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Plant-derived cytostatic drugs

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SUMMARY

Neoplastic diseases represent the leading causes of mortality in developed countries. A number of pharmacological methods are used to treat neoplasms, and chemotherapy is the most commonly applied method of systemic therapy. Plant-derived cytostatic drugs used to treat neoplastic diseases include: cytotoxic antibiotics, podophyllotoxin derivatives, antimicrotubule agents, camptothecin derivatives and enzymes. Anthracyclines: doxorubicin or mitoxantrone, and other antibiotics, such as bleomycin, dactinomycin and mitomycin, are of great importance among plant-derived antibiotics. The above mentioned drugs are mainly used against hematologic malignancies and solid tumors. The examples of plant-derived compounds whose derivatives are administered to treat some of the neoplasms are podophyllotoxin derived from *Podophyllum pelatum* and *Podophyllum emodi* as well as camptothecin isolated from *Camptotheca acuminata*. Inhibition of malignant growth by disturbing the activity of the mitotic spindle, or more precisely by halting an incorrect process of mitosis, applies to Vinca alkaloids, taxanes and epothilones. Interactions with microtubules of the spindle apparatus are most commonly used to treat such neoplasms as ovarian cancer, breast cancer and Hodgkin lymphoma. Asparaginase is an essential and fundamental enzyme used in chemotherapy of acute lymphoblastic leukemia and also of other malignancies, such as non-Hodgkin lymphomas. The application of cytostatic agents is exceedingly limited because of their frequent toxicity for healthy cells. Nevertheless, the above mentioned plant-derived compounds are successfully used in treatment of many malignancies. Furthermore, comprehensive clinical trials on cytostatic drugs contribute to the improvement of their characteristics, antineoplastic potential and safety of chemotherapy.

Key words: chemotherapy; cytostatic drugs; cancer; hospital pharmacy

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INTRODUCTION

Neoplastic and cardiovascular diseases are the leading causes of mortality both in Poland and worldwide. Based on the epidemiological data of the Polish Union of Oncology and Institute of Oncology in Warsaw, which follow WHO reports, the number of new cancer cases is projected to double to 20 million, cancer-related mortality will increase to 70% and complications of cancer will increase from 6 to 10 million to the year 2020. These data clearly illustrate the scale of the problem and emphasize how mandatory it is to create a new and effective system of cancer treatment [1].

Neoplasm (*neoplasma*) is, according to Williams' definition, a group of abnormal cells that grow excessively in the host organism due to uncontrolled cell divisions. This excessive growth is induced by continuous and unstoppable cell proliferation, even when the triggering factor has been eliminated. Cell proliferation is accompanied by cell differentiation disorders, which are harmful and pointless for the organism. A neoplasm may develop from each tissue capable of replication. Carcinogenesis is a complex and multistep process that usually takes many years with no specific symptoms for a long time [2]. Three phases of carcinogenesis have been distinguished: initiation, promotion and progression. In the first phase – initiation – the carcinogenic factor acts upon a healthy cell causing a genetic mutation that is fixed in subsequent divisions. As a result, the expression of genes engaged in cell cycle regulation: proto-oncogenes, suppressor genes or mutator genes, is impaired or enhanced. The promotion phase is characterized by the accumulation of genetic and epigenetic changes that lead to conversion of a mutated cell into a neoplastic cell. An altered cell undergoes uncontrolled divisions and becomes resistant to signals directing it towards apoptotic death. This stage may last even several years. The last phase of carcinogenesis is progression during which a neoplasm develops and gains the ability to infiltrate tissues and metastasize. This process may last from several months to several years.

Methods of pharmacological treatment of cancer encompass chemotherapy, hormonal therapy and immunotherapy. Chemotherapy is the most widely used method and one of the fundamental methods of systemic treatment. It is used for the treatment of disseminated cancers, inoperable tumors and hematologic neoplasms, e.g. leukemia of various types. It is crucial in cancer treatment and can be applied as postoperative therapy or treatment adjuvant to hormonal therapy, immunotherapy or radiation therapy.

Chemotherapy consists in eradicating cancer cells by administering cytostatic or cytotoxic drugs to the patient. Cytostatics are anti-cancer medications that destroy rebel cancer cells by blocking the cell cycle and activating genetically programmed cell death mechanisms (apoptosis). Plant-derived chemotherapeutic agents have contributed to cancer therapy development and its progress [3].

CLASSIFICATION OF PLANT-DERIVED CYTOSTATICS

Cytostatic medications are a very heterogeneous group of compounds in terms of both structure and mechanism of action. The best explored and the most widely used cytostatics are alkylating agents, antimetabolites and plant-derived medications, classified on the basis of the mechanism of action. Plant-derived cytostatic drugs constitute over 60% of antineoplastic medications and can be divided into: cytostatic antibiotics, podophyllotoxin derivatives, antimicrotubule agents, camptothecin derivatives and enzymes.

Cytostatic antibiotics

Cytostatic antibiotics of the greatest relevance are anthracycline compounds that can be divided into the first generation drugs (doxorubicin (DOX), daunorubicin) and second generation drugs (epirubicin, idarubicin, pirarubicin, aclarubicin, zoribicin and mitoxantrone). Anthracyclines are cell cycle phase-specific substances that were first isolated about 50 years ago from *Streptomyces perceturs* and *Streptomyces casesius*. Their mechanism of action consists in binding with the double DNA helix by inhibiting type II topoisomerase, RNA and DNA polymerases, helicases and DNA-repairing enzymes. These compounds cause the production of free radicals, thus inducing cell oxidative stress, which is responsible for their anti-neoplastic action and cardiotoxicity. Anthracycline antibiotics, being ones of the more important anti-cancer medications, are used in treatment of hematologic neoplasms and solid tumors. Doxorubicin, also called adriamycin, is characterized by very good pharmacokinetic properties: a rapid distribution phase and a slow elimination phase. DOX has a broad spectrum of action and is used for the treatment of leukemias, breast cancer, lymphomas, sarcomas and often in multidrug therapies. Adverse effects of doxorubicin include nausea, vomiting, bone marrow damage and alopecia, but the most serious adverse effect is cardiotoxicity in the form of arrhythmias, conduction disorders and cardiomyopathy. The second cytostatic drug, i.e. daunorubicin, is produced from *Streptomyces peucetius*. It rapidly permeates to tissues from blood after intravenous administration. It is metabolized in the liver to an active daunorubicinol compound. Due to significant cardiotoxicity, daunorubicin is currently used in the treatment of acute lymphoblastic and myeloid leukemia. With time, other anthracycline medications have appeared, namely epirubicin and idarubicin, but neither of them has a more potent anticancer effect than doxorubicin or daunorubicin and neither meets the expectations regarding cardiotoxicity reduction. Pirarubicin, aclarubucin and zoribicin are used in anticancer treatment of acute myeloid, myeloblastic and lymphoblastic leukemias as well as in organ cancers and lymphomas [4,5]. The final synthetic compound belonging to second generation anthracyclines in the group of cytostatic antibiotics is mitoxantrone (MTX), characterized by anticancer, immunosuppressive and immunomodulating effects. This drug reduces the activity of type II topoisomerase, damages DNA as well as inhibits T cells, B cells, macrophages and antibody production. MTX is used in the treatment of leukemia, breast cancer, liver cancer, ovarian carcinoma, prostate cancer and gastric carcinoma. It is also used in patients with secondary progressive and relapsing-remitting multiple sclerosis. High cardiotoxicity is also the factor that limits the use of mitoxantrone in anticancer therapy. Cardiotoxicity induced by anthracyclines can be counteracted by Dexrazoxane (Cardioxane) that, by chelating intracellular iron, prevents the formation of anthracycline–iron complexes, which, in consequence, inhibits the formation of oxygen free radicals, thereby protecting the myocardium from damage [6,7].

Cytostatic antibiotics also include bleomycin (BLM), a glycopeptide antibiotic obtained from *Streptomyces verticillus*. This compound forms an active complex with iron, thereby causing DNA strand breakage and cell cycle inhibition at G2 and S phases, which results in cancer cell apoptosis. Anticancer therapy makes use of a polypepide mixture of bleomycin A_2 and B_2 (blenoxane) mainly in squamous cell carcinoma of the neck, esophagus and head, and Hodgkin lymphoma. Bleomycin is characterized by relatively low toxicity. It does not damage the bone marrow, but bleomycin-induced pneumotoxicity is significant [8,10].

Dactinomycin is an example of a phase-nonspecific antibiotic that acts on proliferating cells in all cycle phases and exerts weaker action on cells in G_0 phase. Its mechanism of action consists in the interaction with the DNA minor groove and inhibition of RNA polymerase, thereby suppressing transcription and ribosomal RNA formation. Dactinomycin is used mainly in the treatment of childhood cancers, such as Wilm's tumor, Ewing sarcoma, as well as germ-cell tumors and hydatidiform mole. Some of the more significant adverse effects of this drug include: oral mucositis, nausea and vomiting, alopecia, and myelosuppression [9].

Mitomycin, also called Mitomycin C, is a cytostatic antibiotic derived from *Streptomyces caespitosus*. In the organism, it is reduced to its DNA-alkylating derivative and acts in all cell cycle phases. Mitomycin is broadly used: locally in the treatment of superficial urinary bladder cancer, or in combination with radiotherapy and fluorouracil in anal carcinoma, breast cancer, pancreatic cancer, stomach cancer, and squamous cell carcinoma of the cervix. Adverse effects of this drug are specific for alkylating drugs: nausea and vomiting, oral mucositis, alopecia and myelosuppression [9,10].

Podophyllotoxin derivatives

Semisynthetic podophyllotoxin derivatives, i.e. etoposide and teniposide, also called lignans, are important plant-derived cytostatics. They are derived from *Podophyllum pelatum* and *Podophyllum emodi*. The mechanism of action of podophyllotoxin alone consists in inhibiting tubulin polymerization, as in the case of Vinca alkaloids. Podophyllotoxin consists of a five-ring system containing a lactone ring where modifications at the C-4 position in ring C result in enhanced anticancer activity. However, it is not used clinically due to high toxicity. The mechanism of action of podophyllotoxin derivatives is completely different than that of the mother compound. They act mainly as type II topoisomerase inhibitors, thus suppressing DNA-repair processes and replication. This results in a dose-dependent cessation of cell division in S phase or in early G_2 phase.

Etoposide is used both intravenously and orally in the treatment of acute myeloid and lymphoblastic leukemia, testicular cancer, gastric cancer and lymphomas. When combined with cisplatin, etoposide is used as first-line therapy in generalized small-cell lung carcinoma. Teniposide, however, is administered to patients with Hodgkin lymphoma, non-Hodgkin lymphoma, breast cancer, testicular cancer and CNS cancers. Lignans induce adverse effects, such as: nausea and vomiting, myelosuppression, diarrhea, alopecia and necrosis at the site of administration [10–12].

Antimicrotubule agents

Drugs used in anticancer therapy disrupt cell nucleus division, which precedes the division of the entire cell. This inhibits divisions of pathological cells, leading them to the apoptotic pathway. Restricting cancer cell proliferation by affecting microtubules, which are an element of the karyokinetic spindle, is one of the therapy methods. Inhibition of malignant growth occurs by disturbing the activity of the mitotic spindle, or more precisely by halting an incorrect process of mitosis. Antimicrotubule agents include 3 groups of compounds: Vinca alkaloids, taxoids and epothilones.

Vinca alkaloids are a group of compounds derived from *Vinca rosea Linn.* They include: natural compounds, such as vinblastine and vincristine, and semisynthetic compounds, including vinorelbine, vindesine and vinflunine. *Catharantus roseus G. Don*, i.e. rose periwinkle, produces more than 130 terpenoid indole alkaloids, but only natural vinblastine and vincristine have anticancer properties. All Vinca alkaloids are phase-specific drugs and act on cell cycle phase M. Their mechanism of action consists in bonding with tubulin and inhibition of microtubule formation, and thus karyokinetic spindle formation, resulting in inhibition of mitosis at the metaphase and in apoptosis. These compounds are commonly used in palliative cancer treatment and in treatment with curative intent. Vinblastine, being a natural alkaloid, is broadly used in the treatment of

Hodgkin lymphoma, testicular cancer, breast and lung cancers, non-Hodgkin lymphomas, neuroblastoma, and many other types of cancer. Its toxicity results in bone marrow injury in the form of leukopenia and thrombocytopenia as well as in gastrointestinal injury. Vincristine, however, is used in the therapy of acute myeloid and lymphoblastic leukemia, non-Hodgkin lymphomas, reproductive organ cancers, breast cancer, bladder cancer and Hodgkin lymphoma. Adverse effects of vincristine include neurotoxicity, peripheral neuropathies and muscle weakness. The group of semisynthetic Vinca alkaloids includes vindesine and vinorelbine, which are vinblastine derivatives. The former substance is used in acute lymphoblastic and myeloid leukemia, Hodgkin lymphoma, colorectal carcinoma, lung cancer, melanoma, lymphomas or metastatic breast cancer. Vinorelbine is characterized by a narrower spectrum of use, encompassing non-small-cell lung carcinoma and advanced breast cancer. The latest semisynthetic vinorelbine derivative, i.e. vinflunine, is used in breast cancer, non-small-cell lung carcinoma and urinary bladder cancer [11,12].

The second group of plant-derived compounds acting on the karyokinetic spindle is taxoids, also called taxanes, which include paclitaxel and docetaxel. Paclitaxel was first isolated from the bark of western yew (*Taxus brevifolia*), but is currently produced semisynthetically from *Taxus baccata,* as is its analogue docetaxel. The mechanism of action of taxanes consists in promoting microtubule formation and stabilization through depolymerization inhibition. This leads to suppression of normal cell division in the mitotic phase. The effect is dose-dependent. At high concentrations, microtubule polymerization is stimulated, while at low concentrations, the microtubule dynamics is stabilized with no increase in their mass. It has also been observed that taxoids are additionally capable of promoting macrophages to synthesize TNF (tumor necrosis factor) and interleukin-1.

Paclitaxel and docetaxel are used in chemotherapy of breast cancer, urinary bladder cancer, ovarian carcinoma, non-small-cell lung carcinoma, Kaposi's sarcoma in the course of AIDS, and in head and neck cancers. Both these substances are the most effective cytostatics in the treatment of metastatic breast cancer. Paclitaxel is often used in combination with cisplatin or carboplatin, for instance in chemotherapy of epithelial ovarian carcinoma. Despite such a broad usage of both taxanoids, they are characterized by high neurotoxicity, myelosuppression, gastrointestinal disorders, and the occurrence of unfavorable multidrug resistance [12,13].

Epothilones are new generation natural compounds derived from soil-dwelling bacteria *Sorangium cellulosum,* isolated for the first time in 1993. Two compounds are distinguished as the representatives of the group: epothilone A and epothilone B, which differ from each other in the presence of a methyl group. The mechanism of action is based on cell proliferation inhibition by tubulin aggregation, thereby preventing microtubule depolymerization. This causes cessation of mitosis at phase G_2 and activation of apoptosis. Epothilones are capable of binding with class I and III ß-tubulin, which supposedly makes them superior to taxanes in terms of their efficacy. It is believed that these compounds break cancer cell resistance to taxoids. Five epothilone analogues can be distinguished: ixabepilone, patupilone, BMS-310705, epothilone D, and ZK-EPO. These compounds are a subject of clinical trials, particularly in breast cancer, ovarian carcinoma, testicular cancer, pancreatic cancer, melanoma, colorectal carcinoma and non-small-cell lung carcinoma. Epothilones practically always produce adverse effects in therapy, such as diarrheas, neutropenia and neuropathy, but are a huge step in oncology as they initiate new treatment pathways [14,15].

Camptothecin derivatives

Camptothecin derivatives are type I topoisomerase inhibitors and include irinotecan and topotecan. They are semisynthetic derivatives of a natural quinoline alkaloid, i.e. camptothecin, derived from Tibetan tree *Camptotheca acuminata*. The mechanism of action consists in type I topoisomerase inhibition, which leads to the formation of one-strand DNA fragments that block DNA replication. They stabilize covalent bonds between DNA and type I topoisomerase, which is responsible for DNA strand breakage during replication. As a result, the lack of the DNA helix unity leads to DNA structure damage and cell death. Being well-soluble in water, camptothecin analogues are phase S-specific. The first of the analogues, irinotecan, undergoes enzymatic transformation in the organism to SN-38, a compound of greater activity and more potent cytotoxic action compared to the parent compound. It can be used in the therapy of gastric and esophageal cancers, but it is mainly applied in combination with 5-fluorou-

racil and leucovorin in the therapy of metastatic colon cancer and rectal cancer. Topotecan undergoes hydrolysis in the organism to a pharmacologically active lactam form. It is used mainly in second-line treatment of metastatic ovarian cancer and non-small-cell lung carcinoma. Irinotecan and topotecan are also used in the therapy of cervical cancer, breast cancer, pancreatic cancer, renal carcinoma, liver cancer, and head and neck malignancies. Type I topoisomerase inhibitors cause bone marrow suppression, mainly neutropenia, and gastrointestinal disorders manifesting with nausea, vomiting and diarrheas. The absolute contraindication to the use of irinotecan is gastrointestinal obstruction, as this is life-threatening [11,16].

Enzymes

Asparaginase is a natural and crucial enzyme in cancer therapy. It was isolated from *Escherichia coli* and *Erwinia carotovora*. Asparaginase is characterized by hydrolase activity. It catalyzes L-asparagine cleavage into aspartic acid and ammonia. Anticancer properties of L-asp were discovered in guinea pig serum in the 1960s. This enzyme exerts cytostatic action towards cancer cells characterized by low L-asparagine synthase activity, which results in dependence on the presence of an exogenous amino acid. Exogenous asparaginase leads to asparagine breakage, and then in the inhibition of nucleic acid and protein synthesis in cancer cells. The greatest activity of proliferation inhibition is observed in cell cycle G_1 phase. *E. coli*-asparaginase occurs in the native form and in a form bound with polyethylene glycol. They differ from each other in pharmacokinetic parameters, immunogenicity and adverse effects. That is why dose adjustments to these parameters is essential to achieve therapeutic activity of this drug.

L-asp is one of the fundamental drugs used in the treatment of acute lymphoblastic leukemia and also of other malignancies, such as non-Hodgkin lymphomas. It causes injury to the coagulation system, gastrointestinal tract, liver, kidneys and pancreas. It often causes hypersensitivity in the form of local reactions (erythema, rash), and even generalized symptoms, such as anaphylactic shock or even central nervous system disorders [17].

DISCUSSION

Chemotherapy, being the most common form of treatment in cancer patients, is undergoing constant changes, and its dynamic development underlines the need for further search for new effective therapeutics. In the era of increasing cancer incidence and very common resistance to cytostatics, new data on their mechanisms of action are particularly valuable. Plant-derived substances have a very broad spectrum of therapeutic action and are used in almost all disease entities. There are, however, limitations to their use, associated with relatively frequent and serious adverse effects. Vinca alkaloid- or paclitaxel-specific neurotoxicity or myelosuppression, or cardiotoxicity in anthracycline therapy serve as the examples. New targeted therapies, more and more frequently used in the treatment of solid tumors, have a potential to improve outcomes and limit adverse effects. Apart from toxicity of natural cytostatics, another obstacle in their use is also poor solubility in water, which concerns, for instance, camptothecin. Cancer cell resistance is a significant issue associated with anticancer effect of certain plant-derived drugs. Drug resistance largely limits or prevents effective treatment, while combined therapies yield better outcomes.

CONCLUSIONS

Apart from plant-derived cytostatics approved clinically for use in oncology, a number of plant-derived preparations with anticancer properties are believed to soon become dominant in clinical trials. A careful exploration of anticancer effects of plant-derived substances is incessantly being a subject of investigation. That is why new innovative analogues or forms of drugs containing the aforementioned cytostatics are expected to emerge.

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