Ministry of Healthcare of Ukraine
Ukrainian Center of Scientific Medical Information and Patent Licensing Activity

Use of the National Antineoplastic Drug of Platinum on DNA carrier at Treatment of the Advanced Forms of Malignant Neoplasms

(Methodological Recommendations**)**

Kiev – 2010

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CONTENT

THE LIST OF ABBREVIATIONS

PPL – Polyplatillen
LC – lung cancer
SC – stomach cancer
PC – pancreas cancer
CC – colorectal cancer
BT – beam therapy
CT – standard chemotherapeutic methods of treatment
Surgery – surgical methods of treatment

Introduction

Timely diagnostics and treatment of malignant neoplasms plays a considerable role in preservation of health of the population of Ukraine. Number of patients who were diagnosed with «malignant tumor» is approaching 1 million. Annually doctors define over 160000 of new cases.

Urgency of the problem of rendering of the adequate specialized help to the patients aggravates due to a high proportion of the newly-diagnosed patients with advanced stages of malignant neoplasms – on the average up to 40 %. Within a year from the moment of making a diagnosis lethality makes 35 %. About 66 % of newly-diagnosed patients in Ukraine get antineoplastic treatment, including exclusively surgical treatment – 34 % combined and complex treatment – no more than 32 %.

Today achievement of successes in treatment of oncological pathology is in many respects conditioned by a very rapid development of chemotherapy in comparison with other methods of antineoplastic intervention. New antineoplastic medications are being implemented, treatment regimens are being improved, possibilities are being extended and results of treatment of oncological patients are being improved.

The real breakout in chemotherapy of malignant tumors is application of platinum medications which till now remain the basic component of the majority of modern protocols and treatment regimens. At the same time absence of selective effect on a tumor leads to development of side effects and complications. Accordingly different organs and systems are malfunctioning that additionally raises endotoxicosis of oncological patients and negatively influences the quality of the patients' life.

Modern platinum drugs show high antineoplastic activity, but at the same time nephro - hemato - and other kinds of toxicity.

It is toxicity that owing to chemotherapy in most cases usually limits full range treatment that leads to initiation of the further research of new antineoplastic drugs with strengthening its selective effect on a tumor and decreasing toxicity concerning healthy tissues.

Creation of platinum compound with biopolymer became a defining step in the solution of the specified above problems. Immobilization of cis-isomer of dihlorodiamminplatinum into exogenous high-molecular DNA caused considerable decrease in the general toxicity and also development of tumors resistance to platiniferous cytostatics.

Polyplatillen – chemical name poly(hexacos-[chlorideammineaqua-platinum(II)])-μ-deoxyribonucleate is a compound of cis-isomer of dihlorodiamminplatinum with the high-molecular carrier – deoxyribonucleic acid (DNA), created by national scientists. (The patent for the invention № 86338 "Antitumor agent based on platinum compound with DNA and method of its production" is registered in the State register of patents of Ukraine on inventions on 4/10/2009).

Randomized clinical research was carried out on three clinical bases:
1) *Kyiv Municipal Oncological Hospital.*
Abdominal surgery department.
69, Verhovinnaja Str., Kiev;
2) *Institute of Oncology of the AMSU.*
Department of general oncology and premalignancies.
33/43, Lomonosov Str., Kiev;
3) *Chair of Facultative Surgery of the Lviv State Medical University of Daniel Galitsky*.
Lviv.
(Total number of patients who took part in a randomized clinical research is 1036 patients with LC, SC and PC).
Methodological recommendations present a new solution to the increase of efficiency of chemotherapy of advanced and resistant malignant neoplasms with the use of innovative national antineoplastic drug – Polyplatillen, on the basis of multicenter randomized clinical research taking into account the requirements of evidentiary medicine.
The invention of Polyplatillen medication was distinguished by the Diploma of the winner of the All-Ukrainian competition “Invention-2009” in a special nomination “For development of new technologies in pharmaceutics”.
Methodological recommendations are meant for oncologists and experts who are engaged in organizing the fight against cancer.
Methodological recommendations are prepared in Ukraine for the first time.

1. Pharmacological characteristics of the drug

Pharmacological group of the drug is antineoplastic means, platinum compounds, the international code – ATC L01XA05.
Polyplatillen chemical name is poly(hexacos-[chlorideammineaqua-platinum(II)])-μ-deoxyribonucleate.
PPL is produced in the form of a sterile clear solution (a concentrate to prepare solution for infusions), packed by 250 ml in glass bottles. 1 ml of the concentrate solution contains 1.47 mg of the active substance.
Storage conditions: PPL should be stored in a dark place at temperature +15 – +25 C°, shelf life – 2 years. Sterility of the depressurized drug in the concentrate is 7 days, the increase in opalescence degree is acceptable.
It is not recommended to freeze the drug.
No PPL antidote was found.

2. Features of the mode of action

Selectivity of PPL action on tumor cells was raised due to covalent binding of the active substance – platinate with exogenous high-molecular DNA.
Property of fast proliferating tumor cells to engage substantially exogenous DNA leads to the maximum accumulation of an active component of the drug in a tumor.
PPL causes morphological changes in the cell structure damaging permanently the cells which are at G1-S phase of a cell cycle, through the mechanisms of apoptosis and necrosis that finally leads to permanent destruction of malignant cells.
The main links of the mode of action of the drug are connected with the presence of ions of platinum on DNA-carrier which damage DNA, RNA, ATF-phase and tubulin molecules – the major biological objects of tumor cells.
The PPL mode of action is caused by its ability to get into a cell with its subsequent translocation through plasmalemma with the subsequent distribution in cytoplasm, and also through phagocytosis with transformation of macromolecules in phagolysosomes.
The further destiny of the drug in tumor cells can be various: concentration of derivatives in chromatin with the subsequent cells apoptosis, PPL accumulation in cytoplasm compartments and formation of large autophagic vacuoles, and also diffuse scattering in cytoplasm. PPL presence in nuclear chromatin structure is a morphological confirmation of the influence of this chemomedication on the genetic apparatus of the malignant neoplasms cells.
Being released from platinum ions, DNA molecules can take part in various stages of an exchange of nuclear acids of the recipient, including integration into his genome, strengthening PPL antineoplastic effect.

PPL shows antineoplastic properties due to its ability to brake nuclear DNA synthesis, permanently damages first of all the cells which are in S-phase of the cycle. High antineoplastic activity and reduction of a tumor size is marked already at the first administration of PPL, thus there is no damage of healthy tissues. The medication is effective at therapy of tumors with the acquired medical resistance to another chemomedications.
After PPL infusion concentration-time pattern of the drug in blood plasma is characterized by two phases: the initial phase with the effective half-life 6.4 hours and a wash-out phase – 72 hours.
After a single infusion the average percentage value of platinum which is washed out with urine within 2 days with the intervals of 0-12, 0-24 and 0-48 hours makes approximately 20 % of the administered dose of platinum that indicates considerable not-renal clearance. PPL is washed out through a digestive tract and, unlike others chemomedications, does not show considerable nephrotoxic effect.

3. Results of patients treatment in retrospective. Conclusions of randomized research and clinical experience.

High antineoplastic activity of PPL at relatively smaller toxicity in comparison with antineoplastic medications which are applied at standard schemes of chemotherapy is proved in clinical conditions.
Low hemato-, nephro-, oto-, neurotoxicity of PPL was determined that has provided a possibility of carrying out chemotherapeutic treatment of the patients to whom the standard antineoplastic therapy is counter-indicative.
Efficiency of PPL application for the patients with advanced forms of LC, SC and PC is confirmed by the results of morphological research, according to which PPL in a therapeutic dose does not cause permanent structural changes of internal organs, showing the expressed antineoplastic property.
Morphological research at ultrastructural level testifies to penetration of molecules of the platinum medication into cytoplasm and nucleus of tumor cells that leads to their permanent damage (pathological mitoses, apoptosis).

1. PPL positive influence on the survival rate of the patients with the advanced forms of LC was noted: the maximum life expectancy of the patients was 40 months; the average life expectancy (ALE) – 10.3 ± 0.8 months; with a median – 8.0 ± 0.8 months; for the patients treated under the standard regimens the corresponding indicators were lower and made 22 months, 6.1 ± 0.2 months ± 1 month, 5.0 ± 0.2 months ($p < 0.05$). The established antineoplastic sensitivity
of non-small-cell lung cancer to PPL therapy testifies to the advisability of its application in the treatment regimens of such patients.

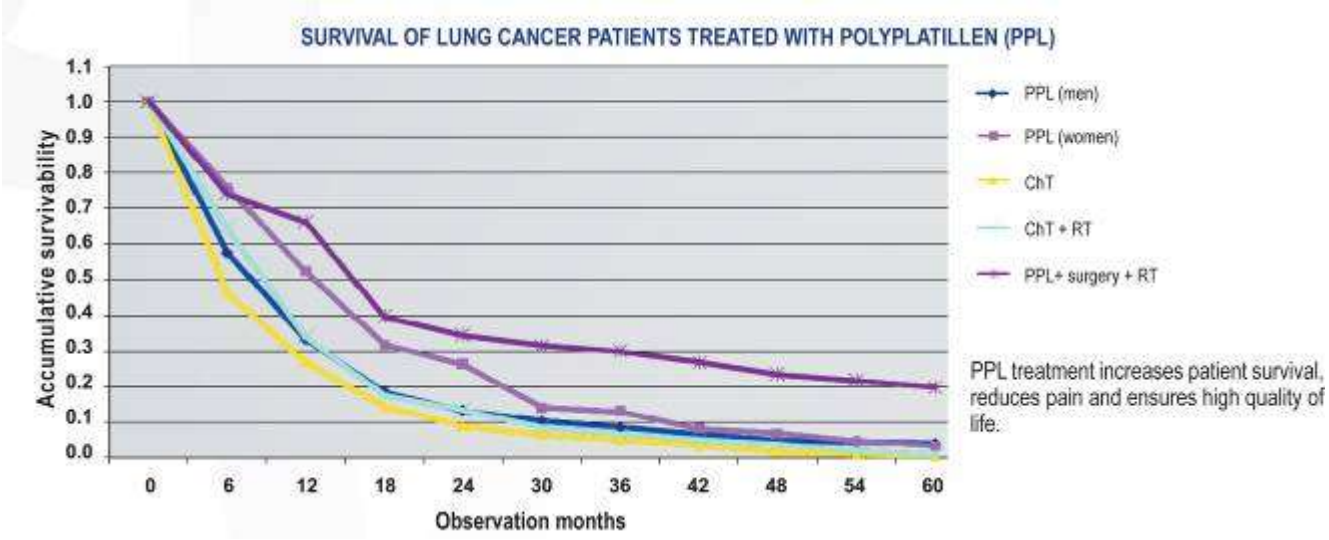
2. PPL application for the patients with the advanced forms of SC without ascites presence significantly increases the average life expectancy by 11.8 months ($p<0.05$), with ascites — by 4.2 months (<0.05) in comparison with the reference group. The patients with ascites manifestations showed the decrease of accumulation or absence of

ascitic liquids at 30 % of cases when treated with cisplatin and at 85 % of cases when treated with PPL.

3. At PPL application for treatment of the patients with the advanced forms of PC the increase in the average life expectancy by 2.9 months is marked, the survival rate medians by 1.5 months, the maximum life expectancy by 10 months in comparison with the reference group ($p < 0,05$) is marked.
According to the data of the National cancer-register of Ukraine for 2010, 1510 of the patients were treated with PPL who had the advanced forms of cancer mainly on III-IV stages of oncological process.
All patients were given from 3 to 6 courses of chemotherapy.
As a result of treatment due to application of PPL medication it was possible to achieve the objective effect (full and partial remission) at 55 % of patients, at 35 % – the stabilization of the oncological process and to prevent metastatic damage of organs and systems.

Results of treatment of the patients with the advanced LC

At treatment of the patients with LC at IIIB-IV stages with PPL application the high survival rate of 3 and 5 years was achieved.
Below is a table of Kaplan-Meier estimates of survival rate for the patients with LC treated with PPL.

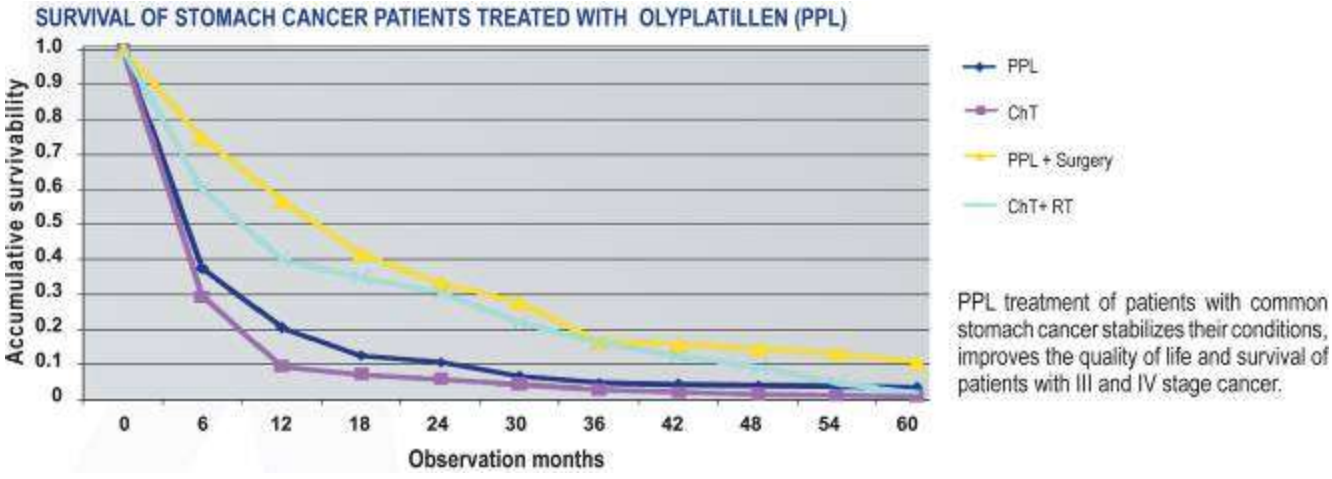


PPL application in the monochemotherapy mode and in combination with other chemomedications allowed us to reach statistically significant improvement of the results of treatment of the advanced forms of LC.
At inclusion of beam therapy in PPL treatment of the patients the tendency of increase of efficiency indicators of treatment of the patients with LC is revealed. Combination of the various chemotherapeutic means influencing various molecular targets of a tumor cell allows to overcome effectively the radio resistance of a tumor and to increase a general antineoplastic effect.
In this connection the expansion of a spectrum of polychemotherapy regimens on PPL basis in combination with beam therapy to increase the treatment efficiency is necessary.
At the same time the expressiveness of PPL medical effect did not depend on a minute

structure of tumors, the drug had almost identical antineoplastic effect on the patients both with small-cell and non-small-cell LC.

Character of antineoplastic action of PPL on the patients with the advanced forms of SC

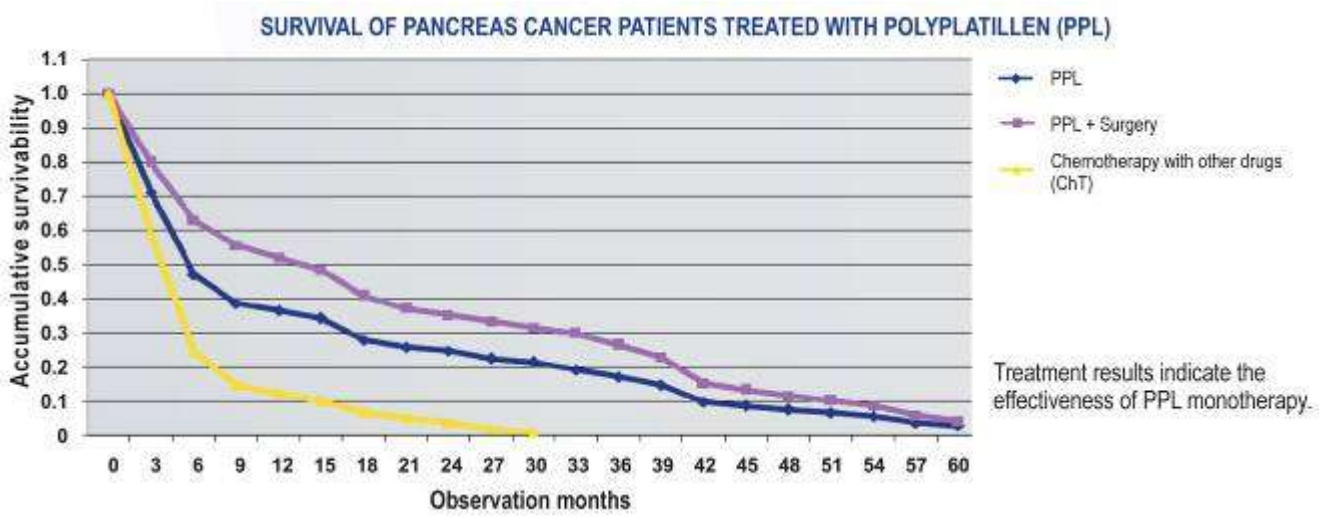
At PPL treatment of the patients with SC at III-IV stage, at 85 % of them who had ascites intraperitoneal administration of the drug caused significant reduction or disappearance of accumulation of ascitic fluid.
PPL application at treatment of the patients with the advanced forms of SC positively improves the quality of life, stabilizes the status of the patient, improves life expectancy indicators of the patients at III-IV disease stages.
The results of adjuvant therapy of SC supplement the data on the efficiency and safety of PPL medication and besides show PPL efficiency at ascitic forms of SC, carcinomatoses and polyserosites.



Improvement of the life quality of the patients is preconditioned by high medical effect of PPL and low toxicity. The results of ultrastructural changes in SC cells after chemotherapy neoadjuvant courses is the evidence to this. These researches were carried out on an operational material after the patients treatment.

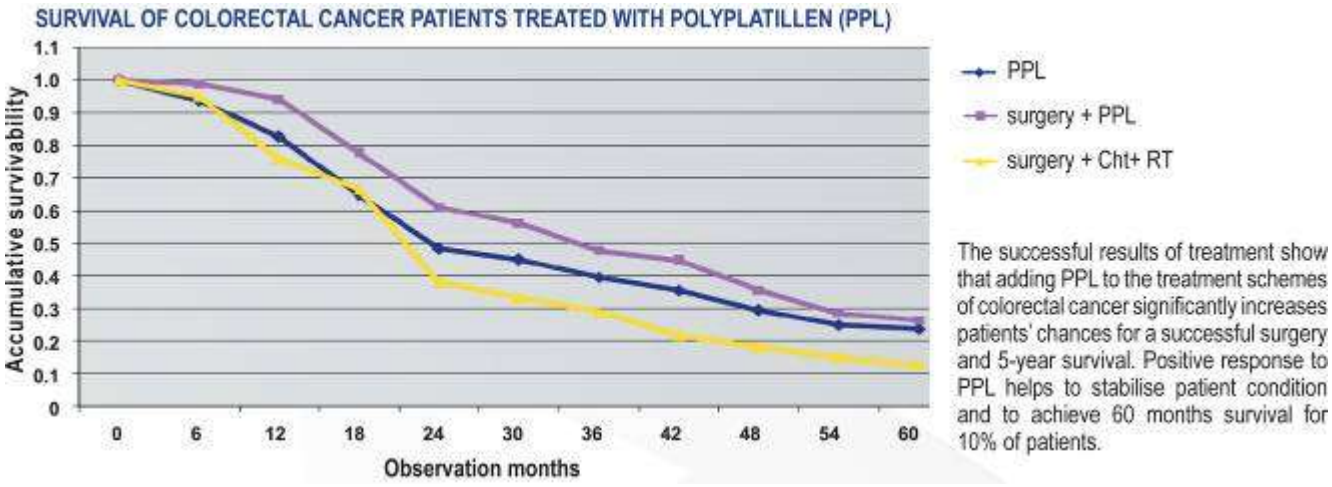
PPL application at treatment of the patients with PC

PC it is usually expressed in the advanced stages and is accompanied by a pain syndrome, obstructive jaundice, cachexia. In this situation PPL was defined as a drug of choice, considering its minimum toxicity.
Direct results of treatment of the patients were characterized by a tendency to the improvement of an objective effect at the patients, in its turn, the 2-year survival rate is observed only in the group of the patients treated with PPL that convincingly testifies to a considerable PPL efficiency in a monochemotherapy mode at treatment of the indicated pathology. The analysis of the survival rate of the patients with PC showed that various morphological types of a tumor show identical sensitivity to PPL.



PPL application at treatment of the patients with CC

Treatment experience confirms that inclusion of chemotherapy in the regimens with PPL into the program of treatment of the patients with CC considerably raises the chances of successful surgery and increases 5-year survival rate.
Also at PPL application there are no expressed manifestations of toxicity at patients that considerably facilitates a course of the disease and allows us to reach remission and stabilization of the oncological process at advanced stages.
PPL prescription was accompanied by a positive reaction, besides the patients showed a long stabilization of the disease, and the life expectancy at 10 % of the experimental subjects made 60 months.
Subjective improvement of the general condition was observed: pain senses and quantity of sanioserous excretions from a rectum decreased, however tumor immobility remained at the former level.
At patients with locally generalized malignant process of a rectum after the second course of the medication administration the improvement of the general condition that showed itself in reduction and in due course in full termination of pain sensations and sanioserous excretions is noticed, the passage of gastrointestinal contents also improved.
The obtained data testifies to the advisability of PPL application for the patients with advanced CC and also to the necessity of the further research of optimum ways of administration of a highly effective drug.



Intraarterial chemotherapy at combination therapy of malignant neoplasms of oropharynx

At intraarterial administration of PPL in chemotherapy regimens (which was supplemented also with its administration in separate days of treatment regimen) expressiveness of local and general toxic manifestations was considerably lower than those developed at the patients receiving other antineoplastic medications.

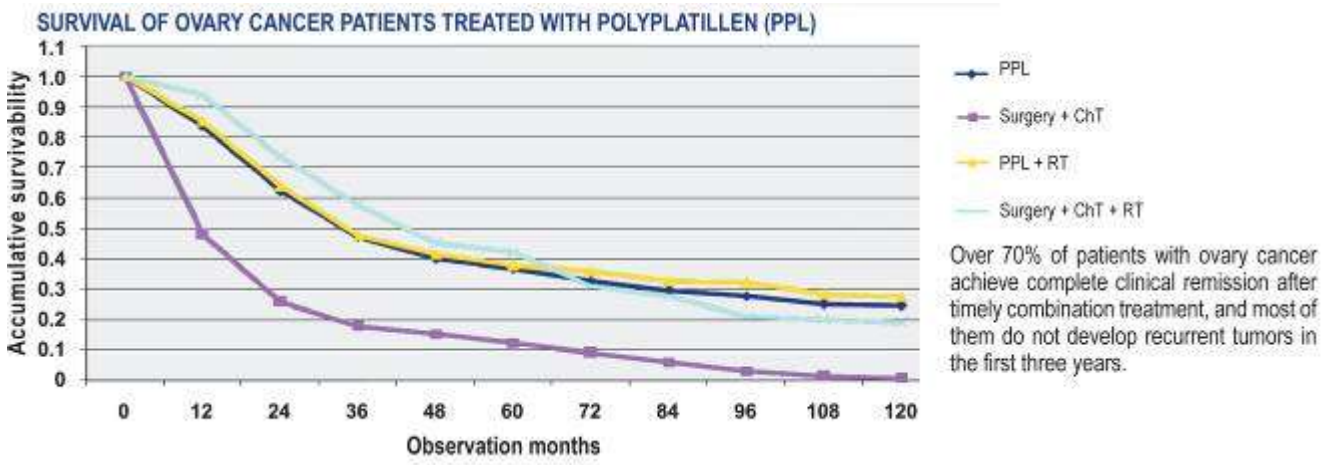
Groups of the patients		**Survival rate, %**		
		Observation period		
Number	**Quantity**	**1 year**	**from 3 to 5 years**	**from 5 and more**
1	n=44	32 (72.7%)	20 (45.4%)	18 (40.9%)
2A	n=37	24 (64.8%)	18 (48.6%)	17 (45.9%)
2B	n=20	18 (90.0%)	14 (70.0%)	11 (55.0%)
3A	n=45	38 (84.45%)	32 (71.1%)	29 (64.4%)
3B	n=21	20 (95.2%)	18 (85.7%)	16 (76.2%)

Application of the medicinal agent PPL in a system mode and also at intraarterial administration caused the best direct results that were shown in greater frequency of full and partial regression of a tumor and also cases of the process stabilization.

Groups: group 1 (only beam therapy); group 2A (polychemotherapy with cisplatin + beam therapy); group 2B (polychemotherapy with PPL + beam therapy); group 3A (intraarterial polychemotherapy with cisplatin + beam therapy); group 3B (intraarterial polychemotherapy with PPL + beam therapy).

The results of treatment of malignant neoplasms depended on three basic indicators: timely diagnostics, adequate treatment, follow-up and observation of the patients during treatment and after it.
Application of intraarterial regional chemotherapy simultaneously with beam therapy at treatment of the patients with malignant tumors of ***oropharynx*** allows us to achieve optimum medical effect. Long regional intraarterial chemotherapy is the most comprehensible way of delivery of the medical substances to a neoplasm.
Application of the modern national medication of PPL in the polychemotherapy regimen in a combined mode or for intraarterial administration gives the best direct and remote results at moderate side effects.

Character of treatment with PPL of the patients with ovarian carcinoma
At PPL application as neoadjuvant chemotherapy at ovarian carcinoma there is a possibility to reach a low profile of toxicity. As the experience shows, inclusion of PPL treatment into the regimens optimizes the results of treatment of the patients.
More than 70 % of the patients with malignant ovarian carcinoma reach full clinical remission after the timely combined treatment, the majority of them do not develop regression within the first 3 years. Treatment with PPL application in regimens is recommended at regression.



4. Indications, contra-indications, mode of administration and doses
PPL it is applied for mono- or polychemotherapy at treatment of the patients with the advanced forms of malignant ovarian carcinoma, liver, stomach, pancreas, large intestine, lung, brain, head and neck tumors, sarcoma of bones and soft tissues, prostatic gland, kidneys, adrenal glands, bladder, thyroid gland, carcinomatoses of an abdominal cavity with ascites, and other types of polyserositis.
The drug is effective at chemoresistant tumors which are not sensitive to the treatment by the standard chemotherapeutic regimens.
Application PPL is not recommended in case of hypersensibility to platinum medications and also at generalization of tumor process, at a terminal condition of the patient, during pregnancy and breast feeding.

Mode of administration and doses

Single doses of the drug of 200-250 mg/m^2 are recommended at intravenous and intraarterial ways of administration. Mode of administration – 3-6 times, by drop infusion, every 24 hours; time of infusions – 3 hours.
The course dose of the drug makes 750-1500 mg/m^2.
The recommended single doses of the drug at administration in an abdominal cavity are 200-250 mg/m^2. Mode of administration – 4 times, by drop infusion, every 48-72 hours, depending on a patient's condition. Time of infusions at intra-abdominal administration makes 4-4.5 hours.
The course dose – 1000 mg/m^2.
At all modes of administration it is necessary to dilute the drug in the ratio 1:1 with a normal saline solution of sodium chloride with addition of 4-8 mg of dexamethasone to the dropper.
It is necessary to repeat the treatment course each 3 weeks.

5. Polychemotherapy regimens
Non-small-cell lung cancer:
Regimen 1
Polyplatillen 200 мг/m^2 intravenously by drop infusion 1-6 day;
etoposide 120 мг/m^2, intravenously by drop infusion on 1, 3, 5 days;
Regimen2
Polyplatillen 200 mg/m^2 intravenously by drop infusion on 1-6 day;
gemcitabine 1250 mg/m^2 1, 8 days.
Regimen3
Polyplatillen 200 mg/m^2 on 1-6 day;
taxotere 75 mg/m^2 1 day;
Regimen4
Polyplatillen 200 mg/m^2 on 1-6 day;
paclitaxel 175 mg/m^2 1 day

Stomach cancer:
Regimen1
Polyplatillen 200 mg/m^2 intravenously by drop infusion on 1-6 day;
etoposide 100 mg/m^2, intravenously by drop infusion on 4, 5 and 6 days;
doxorubicin 20 mg/m^2 intravenously by drop infusion on 1, 6 day.
Regimen2
Polyplatillen 200 mg/m^2 intravenously by drop infusion on 1-6 day;
capecitabine 2000 mg/m^2 a day per os in 2 doses on 1-14 day.
Regimen3
Polyplatillen 200 mg/m^2 intravenously by drop infusion on 1-6 day;
5-ftoruratsil 1000 mg/m^2 a day, intravenously continuously 24-hour infusion from the 1st till 5th day every 28 days.

Colorectal cancer:

Regimen 1
Polyplatillen 200 mg/m^2 intravenously by drop infusion on 1-6 day;
leucovorin 400 mg/m^2 2-hour infusion 1 day, before 5-ftoruratsil;
5-ftoruratsil 400 mg/m^2 intravenously bolus dosing 1 day, after 2400 mg/m^2 intravenously 46-hour infusion;
Regimen 2
Polyplatillen 200 mg/m^2 intravenously by drop infusion 1-6 day;
capecitabine 2000 mg/m^2 a day per os in 2 doses on 1-14 days.

Primary liver cancer:
Regimen 1
Polyplatillen 200 mg/m^2 intravenously by drop infusion on 1-6 day;
capecitabine 2000 mg/m^2 a day per os in 2 doses on 1-14 days;
Regimen 2
Polyplatillen 200 mg/m^2 intravenously by drop infusion on 1-6 day;
doxorubicin 40 mg/m^2 intravenously by drop infusion 1 day;
5-ftoruratsil 600 mg/m^2 intravenously on 1-4 day

Pancreatic cancer:
Regimen1
Polyplatillen 200 mg/m^2 intravenously by drop infusion on 1-6 day;
gemcitabine 1000 mg/m^2 on 1, 8 days.

Skin melanoma:
Regimen 1
Polyplatillen 200 mg/ m^2 intravenously by drop infusion on 1-6 day;
dacarbazine 800 mg/m^2 intravenously by drop infusion 1 day;
vinblastine 1.6 mg/m^2 intravenously1-5 day.
Regimen 2
Polyplatillen 200 mg/m^2 intravenously by drop infusion on 1-6 day;
temozolomide 200 mg/m^2 per os on 1-5 day.

Breast cancer:
Regimen 1
Polyplatillen 200 mg/m^2 on 1-6 day;
cyclophosphamide 600 mg/m^2 on 1 day;
doxorubicin 60 mg/m^2 on 1 day.
Regimen 2
Polyplatillen 200 mg/m^2 on 1-6 day;
taxotere 75 mg/m^2 1 day.
Regimen 3
Polyplatillen 200 mg/m^2 on 1-6 day;
vinorelbine 25 mg/m^2 on 1, 6 day.
Regimen 4
Polyplatillen 200 mg/m^2 on 1-6 day;
capecitabine 2000 mg/m^2 a day 2 doses on 1-14 days

Ovarian cancer:
Regimen 1
Polyplatillen 200 mg/m^2 intraperitoneally every 48-72 hours 4-times administration. Time of infusions 4-4.5 hours.
Regimen 2
Polyplatillen 200 mg/m^2 on 1-6 day;
cyclophosphamide 1000 mg/m^2 1 day.
Regimen 3
Polyplatillen 200 mg/m^2 on 1-6 day;
paclitaxel 175 mg/m^2 1 day.
Regimen 4
Polyplatillen 200 mg/m^2 on 1-6 day;
irinotecan 350 mg/m^2 1 day.

Cervical cancer:
Regimen 1
Polyplatillen 200 mg/m^2 on 1-6 day;
doxorubicin 60 mg/m^2 1st day;
bleomycin 15 mg/m^2 1st day.
Regimen 2
Polyplatillen 200 mg/m^2 on 1-6 day;
taxotere 75 mg/m^2 1st day;
irinotecan 180 mg/m^2 – 1st day.

Endometrial cancer:
Regimen 1
Polyplatillen 200 mg/m^2 on 1-6 day;
doxorubicin 50 mg/m^2 – 1st day;
cyclophosphamide 600 mg/m^2 – 1st day.
Regimen 2
paclitaxel 175 mg/m^2 – 1st day;
Polyplatillen 200 mg/m^2 on 1-6 day.

Adrenal carcinoma:
Regimen 1
Polyplatillen 200 mg/ m^2 on 1-6 day;
doxorubicin 50 mg/ m^2;
cyclophosphamide 600 mg/ m^2 – 1 day;
Regimen 2
Polyplatillen 200 mg/m^2 on 1-6 day;
etoposide 100 mg/m^2 – 1 day;
bleomycin 30 mg/m^2 – 1 day.

Soft tissue sarcoma:
Regimen 1
Polyplatillen 200 mg/m^2 on 1-6 day;

doxorubicin 50 mg/m^2 – on 2, 3, 4 day;
vincristine 1.5 mg/m^2 – on 5 day;
cyclophosphamide 600 mg/m^2 – on 6 day.

Osteogenic sarcoma:
Regimen 1
Polyplatillen 200 mg/m^2 on 1-6 day;
cyclophosphamide 600 mg/m^2 –1 day;
doxorubicin 50 mg/m^2 –1 day.

Testicular cancer:
Regimen 1
Polyplatillen 200 mg/m^2 on 1-6 day;
etoposide 100 mg/m^2 on 1-5 day;
bleomycin 30 mg – every day for 9-12 weeks.

Oesophageal cancer:
Regimen 1
Polyplatillen 200 mg/m^2 on 1-6 day;
epirubicin 60 mg/m^2 – 1 day;
5-fluorouracil – 600 mg/m^2 on 1-6 day.

6. Conclusions

Due to treatment with PPL medication it was possible to reach the high quality of life of the patients with generalization of oncological process on the III-IV stage, to increase life expectancy, to reduce expressiveness of a pain syndrome, endotoxicosis symptoms. Absence of the expressed manifestations of hemato-, nephro-, mielo-, neurotoxicity was noted, that provided a possibility of carrying out a full-scale chemotherapeutic treatment of the patients to whom standard antineoplastic therapy was counter-indicative.
Owing to high antineoplastic activity and low toxicity, PPL application at palliative treatment of the patients with LC, SC, PC considerably improved the life quality of the patients (by ECOG scale) at the expense of reduction of expressiveness of the symptoms connected both with tumor process and influence of antineoplastic therapy. Application of regimens with PPL inclusion did not demand any supporting therapies and hyperhydration methods during treatment which are obligatory when using another medications of platinum.
Indicators of the survival rate of the patients with LC, SC, PC of the IV stage treated with PPL allow us to diverge from a stereotype of treating such patients as hopeless from the point of view of possibilities of increase in life expectancy.
PPL is a modern effective antineoplastic platiniferous medication the evidence to which are the results of the carried out experimental and clinical research. The modes and ways of PPL administration are developed at treatment of the patients with the advanced forms of LC, SC and PC and are recommended to be included in clinical protocols of the specialized help to the patients with malignant neoplasms.

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Advantages of the active substance Polyplatillen in relation to platinum-based medications with the active agents cisplatin and oxaliplatin

Indicators	Active agent Cisplatin	Active agent Oxaliplatin	Active agent Polyplatillen
Effect on the organism	Highly toxic, aggressive systemic action	Toxic	No expressed toxicity, selective effect on the lesion due to the presence of platinum ions on DNA carrier
Tolerability	Unsatisfactory	Satisfactory	Mild
Supporting therapy	Necessary	Necessary	Not necessary. Is recommended for administration both in monoblock and in combined therapy
Life quality	Low	Average	High
Indications	Ovarian carcinoma (III and IV stages), planocellular epithelioma of head and neck, lung cancer, urothelium cancer, cervical tumors	Adjuvant therapy of large intestine cancer of III stage after full primary tumor resection; treatment of metastasizing colorectal cancer	Head and neck cancer, liver, stomach, lungs, kidneys, bowels, ovarium, breasts, prostatic gland, bladder, skin (melanoma) and bones, brain cancer. Ascitic cancer types, carcinomatoses and polyserosites

A short instruction on medical application

Composition: active substance: Polyplatillen; 1 ml of concentrate contains 1.47 mg of Polyplatillen; *Additive agents*: sodium chloride, sodium citrate, sodium hydroxide, fluorouracil (2,4-dioksi-5-fluorinepyrimidine), water for injections.

Pharmaceutical dosage form. A concentrate for preparation of the solution for infusions

Pharmacotherapeutic group. Antineoplastic drugs. Platinum compounds. ATC code: L01XA.

Clinical performance.

Indications. Treatment of the patients with the advanced forms of a malignant tumor (ovarium, liver, stomach, pancreas, large intestine, lung, tumors of brain and neck, sarcoma of bones and soft tissues), including those accompanied by polyserositis with expressed cancerous toxemia, at carcinomatosis of the abdominal cavity and ascites. The drug is applied at chemoresistant tumors tolerant to treatment by generally accepted chemotherapeutic regimens. In a combination with others antineoplastic medications Poliplatillen is applied to treat the patients with the advanced forms of a malignant tumor (ovarium, alvus, liver, stomach, pancreas, large intestine, prostatic gland, kidneys, adrenal gland, bladder, lung, tumors of brain, head and neck, oropharynx, thyroid body, sarcoma of bones and soft tissues).

Contra-indications. Hypersensibility to platinum medications. Generalization of tumor process, terminal condition of the patient, severe liver and kidneys function abnormality. Pregnancy and breast feeding period.

Mode of administration and doses.

Single doses of the drug of 250-300 mg/m^2 are recommended at intravenous and intraarterial ways of administration. Mode of administration – 3-6 times, by drop infusion, every 24-48 hours; time of infusions – 3-3.5 hours. The course dose of the drug makes 650-1300 mg/m^2.
The recommended single doses of the drug at administration in an abdominal cavity are 150-300 mg/m^2. Mode of administration – 3-6 times, by drop infusion, every 24-72 hours, depending on a patient's condition. Time of infusions at intra-abdominal administration makes 4.5-5 hours. The course dose – 650-1300 mg/m^2.
Recommended dose of Polyplatillen under the regimens of the combined therapy makes S from the calculated therapeutic dose.
At all modes of administration it is necessary to dilute the drug in the ratio 1:1 with a normal saline solution of sodium chloride with addition of 4-8 mg of dexamethasone to the dropper. At administration in an abdominal cavity it is recommended to add in a dropper 1 ml (5 000 units) of heparine solution, 10-20 ml of 2 % lidocain solution.
The treatment course can be repeated in 3-4 weeks.

Application during pregnancy and breast feeding. The drug is not applied during pregnancy and breast feeding. While being treated with Polyplatillen it is necessary to stop breast feeding.
Usage pattern. Polyplatillen should be applied by the doctors having experience in antineoplastic chemotherapy.
Interaction with other medical agents and other kinds of interactions. In complex therapy Polyplatillen can be used after methods and means which show mielodepressing and immunosuppressive action. All necessary methods of immunotherapy should be used after carrying out of a complete course of treatment with Polyplatillen.
Pharmacological properties. Polyplatillen is a high-molecular platinum compound with deoxyribonucleic acid, shows antineoplastic properties due to its ability to block the synthesis of nuclear DNA, permanently damages oncological cells which are in G1-S-phase of the cycle. Already at the first administration of Poliplatillen its high antineoplastic activity and the tumor size reduction may be noticed, thus there is no damage to the healthy tissues. The medication is effective at therapy of tumors with the acquired medicinal resistance to other chemomedications.
Shelf life. 2 years.
Storage conditions: PPL should be stored in a dark place at temperature from15 to 25 C°. Sterility of the depressurized drug in the concentrate is 7 days. It is not recommended to freeze the drug during its storage time.