CANCER DISEASES, TREATMENT AND CAUSES OF CHEMOTHERAPY FAILURES

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S u m m a r y. Achieving therapeutic success in the form of remission of changes requires a previously planned strategy. Anticancer treatment regimens are flexible, and are modified along with scientific and technical progress. Chemotherapy is used as an independent treatment, it can also be part of combination therapy as complementary chemotherapy, in order to destroy the remaining tumor foci after surgical treatment.
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INTRODUCTION

In the light of modern research, cancer is considered a genetically conditioned disease. Advances in medicine, especially in classical and molecular cytogenetics, have made it possible to learn and describe multifaceted cell dysfunctions. The specificity of these studies is closely related to the use of the latest technologies, modern laboratory equipment and modern diagnostic tests play a key role in the diagnosis and treatment of cancer [7].

CANCER DISEASES AND THEIR TREATMENT

The application of a specific method of oncological treatment depends on many factors among others, the type of cancer the speed of its growth, ability to create metastases and the place where the pathological (primary) change is. Patients with tumors often treat one, particular method. Often, however, there is a need to use several treatments in addition in a specific order. Achieving therapeutic success in the form of remission of changes requires a previously planned strategy. Anticancer treatment regimens are flexible, and are modified along with scientific and technical progress. The

most commonly used methods of treatment are surgical treatment, chemotherapy, radiotherapy and hormonal treatment (hormonotherapy) [3].

Surgical treatment is the oldest method of cancer treatment , it is nowadays aimed at operating at the earliest possible stage of disease, preventing the generalization of the disease process. The optimal solution is to completely remove the lesion with a margin of healthy tissues or amputation of the entire organs and, if necessary, also the neighboring lymph nodes. Surgical palliative treatment aims to reduce the mass of cancerous tissue and improve the quality of life of the patient. Reconstructive treatment minimizes the effects of the course and treatment of the underlying disease, and provides the ability to sustain last physiological functions [2]. Treatment with ionizing radiation, i.e. radiotherapy is rarely used as an independent method of fighting cancer, it is done as a complementary or strengthening of the therapeutic effect of other treatments, including chemotherapy or surgical treatment. Irradiation and damage is caused by the genetic material of tumor cells, water radiolysis occurs, at the same time, the free radicals are also destructively acting on altered cells. The most commonly used therapy (cobalt bomb) as well as cesium radiotherapy. (137Cs) [5].

Hormonal treatment is a pharmacological method of fighting cancers, it is less toxic and gives fewer side effects compared to chemo – and radiotherapy. It plays a big role in the treatment of so- called hormone – dependent neoplasms, used at the right time to prevent or reduce the division of atypical cells. As supportive treatment, it relieves symptoms associated with underlying diseases, reduces inflammation , edema and pain [3].

Chemotherapy is also a pharmacological way of fighting with cancers. Cytostatic drugs used in this method deprive cells of the ability to share or completely destroy them. Cytostatics work in proportion to the rate of cell division and growth, have the greatest impact on tissues with high dynamics of development and growth, the optional effects of therapy can be obtained in the case of cancers of the blood and gastrointestinal tract, acute leukemia and some cancers of the lymphatic system [5].

Chemotherapy is used as an independent treatment, it can also be part of combination therapy as complementary chemotherapy, in order to destroy the remaining tumor foci after surgical treatment. Palliative treatment uses cytostatics to improve the comfort and quality of life of the patient [7].

Cytostatic drugs can be divided into groups using two main criteria:

– according to the mechanism of action, for example: antimetabolites, alkylating agents
– according to the phase of the cell cycle in which they operate
– - acting during cell division, in a specific phase of the cell cycle, e.g. doxorubicin, mitoxantrone, bleomycin. The increase in the dose of these drugs causes an increase in the number of destroyed cells, up to the end of the given cycle phase.
– operating during the partition cycle, regardless of the phase of cycle, e.g. chlorambucil, nitrosourea derivatives. The increase in the dose of the drug causes a linear increase in the number of damaged cells.
– acting independently of the partitioning cycle and the developmental state of the cells, e.g. cisplatin, cyclophosphamide, anthracycline [9].

During the chemotherapy treatment, several medicines are used at the same time. Established multi-drug therapy programs allow optimal use of kinetic properties of cytostatics, each drug is to affect other phases of the cell cycle of the atypical cells, the combined action is aimed at the maximum destruction of the tumor cells at an acceptable level of toxicity [1].

Depending on the degree of cancer sensitivity, we can divide them into two groups for the treatment of cytostatics:

– tumors that respond very well to the treatment (used most often are chemotherapy), there is a clear improvement in the health of the patient, e.g. colon cancer, breast cancer, retinoblastoma, ovarian cancer and small lung cancer
– cancer in which treatment with cytostatics results in a marked improvement in the quality of life and longer life expectancy of patients, however , does not cause a complete cure, e.g. endometrial cancer, bladder cancer, anal cancer, central nervous system tumors and nasopharyngeal cancer.

Chemotherapy, like many other branches of medicine, is constantly evolving and improving. It seems that further directions of development will be based on:

– the search for new drugs and improved forms and analogies of drugs used so far
– searching for unknown so far actions and anti-cancer activity among drugs previously

used in other disease entities.
– determination of new routes of action of chemotherapeutic agents, e.g. by influencing neovascularization of tumor.
– discovering new methods of introducing cytostatics into atypical cells and counteracting their drug resistance [5].

CAUSES OF CHEMOTHERAPY FAILURES

Despite the steady progress of scientific research on the effective use of chemotherapy, it is often noticed a lack of satisfactory treatment effects. The occurrence of recurrent disease, lack of remission of symptoms or insufficient response of the organism to the drug used causes therapeutic difficulties, psychological burden on the patient, and increase the costs of treatment [6].

The most common reasons for the failure to use cytostatic drugs are:
– pharmacokinetic resistance, i.e. the reduction of the actual amount of anticancer drug that enters the cell and effectively works on it.
– cell resistance, i.e. lack of sufficient sensitivity of the cells to the cytotoxic effect of one or many drugs (multidrug resistance).
– increased ability to grow and divide residual tumor cells [1].

Apart from the above-mentioned main reasons for the failure of chemotherapy, there are also a number of smaller ones, such as delayed use of the necessary drugs or reduction of the recommended doses of chemotherapeutic agents due to excessive undesirable effects, incorrect treatment program selection, polyclonal cancer and therefore different response rates of tumor cells per used drugs. The efficacy of pharmacological treatment depends therefore on a number of factors; the individual patient's compliance, the sensitivity of the drug cell, the professionalism of the medical team, pharmacokinetics and the quality of the medications used [5].

Among all the causes of chemotherapy failure one of the most common is cell resistance to cytostatics. This phenomenon was first described in 1979 during the work on the use of aminopterin, the first cytostatics used in acute leukemia. The lack of response of tumor cells to the cytotoxic effect of specific drugs may have different causes and complex etiopathogenesis [1].

Cell resistance can be:
– external or internal
– selective (simple) or multidrug
– congenital or acquired
– active or passive [8].

External resistance is associated with the inability of the drug to enter the cancer cell, associated with lack of awareness of the inadequate bioavailability of the symptom. Internal resistance depends on the individual characteristics of the cancer cell. It can be selective or multidrug. Selective resistance refers to a single drug or specific mechanism of its action. It is often based on the expression of an enzyme protein that inactivates the drug substance. Multidrug resistance is the simultaneous lack of sensitivity of tumor cells to several types of cytotoxic drugs. The main cause of this type of resistance is usually the activity of specific transported proteins, the so-called protein ABC. They remove the drug molecules from the cell into the extracellular space and thus the action of the cytostatics is negated. An example can be the protein P-gp-glycoprotein encoded by the *MDR1* gene, as well as other proteins like MRP 1-6, BCRP. Other proteins that have similar functions and do not belong to the ABC superfamily are, for example, the protein of the LRP [4].

TYPES OF RESISTANCE

Congenital (primary) resistance is characterized by mechanisms occurring in different types of tissues, also in the proper, characteristic feature of a given tissue and not arising only under the influence of pharmacological treatment. This type of resistance often affects patients with a fresh diagnosis of cancer. Acquired resistance (on the ground) arises in the cells originally sensitive to treatment, after having received chemotherapy or radiotherapy they acquire resilience on the resistance side. Active resistance includes the active expression of specific proteins, e.g. DHFR. Passive resistance is related to the reduction of the activity of the target enzyme, e.g. topoisomerase [8].

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