

# Competent Treatment of Retinoblastoma’s (Analysis of Literature Sources and Own Research – Level of Evidence-4)

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## ABSTRACT

The clinical article describes new sparing methods of the treatment for children. A number of drugs – antioxidants of a special chemical structure, phytopreparations, and justifications for their use are presented.

**Key words:** Cytochrome C, cytoflavin, etiotropic treatment, histochrome, imunofan, mexidol (mexiprim), new drugs for the treatment of retinoblastoma, sparing therapy for children, special structure antioxidants, traditional herbal medicine, tyrosine kinase blockers plants

## INTRODUCTION

In the world, there is a growing share of retinoblastoma in children in recent years; the emergence of retinoblastoma tends to increase. Until now, the treatment methods are chemotherapy and enucleation.

That is why; it was necessary to find an effective Etiotropic treatment, since the root cause of the tumor lies at the molecular level. There is a failure first at the biochemical level – in the Krebs cycle (see the Krebs cycle) and the metabolism develops at the anaerobic level. Then, the lack of oxygen causes tumors (author’s note). And then there is gene expression, when there is a synthesis of nucleotides other than normal, and then there is a gene breakdown both at the level of enzymes and at the level of genes (author’s note).

## THEORY AND PRACTICE OF A CLINICAL PHARMACIST (E. G. DMITRIEVA, 2020)

The author of the book believes that the root cause of modern cancer is gene Expression, when other nucleotides are

formed that differ from the norm (variability of nucleotide microsatellites). Based on this material, I wrote a separate book that requires publication (author’s note). It is important to treat with pharmacogenetic drugs (one of them is Vitamin A).

## EXAMINATION OF THE CHILD

It begins with the collection of anamnesis, a thorough survey of parents, which is conducted to find out the possible hereditary predisposition, the state of health of siblings. Special attention should be paid to the course of pregnancy and childbirth.

The presence of hypoxia in childbirth and hyperoxygenation of the child in the postpartum period can lead to the development of the disease lack of oxygen is dangerous.

Living in an ecologically unfavorable area is of some importance.

## LOCAL DESTRUCTION OF THE TUMOR

These methods include brachytherapy, laser photocoagulation, and cryodestruction. Brachytherapy or

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beta-application therapy began to be prescribed for the treatment of intraocular tumors in the late 40–50s of the last century. These types of therapy are used at the very beginning of the disease.

The author suggests – Cytochrome C (Intravaginal slingplasty for children). There are positive clinical cases (author’s note).

If you implement the author’s treatment in a wide clinical practice, you can avoid chemotherapy at Stage 1 of the disease, from Stage 2 – you need to connect combination therapy (author’s note).

In the eyes cannot Vincristine-eye drops at 0.9% isotonic solution’s.

Inside you can – Vincristine + *Rhodiola rosea* Extract.

Instead of Vincristine – it is better to use for children – pink *Catharanthus* (decoctions) + *R. rosea* Extract – dosage by drops (by the number of years).

## EFFECTIVE COMBINATION TREATMENT

A combination of Vincristine, Carboplatin, and Vepezid<sup>[1]</sup> is the most effective at present. Vincristine, Cyclophosphan, and Doxorubicin are also effective, but recently the first combination has been preferred due to the fact that Cyclophosphan increases the risk of developing second tumors and leads to sterilization of patients.

In recent years, in developed countries, due to good diagnostics, an increase in the number of patients with early stages of the disease has been noted. In these cases, cryotherapy, photocoagulation, and radiation therapy may be sufficient to cure the patient.

Contraindications to Vincristine it is Forbidden to administer Vincristine simultaneously or immediately after vaccination with drugs containing live viruses.

Another contraindication is intrathecal administration of the drug-administration directly into the cerebrospinal fluid system under the spinal cord membranes, since this can lead to the patient’s death.

## THE DRUG IS ADMINISTERED EXCLUSIVELY INTRAVENOUSLY AT WEEKLY INTERVALS

### Vincristine analogs-vinblastine – are better tolerated than vincristine

About 50% of Vincristine is bound to blood elements, mainly platelets, which contain a large amount of tubulin.

A small proportion of the drug, after a jet IV injection, penetrates the blood-brain barrier and can have a negative effect on the central nervous system.

Vincristine metabolism mainly occurs in the liver, presumably due to the cytochrome P450 system (isoform of CYP3A). The dose of Vincristine is reduced if there are liver diseases by 50%.

## TO PREVENT CUMULATIVE TOXICITY, THERE SHOULD BE A BREAK OF AT LEAST 7 DAYS BETWEEN TREATMENT PERIODS

### Preferred combination (author’s method)

Cytochrome C + Vinblastine = the most rational combination!!!

Cytochrome C (Cyo-Mac, Vasonate) treats the tumor and simultaneously eliminates the side effects of Vinblastine!!!

### Sometimes there is only a course of cytochrome C for treatment

Due to possible suppression of the immune system, due to Vincristine therapy, it is possible to reduce the formation of antibodies in response to vaccination. Simultaneous administration of live viral vaccines can lead to an intensification of the development of virus replication, an increase in negative effects, and/or a decrease in antibody production. That is why; it is not necessary to make vaccines at all, so as not to reduce immunity. In cancer, you cannot make vaccines (author’s note), immunity is already reduced. Need Immunomodulators (author’s note).

### They are selected according to the immunogram (author’s note)

**But the author uses a special drug that is not similar to conventional Immunomodulators**

Imunofan, which removes the intoxication of the tumor itself, and the toxicity of cytostatics (author’s note). To use Imunofan, you do not need to do immunograms in children, because it is painful (author’s note).

## TREATMENT FOR ADULTS

Injections are needed – intravitreal drug administration is one of the most reliable ways to transport active substance molecules to the affected area. The drugs are angiogenesis inhibitors and have already proven themselves in the treatment of pathologies. Anti-vascular endothelial growth factors (VEGF), VEGF therapy is the most gentle and long-term method of restoring visual functions.

Tumors that can express VEGF can grow and metastasize. Overexpression of VEGF can cause vascular diseases of certain parts of the body (in particular, the retina). Some medications developed in recent years (Bevacizumab) are able to control or slow down the course of such diseases by inhibiting VEGF.

During intravitreal administration of an angiogenesis inhibitor, the patient is asked to look in the opposite direction. This is not difficult, because the procedure takes no more than 10 min.

Intravitreal injection of the drug should only be performed in a sterile operating room, by the hands of a qualified specialist! A mandatory condition is the use of disposable tools. Intravitreal therapy does not require hospitalization, and a couple of hours after the operation, the patient can go home.

## ANTI-VEGF DRUGS AND THEIR EFFECTIVENESS

Anti-VEGF drugs,<sup>[2]</sup> penetrating the macula, reduce the protein activity of pathological vessels, blocking the growth factor. The latter gradually dissolve, and the retina takes its anatomical shape. After the course of treatment, the condition stabilizes, and a break is appointed for an indefinite time.

But this, treatment is only suitable for adults (author's note).

The production of VEGF<sup>[3-5]</sup> proteins can be triggered in cells that do not receive enough oxygen, so adults are often prescribed Mexidol (Mexiprim), oxygen masks, oxygen cocktails, and other forms of oxygen.

That is why I suggest using a different method of retiotropic treatment for children, affecting the root cause of the disease.

The drug is an antioxidant cytochrome C, which can be successfully used for retinal cancer.

For any cancer, you cannot use antioxidants-vitamins (author's note). However, there are exceptions to the rule. Cytochrome C is such an exception!!!

Cytochrome C-10 mg N 5 vials – for droppers for children. The contents of the glass bottle should be diluted with water for injection in an amount of 4 ml, and administered intramuscularly every day.

Store the drug at a temperature not higher than 20°. Store in the refrigerator. After breeding it is necessary to introduce immediately, releasing the foam.

When administered, there are unpleasant sensations, but you can be patient.

But this drug can be given to children through droppers (author's note).

Cytochrome C is administered intravenously or intramuscularly. Before using the drug, it is necessary to check the sensitivity to it. To do this, enter 0.1 ml intradermally and wait for 30 min. If there is no reaction (urticaria, redness of the face, and itching), you can start injections. The dose is 10–20 mg 1–2 times a day. The course of treatment is 14 days.

But for small cardiac patients, the drug is not suitable!!!

After a course of Cytochrome C, you can prescribe another, similar metabolic drug.

## THE RECOVERY PHASE

Cytoflavin (composition-succinic acid, nicotinamide, inosine, and Riboflavin) – can be administered only in the rehabilitation phase after retinoblastoma.

In children (including premature babies) in the neonatal period, the use of Cytoflavin may cause the development of alkalosis.

## SPECIAL INSTRUCTION

The administration of the drug to newborns (premature) children should be carried out under the control of indicators of the acid-base state of capillary blood at least 2 times/day (both before and during therapy). If possible, serum lactate and glucose levels should be monitored.

## AN ANALOG OF CYTOCHROME C EYE DROPS IS OFTAN CATACHROM

### The active substance of this drug

Cytochrome C-a small heme-containing protein, belongs to the class of cytochromes, iron molecules are present in the prosthetic group during chemical analysis and are able to transition from the oxidation state to the reduced state. As a result, metabolic and redox processes in cells improve, the rate of oxygen utilization increases, and tissue hypoxia stops, regardless of the severity of the pathological condition. This is the basis of the entire process of recovery of the drug.

### Cytochrome for children can be used

There are no age restrictions on using the solution. However, it is forbidden to use eye drops for patients under 18 years of age. There is no information on drug interactions with

other drugs as Analogues of eye drops-Catachrom, Oftan (Composition-cytochrome C + adenosine + nicotinamide). During treatment with Oftan Catachrom, you should not wear soft contact lenses, because the preservative may be deposited in them and have an adverse effect on the eye tissue. Before applying Often Katahama contact lenses should be removed and install them again after 15 min after instillation of the drug.

## HISTOCHROME 0.02% SOLUTION FOR INJECTION (FOR OPHTHALMOLOGY)

Histochrome is a yellow-brown liquid, pH from 6.5 to 7.5, easily oxidized by air oxygen, available in 1 ml ampoules.

## PHARMACOLOGICAL PROPERTIES

12 h after intravenous administration of histochrome, its concentration in the blood plasma decreases by almost half, and then remains at the same level for a long time. Perhaps faster elimination occurs from the blood and well-perfused organs, and slower-from the tissues of the “peripheral chamber.”

Histochrome is a water-soluble preparation of echinochrome. Echinochrome (2, 3, 5, 6, 8-pentahydroxy-7-ethyl-1, 4-naphthoquinone) is a quinoid pigment of marine invertebrates belonging to the echinoderm type, isolated from their shells, and needles. Removed from production!!! All good things in Russia are destroyed!!!

### Types of inhibitors

**There are various drugs that block the growth of blood vessels**

1. Inhibitors that block growth factor (VEGF) from attaching to receptors on cells lining blood vessels. This stops the development of blood vessels. Such drugs are Bevacizumab (Avastin), which are also a monoclonal antibody. However, these drugs do not cure.
2. Inhibitors that block the transmission of signals. Some drugs stop the transmission of growth signals from VEGF receptors to blood vessel cells. These drugs are also called growth factor blockers or tyrosine kinase inhibitors. Sunitinib (Sutent) is a type of ITK that blocks growth signals inside blood vessel cells. It is used in the treatment of kidney cancer and a rare type of stomach cancer-stromal tumors.
3. Inhibitors that affect the transmission of signals between cells. Some drugs have an effect on chemicals that cells use to signal growth to each other. This can stop the development of blood vessels. These drugs are Thalidomide and Lenalidomide (Revlimid).

### But in childhood, the application cannot be used

1. Propolis – with natural butter (for children).<sup>[5,6]</sup>
2. Natural cocoa for children (cocoa pod extract).<sup>[7]</sup>
3. Grapes are good for children.
4. A decoction of chaga (Betulin and tramadolusa acid fungus inhibits the enzyme tyrosinase) – children with retinoblastoma.
5. Phenolic substances of galls.
6. The yellow pigment of safflower carthamin.
7. Natural olive oil.
8. Orange juice.
9. Magnolia flowers.
10. Caffeic acid.
11. Saponins of yakortsov.
12. Yarrow extracts.
13. Putrescin defined in the *Sophora japonica*.
14. Ginger-medicine for the elderly.
15. Originated oregano inhibits the enzyme tyrosinase – suited more for women.
16. Research of alcohol extract of dry onion skin.
17. Biochanin in clover.
18. Hesperidin orange juice (can be taken for children, except for the peel and exclude the period of colds).
19. Resveratrol (adults only).<sup>[4]</sup>
20. Alcoholic grape seed extract (adults only).
21. Extracts of winter honeydew, thanks to 1', 3'-dilinenoyl-2' – linoleyl glycerol.
22. Extracts of flowers *Inula britannica* L., mainly sesquiterpenes inhibit tyrosinase, melanogenesis processes preventing the development of melanoma and retinoblastoma.
23. Water extracts of burdock fruit.
24. Extracts of the flowers of peaches.
25. Hop Phenolic substances.<sup>[7]</sup>
26. Shandra extracts.
27. Mulberry fruit.
28. Extracts of black mulberry fruit and branches.
29. Root bark and black mulberry roots.
30. Extracts of branches and leaves of the white mulberry (due to the content in the roots of mulberries). Dehydroascorbate isolated from the wood of the white mulberry has a pronounced antityrosinase activity.
31. Tree bark of bird cherry.
32. Fennel is.<sup>[8]</sup>

Caper extracts increase tyrosinase activity and stimulate melanogenesis. This opens up the prospect of using the herb to treat vitiligo, nest baldness, and tanning products.

And natural remedies that reduce the activity of tyrosine kinase should be used to treat childhood cancer-retinoblastoma.

Synthetic tyrosine kinase blockers Sorafenib and Sunitinib, multikinase inhibitors of tumor proliferation and angiogenesis.<sup>[9]</sup>

Sorafenib (Sorafenate, Nexavar), Sunitinib (Sutent), but since there are no data from clinical trials for retinoblastoma in children, you can use Traditional herbal Medicine (not to be confused with dietary supplements) (author's note).

### Side effects of tyrosine kinase blockers

The growth of secondary tumors, since substances can activate tyrosine kinase and it is necessary that substances inhibit it. However, this is only possible with Traditional Herbal medicine (author's note).

### The second way to treat retinoblastoma in children

Targeting surviving<sup>[10]</sup> – a protein that inhibits apoptosis or cell death – increases the effectiveness of chemotherapy in cells and mouse models of retinoblastoma, the most common eye cancer in children.

The study demonstrates for the first time that the combination of the YM155 survivin inhibitor and chemotherapy provides a therapeutic benefit for Rb cells and tumors.

While treatment for retinoblastoma varies depending on the size and location of the lesions, most treatments include chemotherapy drugs such as Carboplatin and Topotecan.

Exposure to chemotherapy results in increased survivin levels in two human retinoblastoma cell lines, but not in normal retinal pigmented epithelial cells. Cellular levels of survivin were significantly reduced in Rb cells, but not in retinal pigment epithelium cells when exposed to YM155. The combination of YM155 and chemotherapeutic agents was also most effective in enhancing tumor cell death compared to either alone.

After additional preclinical studies, this combination therapy will give better results to children with retinoblastoma and may reduce the likelihood of chemotherapy, reducing long-term side effects.

Survivin, interacting with Ran, increases the export of certain proteins and RNA from the nucleus, which leads to an increase in the expression of oncogenes such as Transglutaminase 2 and SPARC-related modular calcium-binding protein 2.

## CONCLUSION (APPROXIMATE STANDARD OF TREATMENT FOR RETINOBLASTOMA IN CHILDREN)

### Plan for sparing treatment of children with retinoblastoma

1. Imunofan-candles from 1 year – 1 candle in the rectum in 3 days.
2. Cytochrome C-droppers for children.

3. *R. rosea* Extract (by the number of years of the child) + Vincristine (better Vinblastine or *Catharanthus* pink decoction inside the dose is selected by a Clinical Pharmacist-Phytotherapist).
4. Injections to do in the eyeball in children are not recommended!!!
5. Tyrosine kinase blockers are better than natural ones (see above) (synthetic tyrosine kinase blockers may have a tumor metastasis syndrome when used (author's note).
6. Ochanka – decoctions inside.
7. Vitamin A.

## REHABILITATION

### Cytoflavin tablets

Treatment of children and adult patients should be carried out jointly by an oncologist-ophthalmologist and a Clinical Pharmacist (author's note).

Author gave new treatment for retinoblastoma in children. The sample is small, but it works, because the primary cause of retinoblastoma in children is lack of oxygen. At the same time, I give Etiotropic treatment – the lack of oxygen in the retina is removed. This is a gentle treatment for children without droppers and pain. Toxic substances from the tumor itself and from cytostatics are leveled by the introduction of candles of the drug – Imunofan. The remaining funds enhance the competent etiotropic treatment of retinoblastoma.

This treatment can be monotherapy, as well as include combinations with plant tyrosine kinase blockers. They should be selected by a Clinical Pharmacist – a Phytotherapist.

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