FLARAXIN IN CANCER COMPLEX MEDICAMENTOUS THERAPY

Immune- and phytotherapy lately become one of the most essential components of adjuvant antitumoral therapy. This way must be entered into general strategy of oncologic patients treatment that by now causes on doubt. The application of medicines able to lower manifestation of intoxication symptoms caused by oncologic process progress or chemotherapy complications promotes immune-biochemical homeostasis normalization and is able to change positively the quality of life of these patients.

Several points can be underlined in complex approach plan to treatment of oncologic patients. Thus, particularly, presence of expressed antimetastatic and cytostatic activity in some plants should be mentioned, that allows to recommend them as polychemotherapy component. In the cases when impossibility of chemotherapy is clear because of cytostatics intolerance or process desolation, the use of medicines of immunotropic series can become the only way of treatment. Some sources mention even presence in plants (for example, aconite) the ability to suppress gene of multiple medical stability activity, that makes their application desirable in complex with chemotherapeutic schemes.

Vegetative immunomodulators have particularly no syntactic analogues, but their application, as it is seen, allows to solve a number of important problems. Such as preparation of the patient to chemotherapy and ensuring of its maximal effectiveness and lowering of the risk of side reactions, conducting of independent antirelapse treatment, conducting detoxication on the basis of connecting and further removing of circulating immune complexes, protein products of tumoral catabolism.

Property of vegetative preparations to lower and sometimes prevent algesic syndrome in oncologic patients is also important to mention. Forbidding to narcotic analgetics in such situations is one of the most important moral-psychologic moments.

It is essentially to mention, that preserved deficiency of attention to the given therapy on the side of official oncologic services is essentially based on deep-rooted

point of view about weak oncolytic activity of immunotripic and phytotherapeutic series preparations.

Besides it should be mentioned that sometimes difference between phyto- and chemopreparations has relative character. Such well-known antitumoral chemopreparations as vinblastin, vincristin, etoposid, taxol have vegetative pharmacochemical basis.

The way of medicine extraction from vegetative raw stuff is the essential principle for differentiation of phytopreparation and chemopreparation of vegetative origin. Standard chemopreparations, as a rule, are multicomponent or contain homogenous pharmacochemical groups, extracted from vegetative raw stuff with the help of multistage chemical procedures with obligatory application of powerful extragents and dissolvents.

The received phytopreparations presume application of such methods of extraction, which allow to extract a wide spectrum of medicines, being in such chemico-biological unity they had in native plant. This provides mild ways of extraction (particularly, infusion and decoction) under minimal application of chemical extragents (more often, ethyl spirit).

Probably this is the reason why most of phytopreparations have no allergenic effect peculiar to chemotherapy, and do not promote the development of medicine disease. According to the data of literature most biologically-active substances (BAS) of vegetative origin are not deprived of the mentioned disadvantages.

The principle problem mentioned in oncotherapy is connected with medicines ability to suppress essentially tumoral growth. Scientific point of view that suppression of tumoral growth is necessarily connected with toxic influence on the patient’s organism should be recognized baseless. Apparently this point of view is based on the fact, that antitumoral preparations must kill tumoral cell, that will naturally influence normal cells.

Though, if we address modern conceptions, we’ll see absolutely different situation: tiny effect on cell surface can essentially change cell metabolism through cascade regulation mechanism. Mechanism of apotropic influence on tumoral cell

according to the way of ligand-receptory influence is preferable for many chemopreparations by now. All this testifies to the fact, that tumoral preparation effectiveness stipulates for specific character to transformed cells membranes determinants more than its destructive activity. This mechanism of influence is close to the identical one in antitumoral hormonal preparations. Phytotherapeutic influence on tumor, as it should be considered, is realized through this very mechanism.

Among phytochemical agents, realizing this influence vegetative polyphenols and bioflavonoids famous for their biological importance can be found, as well as *flaraxin,* which is described here, can be related to them.

Short characteristic of vegetatitve polyphenols.

Vegetative phenol compounds (such names as polyphenoles, bioflavonoids are also known) were considered wastes of vegetative organisms with doubtful medical reputation just in the 1-st half of the last century, when impetuous development of organic chemistry began. In plants in comparison with animals, final vital activity products do not eliminated into environment but accrue in organs of local secretion. Cell walls performing this function in plans are much thicker and denser, than in animals. In tree types cortex is formed due to them, which is the most spread source of tannic phenol compounds.

Benzene circle is a structural basis of all phenols, it is interesting that it forms a kind of chemical “water dividing line” between plants and animals metabolism. The latter are not able de novo to synthesize this organic complex, though most of its derivatives (aromatic aminoacids, melanin, etc) are inseparable part of animals metabolism.

This fact forces to think about possible pharmacologic importance of vegetative phenols.

It is known, that biological importance of some vegetative components was proved just in the 19^{th} century, which were later called vitamins. In fact researchers paid attention that the source of vitamins is often found in those parts of the plant, which are usually moved off during food preparation. The most exvisit potential sources of phenol compounds in food allowance of a modern man are cortex and

leaves. That is why vegetative polyphenols particularly come to the organism of a man as biologically active substances or medicines. In vegetative nature biosynthesis of phenol compounds is performed in the way of acetic acid condensation with poly-β-cetosystem formation, which as a result of aldole condensation produces the compound of phenol structure with resorcin or phloroglucin skeleton.

Character of aromatic compound: phenolecarboles, flavonoids, anthraquinones, etc. depends on the way of cyclization and character of organic acid, taking part in condensation together with acetic acid.

The given metabolic way can be considered as an original mechanism of acetic acid utilization in vegetative world, leading to its transformation into biologically active substances. In comparison with plants and microorganisms acetic acid in man in free state does not metabolize but supplies energetic needs of the organism in the way of acetil-KoA through Crebs cycle.

At present organic chemistry of vegetative phenols gives practically exhaustive characteristic of these compounds, that cannot by now be said about understanding of its pharmaco-biological role.

Medical-biological importance of flavonoids

One of the most famous biological properties of vegetative phenols is their antioxidant activity. In natural conditions phenol actioxidants are thought to regulate division of vegetative cells, performing the function of original growth factors.

In 60-70th of the last century classical research by N.N.Emmanuel showed, that free radical reactions play an important role in carcinogenesis. Accumulation of antioxidants in tumoral tissue blockade mechanism of free radical inhibition of cell division, promoting proliferation. Thus under certain circumstances vegetative phenols inserted from outside can strengthen the action of endogen antioxidant system, accelerating tumoral growth. Antitumoral effect of endogen phenols, on the contrary, is explained by their ability to suppress antioxidant synthesis of tumoral cells – ubichinon, tocopherol, etc.

The process of chemical cancerogenesis is associated with antioxidant function. Thus, one of the most famous groups of cancerogenes is aromatic

polycyclic carbohydrates, which obtain mutagenous activity after oxidation transformations in organism with oxydase activity. Microsomal oxidases perform oxidative desactivation of the most part of heterologous toxic organic combinations by several ways: hydroxylation, demetilation, desamination, etc. Thus, polycyclic aromatic cancerogenic carbohydrates are neutralized by hydroxylation.

Presence of additional phenol hydroxyl in a molecule of aromatic cancerogene makes its chemical intercalation difficult – interaction with azotic bases and interbuilding inside nucleic acid spiral.

Except influence on cancerogenesis mechanism, phenol compounds play direct role in tumor growth suppression. Polyphenols estimation as antitumoral preparations is especially interesting for us, though antioxidant activity read above is also connected with this.

Antitumoral effect of vegetative phenols is explained by various mechanisms. Thus, cetachines and leukoantocianidines, being forerunners of tannic substances, have properties of suppressors of free radical reactions. Ellage acid and ellagotanines, as it was proved experimentally, suppress ascite carcinoma growth. For some natural phenols like leukopellargonin, leukoaytacianide, leukodolfinidin presence of potentiating properties relative to antitumoral alkylating preparations was found.

Other factors of neoplastic growth inhibition by vegetative polyphenoles besides antioxidant-antiradical mechanism of influence on tumoral process are considered. Thus, presence of flavonoids of inhibition ability relative to mitochondrial and cytoplastic ATFs is marked, which can cause glycoside suppression, being main source of energy provision in a number of malignant tumors. Ellagotanins antitumoral activity mechanism is also connected with chinines inactivation and blood circulation violation in tumoral tissue. Semichinone and chinone derivatives of pyrokatechine have alkylating effect. Connecting with pirimidin DNA bases, they block division and cause death of tumoral cells. Identical properties are arrogated to pyrogallol and gallic acid derivatives, inhibiting cell cycle in G-1 stage.

Coumarin and its derivatives manifest the ability to violate vaccinability and metastatic potential of experimental tumors, that is explained by microsomal oxidases activity suppression.

Known antitumoral preparations tamoxifen and antrachinone (antracyclin) antibiotics are also phenol complexes. Tamoxifen, derived synthetically, contains three phenol circular structures, which provide blockage of estrogen of tumoral cells receptors, that inhibits their proliferation without system toxic manifestations.

Antracyclin antibiotics have an ability to transform semichinone complexes, connecting with azotic DNA bases. In this case the treatment process is often accompanied by system side effects typical for alkylating compounds.

It is prominent, that wide structural diversification of polyphenol compounds provides many-sidedness of their influence on tumoral process. Besides it is necessary to mention, that because of weak accent and selectiveness of antitumoral activity most of bioflavanoids did not find application in oncologic practice. Though their low toxicity under high biologic activity deserves employment.

Flaraxin as a representative of antitumoral bioflavonoids

Speaking about antitumoral activity of vegetative phenols above, we connected it mainly with mechanism of semichinin-chinin transformation. The more expressive is shift to the right in the system of “phenol-semichinin-chinon”, the higher is pharmacologic activity, and the toxicity grows essentially.

Taking into account nontoxicity of most vegetative phenols, we must address other chemical mechanisms of their biological activity realization. This demand is especially actual if we address flaraxin clinical characteristic. Thus, we wanted to pay attention to the bioflavonoids reactions with tyol-disulphic proteins system.

Essential role belongs to tyol-disulphic links in tertiary-quarter protein molecule organization. Tyol groups are included into active centers of the whole row of ferments and define specificity of their activity.

Usually tyol-disulphic transformations under interaction with flavonoids are explained by the reactions of phenol hydroxiles (OH-) with tyol (SH-) protein groups. In this case disulphic (SS-) links are formed on account of tyol groups loss, protein

redox-potential is decreased and rigidity of protein molecule increases, i.e. its ability to enter biochemical reactions lowers.

This mechanism of interaction with proteins is well shown on example of cytostatics.

At the same time clinico-pathophisiological research showed, that flaraxin activity on serous proteins has no typical character. On the contrary, sometimes this interaction leads to increase of protein redox-potential under tyol groups growth and decrease of disulphic links. Thus, flavonoids activity can be accomplished not only through ferment activity inhibition, but also through its activation. Immunomodulating and other sanogenic effects by some vegetative phenols we observed on the example of flaraxin can develop in the same way.

Flaraxin treatment characteristic

The application of flaraxin as antitumoral preparation is essentially connected with its immunomodulating and adaptogenic influence on organism. Early research in vitro showed the ability of flaraxin to induce production of endogen interferon (gamma and alpha) and tumor necrosis factor.

Our clinoco-pathophysiological observations of oncologic patients who got flaraxin, also manifested expressed positive immunotropic effect of the preparation. It was expressed in immune status normalization, particularly in such functional indices of cell immunity as cytotoxic (killer) lymphocyte activity and increase of T-lymphocytes relative number. These changes were marked both in patients being in the state of remission and under metastatic oncologic process. In last cases it was seldom possible to stabilize the state of the patient for a long term (up to 1,5 year), reducing or eliminating negative clinic symptoms (pain, appetite lowering, weakness, etc).

Besides, it should be mentioned that flaraxin oncologic effect does not exceed, according to our observations, 1-2%. Though, under mutual application with cytostatics the preparation can essentially strengthen antitumoral influence.

Thus, under injecting flaraxin in standard regime with additional application of one of recommended cytostatics (cyclophosfan, 5-fluorouracil, cytabarin) in doze 1/5

– 1/10 of the date doze, we marked essential improvement of clinical results, than in the case when only flaraxin was applied. All mentioned patients were with desolated forms of cancer process and had essential risk for standard schemes of polychemotherapy performing. The treatment scheme suggested by us not only caused no complications, but even allowed to reach improvement of general blood analysis indices (level of hemoglobin, number of erythrocytes, SES) and immunograms (first of all we pay attention to lymphocyte killer activity increase)

Thus, accounting accruing experience of flaraxin clinical application as well as clinic-pathophysiologic and experimental research, we can summarize most optimal regimes of flaraxin application in oncologic patients.

Thus, application of flaraxin is quite justified for conducting antirelapse treatment, independently from the character of oncologic process. The treatment can begin at once (in the first week) after operation or finishing radial therapy. If after finishing radial treatment or chemotherapy abrupt lowering of hematologic indices or immunodepression takes place, i.e. requires special therapeutic correction, the application of flaraxin should be postponed up to the end of the mentioned correction therapy. But the application of the preparation should not be delayed if it was not managed to normalize negative consequences of cytostatic and radial therapy. In such patients the application of flaraxin can be combined with hematotropic and immunotropic medicines.

The antirelapse course itself is preferable to conduct in the way of 16-days injections (150 mg a day). The break after 8 injections (not more, than a week) is possible, if there were problems with intravenous injections and undefined complications on the intolerance of the preparation were noticed. Before and after treatment it is preferable to conduct immune indices control.

In patients tolerant to injections course we marked, as a rule, increase of killer lymphocyte activity (up to 70% and more) and relative number of T-lymphocytes (80% and more).

If the patient feels general tiny discomfort during the course of treatment (as a rule it is revealed in the form of some weakness), temporary increase of temperature

up to 37,5^{0}C, it is advisable to prolong intervals between the injections up to 1-3 days and make breaks between semi-courses (8 injections) up to 10-14 days.

Under expressed negative symptoms (they often manifest in the way of abrupt intestinal violations and long-term increase of temperature up to 38 – 38,5^{0}C the application of the preparation should be stopped.

Negative reaction on flaraxin, as our observation showed, strengthened by clinic-pathophisiologic research, are not the consequence of its toxicity but the result of the sensibilization of the patient, who received preparations containing polyphenol groups. More often biologically active substances (BAS) served as densibilizators, containing bioflavonoid components. Sometimes it was noticed in patients who for some time (not less than two weeks) received suppositories with flaraxin. On this ground we consider receiving of suppositories with flaraxin unwanted before and between injection courses of the preparation.

If the patient receives antirelapse course of chemotherapy, it is better to prescribe flaraxin between such courses. In this situation the course can be limited by 8 injections. It is better to check the use of the preparation effectiveness by immunology indices dynamics.

As for general number of antirelapse therapy courses it is possible to take into account general practice, i.e. recommend not more than 7 courses (16 injections in each). Though practically direct follow-up to chemotherapeutic schemes is hardly possible. Thus, breaks between flaraxin courses is preferable to make not less than 2 months in duration. This term is necessary for decrease of possible sensibilization to the preparation, it is stipulated for minimal time, necessary for natural immune complex elimination.

If the signs of sensibilization appear at the end of the course (worsening of the preparation intolerance) it is preferable to add the final of the course with some plasmapharesis sessions (not less than 5, if sedimentational or gravitational method of plasma separation is used or both under membrane plasmopharesis).

However even under good initial intolerance of the preparation after the 2-nd – 3-rd courses symptoms of sensibilization of the preparation are noticed. They are

more often noted if the patient received BAS, medical herbs, suppositories with flaraxin. If in this case negative dynamics of immunology indices is revealed, it is preferable to refuse receiving flaraxin.

Attention should be paid to the following moment: in oncologic patients having no burdened anamnesis (inclination to allergic reactions, receiving BAS, etc.), early development of sensibilization symptoms (after one or two injections), have negative prognostic hue. As a rule, it points on the presence of atypical proteins in the patient organism, inclined to the formation of complex antigens with medicines.

The application of flaraxin under desolated forms of cancer process is at present practically the main way of the preparation application. In most cases the patients who were refused in chemotherapy and who were subjected to all the stages of standard treatment turn to flaraxin. These patients often manifest the signs of cancer "intoxication", i.e. high level of atypical serous proteins, inclination to hypersensibilization and other homeostasis violations.

We did not manage to perform treatment approximately in half of such patients: after 2-3 injections expressed negative symptomatic was developed. As a rule, practically in all alike cases we managed to find the reason of hypersensibilization, stipulated for receiving of medicines or BAS identical with flaraxin in pharmacochemical characteristic.

Besides, it should be mentioned, that in single cases the identical pharmacologic anamnesis can practically be excluded up to 100%. Though the patients gave negative symptomatic, particularly on first injections of the preparation. Clinically it was usually revealed by abrupt pressure lowering, increased general weakening during first hours after the injection and remained for 1-2 days.

As the following retrospective analysis showed all these patients were in preterminal or terminal state (in some cases injections were performed in 1-2 days before death. We consider, that the given reaction on the preparation in such patients can be explained by the beginning of proteins denaturation. It is confirmed in the research, which showed, that in terminal period (it is true not only for oncologic patients) growing lowering of redox-potential of serous blood proteins takes place.

Possibly new-formed disulpheric links make serous proteins so rigid, that they are unable to connect medicine under its intravenous injection. In this case receptors of tissue homeostasis have to receive the whole “pharmacologic blow” on themselves that is revealed by corresponding negative symptoms.

If under presence of metastatic process the patient feels relatively satisfactory, the scheme of flaraxin injection can be the same as under antirelapse therapy. In this case it is better to repeat 16-days courses not earlier, that in 2 months. Special attention should be paid on change of preparation tolerance during the last third of the course. Appearance of hyper sensibilization symptoms and negative immunology dynamics during the course of treatment must be restraint moments for the following course of treatment. However, among such patients successful 4-5 courses on the background of stable clinical symptoms often happen during 1,5-2 years.

As the result it should be mentioned, that injection preparation flaraxin can be considered as a reserve medicine in treatment of oncologic patients. In the basis of flaraxin antitumoral activity immunomodulating and commiting mechanisms of influence on organism and tumor are found.

The first is manifested by immune system cell link activation, the second – by direct influence on tumoral cells, first of all on their membrane receptors.

Interaction of thiolotropic flaraxin groups with conformationally unstable (atypical) proteins, produced by tumoral cells, to our mind, is a biochemical basis of both mechanisms. Copies of these proteins are initially present on tumoral cells membranes and secondary adsorbing on other cells, probably mainly on immune system cells.

Elimination of such proteins, often observed by us in the process of flaraxin treatment is in itself a positive moment, as it lowers negative system influence of the tumor on organism, normalizes immune-biochemical homeostasis.

Thus, flaraxin can be considered as a preparation of not only direct antitumoral activity, but also of system immunotropic and adaptogenes influence, that is especially important under complex influence on oncologic process. 05.12.13

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