglobuline production. The short-time high dosage of these drugs, however, mainly affects the granulopoiesis. The local application allows an increasement of dosage with the aid of an intraarterial or intralymphatic infusion or regional perfusion and makes thus possible a higher concentration of cytostatic drugs in tumor tissues.

The activation time markedly influences the selectivity of action. Quickly, inten-

sively and temporarily acting drugs like nitrogen mustard and tris-ethylene iminoquinone (Trenimon) give a broad scale of actions with an affection of the lymphopoiesis and thrombopoiesis being exceptional intensive. Cytostatic agents, however, with a retarded effect enable a better utilization of extracellular and intracellular concentration differences, and one achieves a greater local effect in the cytoplasm. The influence on higher differentiated cells, especially of late granulopoiesis, of the plasma cell system and of certain carcinomata is therefore more favorable. This retarded activation may be reached by oral application, by a low solubility of 1.4-dimethanesulfonyloxy-n-butane (Myleran) and 1.6-dibromo-1.6-dideoxy-D-mannitol (Myelobromol), for instance, or by encoding the molecule. After the metabolization in the liver, it sets free the cytostatic active groups. This is demonstrated by cyclophosphamide (Endoxan = Cytoxan), P-di(2-chloroethyl)amino-L-phenylalanine (Alkeran), thiadiazole-phosphoramide (Azetepa) and azathioprine (Imuran).

Metabolites of cytostatic compounds may for their part induce cytostatic effects, which influence the scale of actions and the degree of side effects. Thus the transformation in the liver of cyclophosphamide being inactive in vitro and therefore intramuscularly injectible yields only about 10% cytostatic active intermediate products. The active concentration is kept in the serum for 6 hours. Ninety per cent of the compound, however, are excreted by the kidneys, metabolized or unchanged. Thirty to forty per cent of this fraction appear as a cytostatic active form within 9 hours in the urine. Dependent from the time of contact and the given total dose the affection of the mucous membrane of the bladder is not rare. There is an excess formation of preactive metabolites, which is, however, dependent from a minimum concentration of Endoxan applied. Therefore the affection of the bladder is far more frequent after high dosage therapy than after repeated administration of low single doses.

For Myelobromol the mode of excretion favors a retarded activation. After the absorption this compound is excreted in high concentrations through the bile and then is slowly reabsorbed.

The selectivity of cytostatic effects are essentially influenced also by the proliferating tissues themselves. Experiments show that certain tumor cells are sensitive to certain cytostatic drugs almost specifically. Due to the heterogeneous origin of neoplastic cell populations the tumor tissues are composed from a variety of cells with different drug sensitivity.

By a simultaneous or alternate combination of certain antitumor compounds with different action the neoplastic proliferation in the whole may be affected more selectively than by the continuous administration of a single cytostatic agent. This is of special importance in cases of adenocarcinoma, squamous carcinoma, sarcoma and acute leukemia. In cases of carcinoma the response of cytostatic agents is markedly better, when a poor differentiation of the cells is present. In leukemias, however, the degree of response to therapy decreases with increasing dedifferentiation.

A minor modification of the cell sensitivity may be caused by local high temperatures, changes of the ionic strength of tissue by preceeding injections of glucose

or in cases with pulmonary metastases by an increased fibrinolytic activity. It is lower after the acquirement of a specific resistance.

The initial and individual condition also does influence the respond to cytostatic compounds; the degree of malnutrition, dysproteinemia and anemia affect the metabolic properties and the detoxication ability. Furthermore, there should be mentioned the age of the individual and nature of the disease, intercurrent infections and pretreatment. They influence the regenerative property of damaged non tumor tissue. Principally each proliferating tissue reacts in a different way with different time intervals necessary for regeneration. The protection of hemopoiesis by bone marrow transplantation or by a localized cytostatic action during perfusion is very limited.

The knowledge and the consideration of different selective cytostatic effects is a condition for optimal clinical results (Fig. 1). If the clinical effect of cytostatic agents being well to the fare and their different indications are examined to the present state it becomes obvious, that each antitumor drug possesses special indications. On the other hand only a few compounds are acting in an optimal way in a given indication. In cases of polycythemia the ethyleneimines have proved to be active besides the administration of radioactive phosphorus. In acute leukemia antimetabolites like methylglyoxal, vincristinsulfate (Oncovin) and cytosine-arabinoside are

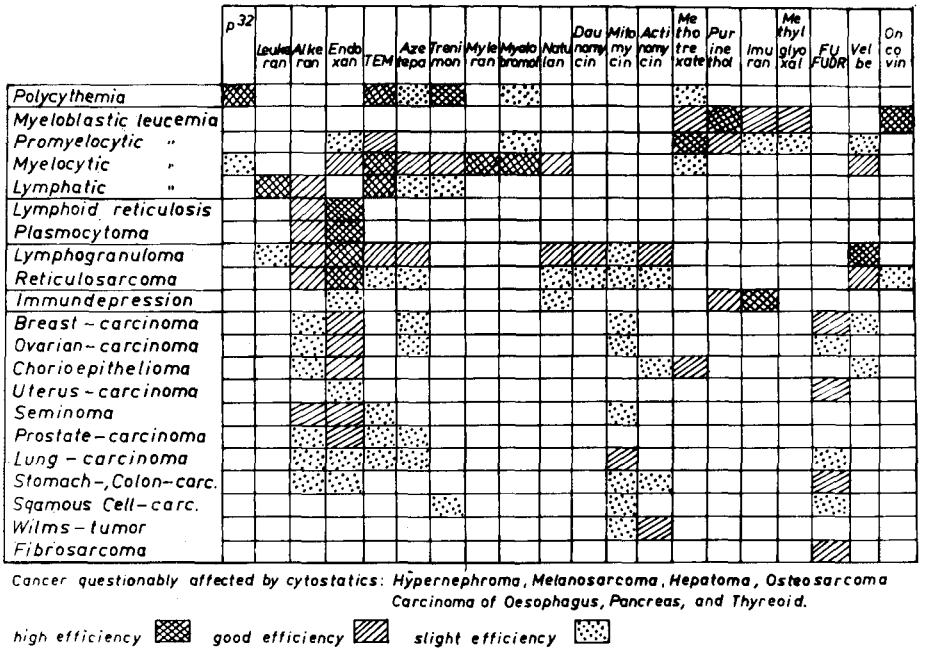

Fig. 1

valuable. Alkylating agents, however, have little effect. On the other hand, chronic myeloid leukemia can be influenced especially by Myleran, Myelobromol and ethyleneimines; also methylhydrazine (natulan), vinblastinsulfate (Velbe) and cyclophosphamide (endoxan) are yielding valuable results. The treatment of lymphatic leukemia now as before is limited to triethylenemelamine (TEM) and chlorambucil (Leukeran). Recently developped cytostatic compounds have given poor results. In cases of plasmocytoma and malignant reticulosis accompanied by paraproteinemia exclusively the nitrogen mustards are successful, provided that they are suitable for continuous treatment due to a delayed activation. In this connection Endoxan was preferred to Alkeran, because the thrombopoiesis was less affected.

Out of 37 continuously treated patients, 20 i. e. 54% showed a marked regression of the paraproteinemia, which was accompanied by a corresponding decrease of the plasma cells and of the lymphoid reticulum cells in the bone marrow. Under an average dosage of 62 g cyclophosphamide given throughout a period of 22 months the serum protein level fell in the mean by 2 g%, due to a decrease of the paraprotein fraction about 20%. The remaining globulin fractions in general were not influenced. In most cases a marked regression of the paraproteins combined with an almost complete normalization of the electrophoretic pattern may be reached not before 6 to 15 months have passed. These improvements usually continue during long-term treatment for years. Only in a final stage the paraprotein levels use to rise again slightly. A statistical comparison of 205 patients with plasmocytoma revealed that the Endoxan-treated group survived more than 22 months and longer in the average.

Similar favorable results can be obtained by a continuous therapy or also by an intermittent shock-therapy in cases of lymphoblastoma. Cyclophosphamide and vinblastinsulfate had especial beneficial effects due to the low thromboclastic action. Alkeran, ethylenimines, actinomycine and, last not least, methylhydrazine, however, give also satisfactory results.

Recently the application of cytostatic agents for the suppression of immune responses has become a new and interesting fact. The proliferation of " potentially competent " cells and their maturation to " competent " plasma cells and lymphoid reticulum cells is the supposition for an antibody formation. It is remarkable, however, that alkylating agents were less active than purine antagonists. The most favorable results were obtained with Imuran. The action of Imuran can be followed up with most precision in cases of kidney transplantation by repeated controls of serum globulin pattern. In one of our patients with a survival of 8 months after renal transplantation, there was observed an increase of the gammaglobulin level despite a high dosage. A distinct decrease followed during a period of additional 3 months which was broken up not until ante finem. In this period of the extreme lack of gammaglobulin all immune globulins were markedly decreased. There was a complete lack of the γ_A precipitation and a weak one of γ_M and γ_G.

For the treatment of liver cirrhosis and fibrosis Imuran was used at first in 10 patients. The mean total dose during a period of 6 months was 28 g. A continuous therapy was established. The mean daily dose was 148 mg. The clinical picture

was favorably modified in all cases. An occasional transitory increase of serum phosphatase values in connection with a short time leukopenia may be regarded as an increased susceptibility of the intrahepatic bile ducts to inflammation.

Electrophoretic controls from 8 patients showed a lasting decrease of serum gammaglobulins up to 0.7 g% in 5 patients, a transitory effect was observed in 3 patients. In controls by ultracentrifugation a mean decrease of the macroglobulin fraction from 6 to 4% and a decrease of the globulins from 32 to 29% were proved. By immune electrophoresis a quite regular decrease of the immune globulins γ_A and γ_M was found in cases with an increase of these fractions before treatment. Thus in one patient was observed a markedly increased γ_G-globulinfraction by agargel- and immune electrophoresis and a distinct increase of γ_A and γ_M immune globulins against polyvalent antiserum and in isolated tests against purified fractions as well.

Five months later the γ_M precipatation line against polyvalent antiserum was not as clearly visible as before. The isolated γ_A and γ_M precipitation did not differ significantly from normal serum at this time. Corresponding to these findings a distinct decrease of the gamma globulins combined with a relative increase of the albumins and decrease of the total protein content was visible by paper electrophoresis.

Cytostatic agents with a marked inhibition of hemopoietic cell systems are less suitable for the treatment of malignant tumors. From alkylating agents only those are valuable for a continous therapy, which are characterized by a delayed activation (cyclophosphamide). Beneficial results are obtained with Actinomycine and Mitomycine. These compounds, however, induce remarkable side effects. Valuable, too, are FU and FUDR and also Oncovin for a combined therapy.

Clinical experiences show that favorable results cannot be obtained in most cases of hypernephroma, squamous carcinoma, melanosarcoma, carcinoma of the esophagus, pancreas and thyroid gland.

The limited selectivity of cytostatic agents and the toxicity of their metabolites impairs a sufficient chemotherapy in the clinic. A comparison of listed main side effects during clinical treatment with antitumor compounds shows that these agents generally induce leukopenia (Fig. 2). In the treatment of malignant tumors this leukopenia is considered yet to be a yardstick for a satisfary chemotherapy. In this connection the decrease of the leukocyte count is combined with a variable decrease of erythrocytes and thrombocytes, too. Trenimon and Mitomycine depress the platelets rather thoroughly. Cytostatic agents with a retarded activation like Myleran, Imuran and especially Endoxan, Natulan and vinca rosea alkaloids this effect is remarkably low. Nausea and vomiting are considerable after natulan, methylglyxal, 5-fluorouracil and 5-fluorodeoxyuridine. These signs are less obvious after Myleran, Purinethol, ethyleneimines and also Methotrexate and Velbe.

Ulcerous stomatitis is observed with some regularity and in a marked degree after antimetabolites. After alkylating agents this phenomenon infrequently occurrs. Diarrhoea is comparably frequent after mitotic inhibitors and after some antimetabolites. Alopecia follows especially the administration of mitotic inhibitors, Endoxan

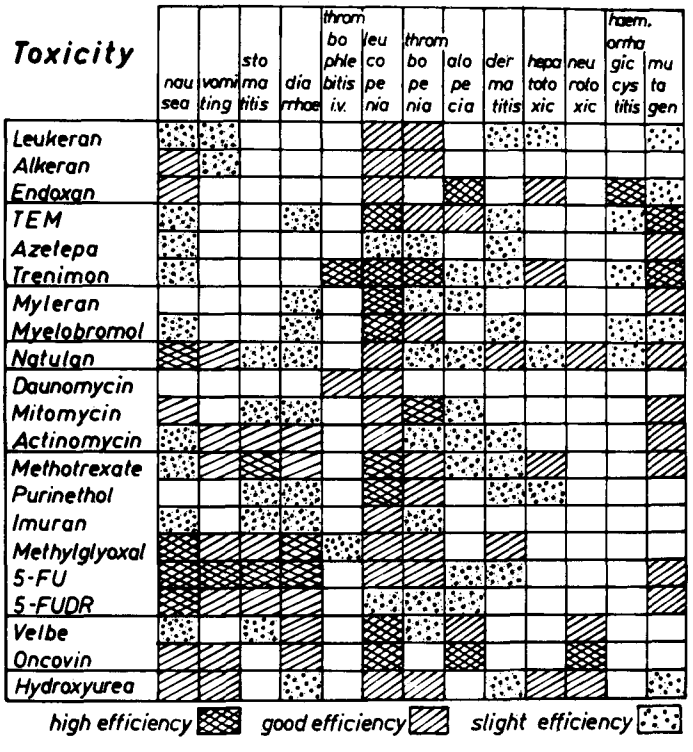

Fig. 2

and TEM. Almost as a rule a hemorrhagical cystitis is observed after alkylating agents, especially after Endoxan.

Remarkable neurotoxical effects are induced by mitotic inhibitors, especially oncovin. Changes of liver functions preponderantly follow the combined application of cytostatic agents and corticosteroids. Various factors influence these changes additionally. The mutagenicity is closely dose dependant and becomes obvious especially in alkylating agents. Some compounds are not mutagenous.

The selectivity of clinical effects of antitumor agents will always be dependant from a variety of factors, which are to consider by the physician. Statements on the selectivity of a cytostatic agent will be always contain comparative data to other cytostatic agents. A thorough knowledge of the remarkable differences of action is necessary for an optimal treatment of the patients.

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Summary

The selectivity of cytostatic action depends of the following factors:

a) the compound, its mode of action, the applied dosage, the localization and the speed of activation, its metabolites and excretion;

b) the sensitivity or resistance of the proliferated tissue;

c) the individual general condition of the patient, the degree of malnutrition, the integrity of defense mechanisms and the ability of detoxication and the regenerative capacity of hemopoiesis.

The action of cytostatic agents directed against specific cell functions of different cell systems develops distinct differences in clinical effects and toxicity among alkylating agents, antimetabolites and mitotic inhibitors. Comparative data of these compounds are given. Due to its selectivity of action each cytostatic agent possesses a specific optimal indication in hemoblastoses, neoplasias or immune reactions.

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RIASSUNTO

La selettività degli effetti citostatici dipende dai seguenti fattori:

a) il medicamento, la dose, la localizzazione e, in particolare, la velocità della loro attività, i prodotti intermedi del loro metabolismo e la loro alimentazione;

b) la sensibilità o resistenza del tessuto proliferato;

c) le condizioni generali del paziente, il grado della sua malnutrizione, integrità dei meccanismi di difesa e capacità rigenerativa dell'emopoiesi.

L'azione degli agenti citostatici diretta prevalentemente contro le funzioni cellulari specifiche di diversi sistemi cellulari, presenta notevoli differenze negli effetti clinici e nella tossicità fra gli agenti alchilanti, gli antimetaboliti e gli inibitori mitotici. Di tali composti vengono indicati dati comparativi. Per la sua selettività d'azione, ciascun agente citostatico possiede una indicazione ottimale specifica in emoblastosi, neoplasie o reazioni immunitarie.

RÉSUMÉ

La sélectivité des effects cytostatiques dépend de:

a) la drogue, la dose, la localisation et, en particulier, la vitesse de leur activité, les produits intermédiaires de leur métabolisme et leur élimination;

b) la sensibilité ou résistance de la tile proliferée;

c) la condition générale du malade, le degré de sa cachexie, la capacité des ses forces défensives et la force de régénération de son hémopoïèse.

Quant à l'effet des cytostatiques, qui se tourne surtout aux fonctions cellulaires différentes, on connait de différences distinctes aussi de l'efficacité clinique et de la toxicité entre les substances alchylantes, les antimétabolites et les antimitotiques, qui sont comparés.

A cause de sa sélectivité d'effet chaque cytostatique possède une indication optimale particulière dans des hémoblastoses, des néoplasies ou des réactions d'immunité.

ZUSAMMENFASSUNG

Die Selektivität cytostatischer Effekte steht in Abhängigkeit von:

a) der Droge, ihrer Dosis, der Lokalisation und insbesondere der Geschwindigkeit ihrer Aktivierung, den Zwischenprodukten bei der Verstoffwechselung sowie ihrer Ausscheidung;

b) der Empfindlichkeit oder Resistenz des proliferierten Gewebes sowie;

c) dem Allgemeinzustand des Patienten, dem Ausmass seiner Kachexie, der Leistung seiner Abwehrreaktionen sowie der Regenerationskraft seiner Hämopoese.

Die vorwiegend auf spezielle Zellfunktionen verschiedener Zellsysteme gerichtete Wirkung der Cytostatica lässt deutliche Unterschiede auch in der klinischen Wirksamkeit und der Toxizität zwischen den alkylierenden Agentien, den Antimetaboliten und den Mitoseblockern erkennen, die vergleichend dargestellt werden.

Auf Grund seiner Wirkungsselektivität besitzt jedes Cytostaticum eine eigene optimale Indikation bei Hämoblastosen, Neoplasien oder Immunreaktionen.

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