Переклад виконано з української та російської мов на англійську мову
Translated from Ukrainian and Russian into English

UKRAINIAN SCIENTIFIC-RESEARCH INSTITUTE FOR ONCOLOGY AND RADIOLOGY OF UKRAINE

Scientific Research Institute for Experimental Pathology, Oncology and Radiobiology named after R. E. Kavetskiy, National Academy of Sciences of Ukraine

"Approved"
Signature
by Director
of KIEV SCIENTIFIC-RESEARCH INSTITUTE
FOR ONCOLOGY and RADIOLOGY,
Professor: Mr. S. A. SHALIMOV
October 14, 1993

Seal: *Ministry of Health of the Ukrainian Soviet Socialist Republic*
Kiev Scientific-Research Institute for Oncology

REPORT
on the results of clinical investigations
of "FLARAXIN", the new antineoplastic drug
/stage 2/

Chairman of the Commission
on clinical investigation of "Flaraxin",
Head of the Scientific-Research Department
for tumours of the head and neck
and for the modified methods of treatment,

Doctor of Medical Sciences, Professor *Signature* V. S. Protsyk

REPORT
on the results of clinical investigations
of "FLARAXIN", the new antineoplastic drug
/stage 2/

As is known, the chemotherapy against melanoblastomata, both alone and combined with radiotherapy and the surgical intervention are inefficient. In this regard, looking for the medicaments against melanoblastomata is the relevant objective of the treatment in the modern medicine.

We studied within the frame of the 2nd stage of clinical investigation the therapeutic action of the "Flaraxin" in the patients with the advanced forms of the malignant melanomas. The total number of the treated patients having had the stage IV over the period between December 1992 and October 30, 1993 is 10. All the patients have the diagnosis of the melanoblastoma; it was confirmed by the histological examination.

The therapy with "Flaraxin" was executed in compliance with the advice of the Pharmacological Committee. The contents of the bottle, 150 mg of the lyophilized pulvis of "Flaraxin" were diluted in 20 ml of 5% glucose solution and was administered intravenously, in a single-stage, once every twenty-four hours. The period of treatment makes 20 intravenous infusions. The toxic action of "Flaraxin" as well as its therapeutic effect were studied with the patients /degree and duration of the remissions/.

In the course of clinical investigations it was recorded that "Flaraxin" had no negative effect on the functions of the central as well as peripheral nervous systems, cardiovascular system, liver, kidneys, gastrointestinal tract, has no influence on the blood morphology as well as blood formation. The toxicity of "Flaraxin" is considered to be nought according to the estimates of the World Health Organization ("Antineoplastic therapy", M., Medicine, 1986, p.166).

The therapeutic effect of "Flaraxin" at the advanced forms of melanoblastomata showed itself in all the 10 patients. The direct correlation between the therapeutical effect and disease's remoteness is to be recorded, - the earlier the therapy is started, the more expressed is the therapeutic effect. The general well-being mend, the regression of the tumor nodes up to 30-35%, process stabilization as well as remission over 6 months are to be recorded. (see Table 1).

In the very advanced cases the effect of the therapy with "Flaraxin" was low expressed. In the case of the lung, liver and other vital organs' metastases, only general well-being mend, the size reduction of the tumor nodes up to 15% are to be recorded.

Table 1. The list of the patients with melanoblastomata, who were treated with “Flaraxin”.

Pos.	SURNAME, first name, patronymic and case number	Sex, age	Diagnosis	General state of health before the treatment	Administration route	Daily dose	Course duration	Change of leucogram	Side effects and epiphenomena	Therapy results		Remission term after treatment with “Flaraxin”
										Objective ones	Subjective and symmetric ones	
1.	Vasilchenko Lyudmila Nikolayevna, case history No.: 4808/93	f, 52 years old	MBL of the skin of the neck, lymph nodes metastases, the 4th clinical group	pain in the nodes	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	size reduction of the nodes by 25%	Pains are disappeared.	from 08.03.93
2.	Skurchinskaya Lidiya Nikolayevna, case history No.: 0369/93	f, 62 years old	MBL of the skin of the forehead; parotic lymph nodes metastases, the 4th clinical group	pain and itching in the lymph nodes	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	size reduction of the tumor nodes by 50%	Pains are disappeared.	from 11.01.93
3.	Zingel Galina Vasilyevna, case history No.: 913/93	f, 43 years old	MBL of the skin of the left eyebrow area; maxillary lymph nodes metastases, the 4th clinical group	pain in the eyebrow area	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	involution of the tumor nodes by 50%	Pains are disappeared.	from 13.01.93
4.	Salnikova Olga Alexandrovna, case history No.: 507/93	f, 23 years old	MBL of the skin of the parotic area; cervical lymph nodes metastases, the 4th clinical group	pain in the parotic area	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	regression up to 40%	Pains are disappeared.	from 09.02.93
5.	Yatsenko Alexandra Al-na, case history No.: 786	f, 42 years old	MBL of the occipital region of head.; cervical lymph nodes metastases, the 3rd clinical group	pain in the tumour nodes	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	size reduction of the nodes up to 40%	Pains are disappeared.	from 10.02.93
6.	Grivkovskaya Lyudmila Silvestrovna, case history No.: 6574/93	f, 69 years old	MBL of the skin of the head; cervical lymph nodes metastases	pain in the tumour nodes	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	size reduction of the nodes up to 60%	Pains are disappeared.	from 29.03.93
7.	Shchedrina Tatyana Nikolayevna	f, 40 years old	MBL of the skin of the face; cervical lymph nodes metastases	pain in the tumour nodes	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	size reduction of the tumour up to 50%	Pains are disappeared.	from 18.02.93
8.	Leykin Ivan Vasilyevich	m, 52 years old	MBL of the skin of the face; cervical lymph nodes metastases	pain, tumor	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	regression of the tumours up to 20%	Pains are disappeared.	from 03.01.93
9.	Vorobey Leonid Timofeyevich, case history No.: 1050	m, 52 years old	MBL of the skin of the head; metastases in the lungs	weakness, cough	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	general well-being mend	-	from 12.02.93. The patient died 2.5 months later after therapy termination.
10.	Mogilnaya Valentina Ivanovna	f, 26 years old	MBL of the skin of the back of the head; metastases in the liver	weakness, abdominal pains	intra-venously	2 mg/kg	20 bottles, 20 days	no	no	general well-being mend /td>	-	from 09.01.93. The patient died 1.5 months later after therapy termination.

Ministry of Health
of the Ukrainian Soviet Socialist Republic
Kiev Institute for Pharmacology
Our. Ref.: 443
Date: 18.11.1993

Attn: Mr. A. V. Stefanov,
Director
of the Institute for
Pharmacology and Toxicology
of the Academy of Medical
Sciences of Ukraine,
Doctor of Biological Sciences

Institute for Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine, according to the Decision of the Pharmacological Committee of Ukraine, have completed the clinical investigations (stage 2) of "Flaraxin", the anti-melanoblastoma drug.

Please, find attached the report on the conducted work.

Appendices: The above mentioned report, 2 copies,
every thereof - on 5 pages.

Deputy Director for Science,
Professor *Signature* /Y. L. Grinevich/

Conclusion

1. The daily dose of “Flaraxin” of 2 mg/kg by the intravenous introduction over a period of up to 20 days has no toxic effect on the central as well as peripheral nervous systems, cardiovascular system, vital organs, blood as well as blood formation.

2. The curative effect of “Flaraxin” at the generalized forms of melanoblastomata depends on duration of the disease, on the nature and degree of the viscera lesion. It is declaring itself trough the patients' well-being mend, process stabilization and the regression of the tumour nodes on an average of up to 50%.

3. To recommend to the Pharmacological Committee of Ukraine to allow the clinical use of the “Flaraxin” medicament for curing the melanoblastomata.

Chairman of the Commission
on clinical investigation of “Flaraxin”,
Head of the Scientific-Research Department
for tumours of the head and neck
and for the modified methods of treatment,

Doctor of Medical Sciences, Professor /Signature/ V. S. Protsyk

Stamp: *True*
/illegible/
/Signature/
October 21, 1993

EXTRACT

from the report on the clinical study of the new antineoplastic drug – "Flaraxin" – performed at the Kiev Oncology Scientific Research Institute in 10 patients with melanoblastomata /Stage II/, only advanced. The investigations have being performed in the period between December 1992 and October 30, 1993.

1. The daily dose of "Flaraxin" of 2 mg/kg by the intravenous introduction over a period of up to 20 days has no toxic effect on the central as well as peripheral nervous systems, vital organs, blood as well as blood formation.
2. The curative effect of "Flaraxin" at the advanced forms of melanoblastomata depends on duration of the disease, on the nature and degree of the viscera lesion. It is declaring itself trough the patients' well-being mend, process stabilization and the regression of the tumour nodes on an average of up to 50%.
3. To recommend to the Pharmacological Committee of Ukraine to allow the clinical use of the "Flaraxin" medicament for curing the melanoblastomata.

Chairman of the Commission on
the clinical investigation of the "Flaraxin",
Head of the Scientific Research Department
for tumours of the head and neck
and for the modified methods of treatment,
Doctor of Medical Sciences,
Professor *Signature* V. S. Protsyk

Seal: *Ministry of Health of the Ukrainian Soviet Socialist Republic*
Kiev Scientific-Research Institute for Pharmacology and Toxicology

Stamp: *True*
Secretary
Signature

Цей переклад з української та російської мов на англійську мову виконано мною, перекладачем **Ачкасовим Сергієм Володимировичем _____.**

This document is translated by ***Sergiy Volodymyrovych Achkasov***, from Ukrainian and Russian into English *Signature*

Місто Харків, Україна

Двадцять п’ятого травня дві тисячі одинадцятого року.

Я, **Цигіпова О.Г.**, приватний нотаріус Харківського міського нотаріального округу засвідчую справжність підпису перекладача **Ачкасова Сергія Володимировича**, який зроблено у моїй присутності.

Особу перекладача встановлено, його дієздатність та кваліфікацію перевірено.

Зареєстровано в реєстрі за № _____
Стягнуто плати ***за домовленістю***

Приватний нотаріус
Харківського міського
нотаріального округу Цигіпова О.Г.

City of Kharkiv, Ukraine

Twenty-fifth of May two thousand and eleven.

I, **O.G. Tsygipova**, Notary Private of Kharkiv City Notarial District hereby certify the authenticity of the signature of translator **Sergiy Volodymyrovych Achkasov** made before me.

The identity of the translator is established, his capacity and competence are proved.

Registered in the Register under No. ___.
Fee received ***as agreed***

Notary Private
of Kharkiv City Notarial District
Signature O.G. Tsygipova

*Seal: Notary Private Olena Georgiyivna Tsygipova *Kharkiv City Notarial District in Kharkiv Region*

Всього прошито, пронумеровано і скріплено печаткою **13 (тринадцять)** аркушів.

Приватний нотаріус
Харківського міського
нотаріального округу Цигіпова О.Г.

The sewed together, numbered and sealed pages total **13 (thirteenth).**

Notary Private
of Kharkiv City Notarial District
Signature O.G. Tsygipova

*Seal: Notary Private Olena Georgiyivna Tsygipova *Kharkiv City Notarial District in Kharkiv Region*

Переклад виконано з української та російської мов на англійську мову
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MINISTRY OF HEALTH OF UKRAINE
KIEV SCIENTIFIC-RESEARCH INSTITUTE
FOR PHARMACOLOGY AND TOXICOLOGY

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613.1/2/017.14615.033.034

RESTRICTED

"APPROVED"

by Director
of the Institute,
Corresponding Member
of the Academy of Sciences of Ukraine

Signature I. S. Chekman
December, 4 1991

Seal: Ministry of Health of the Ukrainian Soviet Socialist Republic
Kiev Scientific-Research Institute for Pharmacology and Toxicology

TO INVESTIGATE "FLARAXIN", THE PHARMACOLOGICAL AGENT, CONCERNING THE OPINION ABOUT THE POSSIBILITY OF ITS CLINICAL USE AS ANTINEOPLASTIC DRUG.

Stage of 1991: Limited clinical testing.
Pre-clinical investigation of "Flaraxin".
Development of the normative and technical documentation.

Deputy Director for Science,
Doctor of Medical Sciences, Professor /Signature/ *Mr.* Y. I. Gubskiy

Supervisors of studies:

Corresponding member
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Candidate of Medical Sciences,
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Kiev, 1991

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THE LIST OF THE ADOPTED ABBREVIATIONS

ФАВ	- physiologically active substances
ЧСА	- human serum albumin
ПОЛ	- lipid per-oxidation
Y	- volume of distribution (VOD), l/kg
CI	- clearance, l/hour
$T_{1/2}$аб	- half-absorption period, hours
$T_{1/2}$эл	- half-elimination period, hours
S	- area under the “concentration-time” curve (AUC), mg. hours/l

SUMMARY

Book I of the report: 114 pages, volume I, 114 pages, 25 tables, 37 sources.

Toxicity (acute and chronic ones), cumulation, immune system, pharmacokinetics of “Flaraxin”.

The pharmacological properties of “Flaraxin” were investigated experimentally.

The pharmacological, toxicological, biochemical, physicochemical and other investigative methods were being used.

It was established, that “Flaraxin” possesses the expressed antioxidant properties *in vitro* as well as *in vivo*. “Flaraxin” is a low accumulating agent, has no negative influence on the humoral component of the immune system.

The pharmacokinetic parameters were determined; it was found out, that “Flaraxin” enters into kidneys and liver the least actively, the most actively – into the skin, into the mucous membrane of the small intestine and into eyes.

The medical exercises project is developed.

Presently, “Flaraxin” is under the stage I of the clinical investigations as the agent for curing the melanoblastomata.

C O N T E N T S

Performed at the Oncology Department of the Kiev Medical Institute in the period between September, 1990 and January, 1991.

5. CLINICAL INVESTIGATIONS

Stage I

5.1. REPORT ON THE CLINICAL INVESTIGATION OF "FLARAXIN", THE NEW ANTINEOPLASTIC DRUG, IN CURING THE MELANOBLASTOMATA OF VARIOUS SITES AND STAGES

Time range: from September, 1990 to January, 1991.

The goal of the clinical study

The estimation of the optimal curative doses, the duration of administration, the effectiveness of treatment, the toxicity assessment. The investigation of "Flaraxin", placed at disposal by the Kiev Scientific Research Institute for Pharmacology and Toxicology of the Ministry of Healthcare of Ukraine, and is based on the allowance of the Pharmacological Commission of the Ministry of Healthcare of Ukraine for the stage I of clinical investigations as well as on instructions on clinical investigation of "Flaraxin". In the course of studying the "Flaraxin" they were guided by the practical policies on the initial studying the new antineoplastic drugs, approved by the Pharmacological Committee of the Ministry of Healthcare of USSR (M., 1975, p. 84-97). In the period till June 15, 1991, 30 patients with the melanoblastomata (MBL) with histological confirmations of the diagnosis are treated and being observed by the staff of the Oncology Department of the Kiev Medical Institute and of the Surgery Department I of the Kiev Municipal Cancer Centre with the counselling assistance by the creator of "Flaraxin", the oncologist Mr. I. A. Kulik. The list of patients is presented in the Table 1, drawn up according to the F.1 of the practical policies on the initial trial of the new antineoplastic drugs.

The treated patients with the melanoblastomata (MBL) who are being observed – they are men and women aged of 27 up to 77 years old. Sex and age distribution of the patients is presented in the Table 2.

The growth dynamics of the tumours was being controlled trough the daily measuring the diameters of every tumour in three mutually perpendicular flats with further calculation of the average volumes of the tumours concerning every group for every term.

The curative doses of the "Flaraxin" have no toxic effect on blood and blood formation, liver, kidneys, cardiovascular system, lungs and gastrointestinal tract. Its toxicity is considered as 0 (zero) according to the estimates of the World Health Organization. However, it is to be remarked, that sometimes the nausea and vomiting have been registered in those patients who were treated before by polychemotherapy, particularly, combined with radiotherapy.

Table 1. Form 1. (The Table is to be improved; a part of data is lost). Kiev Municipal Cancer Centre. Oncology Department of the Kiev Medical Institute.
The list of the patients treated with the drug of "Flaraxin" under procedure of the stage I of the study from July 8, 1990.

Pos.	Name, initials, age	Sex	Diagnosis	General state before the treatment	Admi-nistration route	Prevailing single dose	Course duration	Change of leucogram and thrombogram	Side effects and epiphenomena	Therapy results		Remission term after treatment with "Flaraxin"	Срок ра ти МБ (months)
										Objective ones	Subjective and symmetric ones		
1.	Primak Y. M.	f	MLB of the skin of the left shin, operated in 1986.	1	intra-venously	2 mg/kg	15 days	Not registered.	Up to 8 infusions; the heaviness of the body became stronger	Complete regression of the tumour nodes.	The patient became active	from 08.1990	1
2.	Khatunkina V. V., 52 years old	f	MLB of the skin of the left shin, metastases in the inguinal area	3	intra-venously	2 mg/kg	The 1st course of 15 days, the 2nd course – 20 days	Not registered.	Not established.	Complete regression of the inguinal nodes, the tumour nodes.	Satisfactorily.	from 10.02.91	1
3.	Koshevich G. R., 56 years old	f	MLB of interscapular region	3	intra-venously	1,8 mg/kg	21 days	No changes.	Irritation of the left ulnar vein	Complete regression of the tumor node; clearing of the initial focus.	Satisfactorily.	from 20.02.91	2
4.	Junkovskiy A. V., 54 years old	m	MLB of the skin of the back; metastases in the both axillary spaces	3	intra-venously	2 mg/kg	18 days	Not registered.	Not established.	Regression of the tumour up to 60%.	Satisfactorily.	from 15.02.91	С вич оча 6
5.	Panchenko I., 58 years old	m	MLB of the skin of the temporal region; metastases in the cervical lymph nodes	3	intra-venously	4 mg/kg, 14 days, 2 mg/kg, 12 days	The operation follows 14 infusions. In the post-operative period: 12 days (24 days) + course repetition in 1month with imbibition of the tumour node	10 infusions every 0,8 thousand ---------- stimulation every 1,5 thousand	Not established.	Regression of the tumour over 60%.	Satisfactorily.	from 18.02.91	С ви оч8(пн еоп
6.	Kovalenko V. G., 48 years old	m	MLB of the skin of the left antebrachium; generalization; metastases in lungs	3	intra-venously	2 mg/kg	The 1st course – 15 days in 3 weeks ---------- The 2nd course, 20 days in 4 weeks + intrahumoral	Not registered. ---------- Not registered. Reaction like inflammation and pain, which disappeared 3 days later.	Not established. ---------- Not established.	Regression of the tumour nodes; partially complete regression. In the rest thereof up to 50%.	Satisfactorily.	from 20.12.90	В 1 опе В 1 нач ген за
7.	Pilipenko G. M., 40 years old	f	MLB of skin	3 the 1st& 2nd course, the 2-3rd course	intra-venously	Treatment: 3 courses with "Flaraxin" + 5 courses with	15 days, pause, 3 weeks, 20 days,	The 3rd course with "Flaraxin" + "Vincristine", decrease of the	Irritation of the ulnar veins during the 3rd course of treatment	Complete regression of the cervical node. The operation follows the 2nd course.	The 3rd course with "Flaraxin" + "Vincristine", sustained the	from 10.10.90	from 19

				- with "Vincristine"		"Vincristine", 2 mg/kg	pause, 1 month, pause, 3 weeks, 20 days + "Vincristine"	white blood cells up to 3000.			therapy badly.		
8.	Klininskiy K. I., 68 years old	m	MLB of the skin of the back; metastases in the both axillary creases	3	intra-venously	2 mg/kg	18 days + operation	Stimulation of the white blood cells by 1000	Not established.	Regression of the metastases of the lymph nodes up to 60% + operation.	No changes of feeling.	from 15.02.91	6
9.	Basov V. N., 52 years old	m	Metastasis; MLB of in the both axillary spaces	3	intra-venously	1,8 mg/kg	15 days + operation repeated course	Stimulation of the white blood cells by 5000	Not established.	Regression of the metastases of the nodes up to 60%.	No changes of feeling.	from 23.01.91	7
10.	Lesnik G. V. 36 years old	f	MLB of the supraclavicular area; metastases in the spleen and in the supramaxillary joint	3	intra-venously	The 1st course 4 mg/kg ---------- the 2nd course 2 mg/kg	---------- April	Decrease of the white blood cells from 9000 to 5000 ---------- No changes.	Not established. ----------	Stabilization of the process. ---------- Stabilization of the process.	The pains in the joint have remitted ---------- The pains of the manducatory joint disappeared.	from 27.02.97	7
11.	Petrenko A. P., 41 years old	m	MLB of the auricle, metastases in the cervical lymph nodes	3	intra-venously	2 mg/kg. total: 3000 mg + operation	20 days + operation	No changes.	Irritation of the left ulnar vein	Regression of the tumour nodes up to 30%.	Sustained the therapy satisfactorily.	from 06.10.90	6
12.	Kozerog Y. T., 71 years old	m	MLB of the skin of the occiput; metastases in the cervical lymph nodes	3	intra-venously	1,8 mg/kg	17 days + operation	No substantive changes	Irritation of the right ulnar vein	Regression of the nodes' mass from 50% to 80%.	Sustained the therapy satisfactorily.	from 06.10.90	3
13.	Kuzmenko Y. V.	m	MLB of the head skin; generalization of the process	3	intra-venously	2 mg/kg	20 days	Increasing of the white blood cells by 1,3 thousand platelets	Not established.	Regression of the tumour nodes up to 60%.	Sustained the therapy satisfactorily.	from 15.03.91	metastases over 5 months
14.	Boryak N. N., 52 years old	m	MLB of the back, metastases in the right axillary space. Diabetes mellitus, severe form	3	intra-venously	2 mg/kg by 1 mg/kg in the morning & in the evening	20 days	No changes were recorded.	Not established.	The primary spot of the metastases disappeared. The node decreased by 50%.	Sustained the therapy satisfactorily.	from 10.03.91	progression of metastases over 4 months
15.	Gutsulyak P. V., 32 years old	m	MLB of hair, of the part of the head; metastases in shoulder girdle and lungs	3	intra-venously	The 1st course, 2 mg/kg ---------- the 2nd course, 2 mg/kg	20 days ---------- 20 days	No changes. ---------- No changes.	Not established. ---------- Irritation of the right ulnar vein	The pains of the shoulder joint disappeared. ---------- Regression of the tumour nodes up to 40 %.	Sustained the therapy satisfactorily.	from 04.09.90	progression of metastases 10 months

16.	Savicheva I. V.	f	MLB of the hip skin; metastases in inguinal lymph nodes	3	intra-venously	1,5 mg/kg	19 days + operation	Lymphocytes went up by 0,8 thousand	Not established.	Regression of the tumour nodes over 30%.	Sustained the therapy satisfactorily.	from 17.02	progression of metastases over 6 months
17.	Mogilnaya V. I., 39 years old	f	MLB of the skin of the of the right shin; metastases in the cranial bones and dexter lung	2	intra-venously	2 mg/kg by 1 mg/kg in the morning & in the evening	17 days	No changes.	Not established.	The nodes of the liver decreased (palpatory).	The pains in the circulatory subcostal area have remitted.	from 2	from 1988
18.	Gorobets L. T., 52 years old	f	MLB – the diffuse relapse of the postsurgical cicatrix of the neck	3	intra-venously	1,8 mg/kg	20 days	No changes.	Not established.	Clearing of the dark-bluish area; the infiltration decreased.	Sustained the therapy satisfactorily.	from 01.03.91	from 02.1990
19.	Yakushenko Y. N., 54 years old	M	MLB of the skin of the of the left shin, metastases	3	intra-venously	2 mg/kg	20 days	No changes.	Not established.	Regression of the tumor nodes from 10cmX8cm to 8cmX6cm.	Sustained the therapy satisfactorily.	from 20.02.91	7
20.	Rodionov A. V., 60 years old	m	MLB of the skin of the left buttock; generalization of the process	3	intra-venously	4 mg/kg	27 days	Decrease of the white blood cells from 10000 to 6000	Not established.	Axillary / inguinal nodes are decreased, opened.	Sustained the therapy satisfactorily.	from 17.04.91	from 12.1989
21.	Kukhar A. T., 31 years old	f	MLB of the skin of the back	3	intra-venously	2 mg/kg Infiltration of the tumour nodes, “Flaraxin”	15 days, 1 day	Decrease of the white blood cells by 0,8 thousands	Not established.	Large nodes decreased up to 50%, Regression # 3.	Sustained the therapy satisfactorily.	from 22.04.91	from 11.1989
22.	Khilchevskaya A. L., 65 years old	f	MLB of the skin of the right axillary region; metastases in the lymph nodes	3	intra-venously		14 days	Not registered.	Not established.	Regression of the metastases of the node.	Sustained the therapy satisfactorily.	from 15.01.91	from 02.1990
23.	Fedorchenko S. V., 27 years old	f	MLB of the skin of the left shin; metastases; generalization of the process	3	intra-venously	2,3 mg/kg	14 days	Vein irritation	Vein irritation	Regression of 3 tumour nodes. The rest thereof – up to 50%.	Sustained the therapy satisfactorily.	from 11.01.91	from 12.1990
24.	Lyakhovskaya N. P., 52 years old	f	MLB of the rectum, metastases in the pelvic bones	3	intra-venously		20 days	Not registered.	Not established.	Regression of the anus tumour by 2/3.	Sustained the therapy satisfactorily.	from 15.05.91	5
25.	Dobrenko M. I., 43 years old	f	MLB of the skin of the mammary gland; metastases in lymph nodes of the axillary creases	3	intra-venously	Post-surgical histopathological opinion: metastases in the lymph nodes, 2 mg/kg	16 days of the preventive course	Not registered.	Not established.	-	Sustained the therapy satisfactorily.	from 28.02.91	from 11.1990
26.	Kostenko A. G., 40 years old	m	MLB of the skin of the right earlobe	3	intra-venously	Post-surgical histopathological opinion:	1*20 days, every 3 weeks,	Not registered.	Not established.	-	Sustained the therapy satisfactorily.	from 20.02.91	2

						in the lymph nodes, metastases of the MBL, 2 mg/kg	2 mg/kg, 15 days						
27.	Gorbunova N. I., 34 years old	f	MLB of the left hip	3	intra-venously	Post-surgical histopathological opinion: metastases in the lymph nodes, 1,5 mg/kg	21 days of the preventive course	Not registered.	Not established.	-	Sustained the therapy satisfactorily.	from 17.05.91	from 12.1990
28.	Stepanenko G. I., 27 years old	f	MLB of the left shin	3	intra-venously	Post-surgical histopathological opinion: metastases in the lymph nodes, 2 mg/kg	10 days of the preventive course	Not registered.	Not established.	-	Sustained the therapy satisfactorily.	from 07.02.91	from 02.1990
29.	Maslovskaya N. V., 31 years old	f	MLB of the neck	3	intra-venously	Post-surgical histopathological opinion: metastases in the lymph nodes, 2 mg/kg	10 days of the preventive course	Not registered.	Not established.	-	Sustained the therapy satisfactorily.	from 17.05.91	from 12.1990
30.	Momitko S. I., 36 years old	m	MLB of the skin of the mammary gland	3	intra-venously	Post-surgical histopathological opinion: metastases in the lymph nodes, 2 mg/kg	10 days of the preventive course	Not registered.	Not established.	-	Sustained the therapy satisfactorily.	from 04.04.91	from 04

Table 2. Sex and age distribution of the patients.

Sex	Age (years old)						Total
	20-29	30-39	40-49	50-59	60-69	70-79	
Men	-	6	3	4	2	1	16
Women	2	3	2	4	2	1	14

Effectiveness of curing the melanoblastomata (MBL) with “Flaraxin”

As a criterion for the effectiveness of treatment of the patients suffering from MBL with “Flaraxin” served the extent of the regression of the tumour nodes as well as the changes of the feeling of the patients. The 100% effectiveness of curing the MBL is to be noted, but its expression differs. The effectiveness of treatment of the patients with extensive forms of MBL is significantly below. At the beginning the patients only with generalized forms of MBL or with metastases in vital organs took “Flaraxin”. After being convinced of manifestation of the anti-melanoblastoma effect, which was expressed in partial regression of the tumour nodes and feeling better, we started to treat less advanced cases.

The effectiveness of treatment of the patients who were treated before by polychemotherapy (PCT) and radiotherapy (RT) as well as the improvement of the effectiveness in the absence thereof is registered. The distribution of the patients with the relapses of MBL, who were treated before by mono- or combined therapy (not earlier than 3 months before the treatment with “Flaraxin” is presented в Table 3.

While curing with “Flaraxin”, the dependence of the effectiveness on duration of the disease was to be recorded both initial and recurrent melanoblastoma (MBL). The comparative evaluation thereof is presented in the Table. 4.

The patients who were primary treated with “Flaraxin” are worth noticing: Patient: Mr. B., 52 years old. Diagnosis: Melanoblastoma of the interscapular region, metastases in the dexter axillary space. Diabetes Mellitus.

Table 3. Group distribution of the patients with the **relapses of the melanoblastomata** (MBL), been treated before (before the treatment with "Flaraxin") by mono- or combined conventional therapy (not earlier than 3 months).

	The treatment only with "FLARAXIN"	**Surgical treatment**	**Surgical treatment + polychemotherapy**	**Surgical treatment + polychemotherapy + radiotherapy**
Patients' number	2	13	10	5
among them with the relapses	-	6	5	2

Table 4. The effectiveness of treatment with "Flaraxin" at the different steps of the **course of melanoblastoma**.

Duration of the disease	**Not over 2 months**	**From 2 to 6 months**		**Over 6 months**	
Result of the treatment, %	100%	Under 50%	Over 50%	Under 50%	Over 50%
Number of the treated patients	3	6	4	9	2

severely, post-infarction cardiosclerosis. He was treated by the fractional doses of 1 mg per 1 kg of the body weight, in the morning as well as in the evening throughout 20 days ("Flaraxin" was diluted in physiological salt solution). The diagnosis was confirmed by the results of the biopsy of axillary node 1 month before the treatment with "Flaraxin". The melanoma macula of the interscapular region disappeared, the surrounding satellites remain, which got higher colour. The axillary metastasis node reduced by 50%. The stabilization of the process was to be observed throughout 2 months. The refresher course of treatment with "Flaraxin" is being carried out combined with 2 "Vincristine" infusions.

The patient, Ms. K., 56 years old. Diagnosis: Melanoblastoma of the back's skin, metastases in the axillary lymph nodes (there is a keratinized area of 2.5 cm x 3 cm x 3 cm in the centre of the melanoma macula). She was treated with "Flaraxin" by the dose 2 mg per 1 kg of the weight throughout 20 days, daily. After the treatment, the full regression of the axillary lymph node and the clarification of the melanoma macula were to be observed. The keratinized area is excised surgically.

Application of Vincristine associated with "Flaraxin"

The patient, Ms. P., 40 years old. Diagnosis: melanoblastoma of the dexter shin. The operation was performed in 1989; there are recurrent metastases in the regions of neck, the paraspinal area of the thoracic cage and the dexter inguinal region. Large tumour nodes are of the diameter up to 12 cm. From 10.10.1990 to January 1991 she took 2 courses of treatment with "Flaraxin", the daily dose was 2 mg/kg, 20 days every course. As a result of the treatment, the cervical ganglion regressed completely, the nodes on the back and in the groin decreased by one third. The 3rd course was given combined with the operation. After 10 days of the treatment with "Flaraxin", the excision of the residuary nodes as well as subsequent 8 infusions of "Flaraxin" were combined with the administration of Vincristine, 4 times, were performed. In February, the alopecia was to be observed in the patient; 3 months later, after the treatment, the recurrent tumour node occurred in the dexter inguinal region. The 0,2% solution of "Flaraxin" was administered into the node. In the area of the node, the swelling and pain occurred which disappeared on the 3rd day. Thereupon the node decreased and within 1.5 months its stabilization is to be observed.

Intranodal infiltration associated with the intravenous infusions of "Flaraxin" was applied for 4 patients, at first the responsive enlarging of the nodes as well as pain occurred, thereupon these occurrences disappeared and the nodes decreased to getting the original size. Two patients came in the period of process generalisation. In the first 10 days the new small nodes appeared while curing with "Flaraxin".

Method of application of "Flaraxin" and optimal curative doses

After being convinced of no toxicities after 20 infusions of "Flaraxin" in the dose of 2 mg/kg in those cases where the complete regression was not attained, we increased the number of the injections to 30. In two cases with the intratumoural infiltration and intravenous infusions of "Flaraxin", the constant stabilisation of the active MBL is to be recorded. The question of the further operative therapy after the courses with "Flaraxin" at the incomplete regression of the nodes has been still not solved. One has the impression of the inexpediency of the operation, as curing with "Flaraxin" to our way of thinking causes a longer remission, than one with application of the surgical interventions.

The application of the doses over 2 mg/kg/day is inexpediency, as in the dose of 4 mg/kg/day for a period of 15 days of administration, the decrease of hemoglobin and white blood cells by 10-15% is to be recorded, whereas the daily average dose of 2 mg/kg somewhat stimulates the blood formation, and the regression of the tumour nodes is identical. What is more, the dose of 4 mg/kg sometimes causes the nausea and discomfort in patients.

SUMMARY

1. “Flaraxin” interacts with human serum albumin and cytochrome-C with the participation of tyrosin and tryptophanic residua. The application of the 5% glucose single-order inhibits the reaction between the human serum albumin and “Flaraxin” stimulates accelerating the interaction with tyrosin residua and inhibiting the interaction with tryptophanic ones.
2. The acute toxicity of “Flaraxin” at the intravenous introduction to the rats is 4 to 5 less than one of the base material of “Flaraxin”.
3. “Flaraxin” is a low-cumulating substance and does not change the body weight, liver and spleen of the mice.
4. “Flaraxin” possesses the antioxidant effect, that shows itself by the increasing the survival value of the animals, poisoned by tetrachloromethane. The antioxidant characteristics of “Flaraxin” in vitro show themselves more than ones of α-tocopherol.
5. “Flaraxin” in the dose of 10 mg/kg intramuscularly over a period of 6 to 15 days before immunization has no negative effect on the indices of humoral and cellular part of the immune responsiveness of an organism.
6. The expressed symptoms of the “Flaraxin” overdose during the experiment on the dogs appear with the drug doses by 40 times higher than the daily curative one. To cure such poisonings the complex of those remedies is to be used, which influence positively the tissue respiration (nicotinamide), the vessels (calcium gluconate) and possess the antihistamine action (diphenhydramine hydrochloride).
7. At the intravenous injection to the rats, “Flaraxin” is actively distributing in the organisms of animals (volume of distribution in the blood plasma is 3.40 l/kg). The maximum content of the drug in the organs and tissues of the animals is to be determined in 1 hour after injection and it exceeds the level in the blood plasma of 9.19 mg/l by 75-178 %. “Flaraxin” circulates in the blood plasma of animals over a long period of time – the half-elimination period lasts 5.8 hours. The main excretion way of “Flaraxin” and/or of its metabolites from the organisms of animals is one by kidneys.
8. The medical exercises project and process regulations are developed.
9. The treatment of 30 patients suffering from melanoblastomata with “Flaraxin” in the daily dose of 2 mg/kg was effective in the most cases. The drug of such dosage has no negative effect on blood formation, the central as well as peripheral nervous system, cardiovascular system, breathing, liver and kidneys’ functions.

Sustained remission with the complete regression of the melanoblastoma nodes was to be seen at the not advanced tumours. Curing the advanced melanoblastomata with “Flaraxin” may be combined with “Vincristine” as well as with the infiltration of the tumour nodes with “Flaraxin”.

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EXTRACT

From the report on the clinical study /stage I/ of the new antineoplastic agent – "Flaraxin" – performed at the Oncology Department of the Kiev Medical Institute in the period between September 1990 and January 1991.

1. "Flaraxin" of the curative dose (2 mg/kg) is not toxic; it is good sustained by the patients.
2. "Flaraxin" can be administered not only intravenously, but also intratumourly.
3. The therapeutic action of the "Flaraxin" is registered in 100% of the patients and declares itself through the general well-being mend, size reduction of the tumour nodes or of their full regression.
4. The most favorable results are to be observed with assigning "Flaraxin" at the early disease stages as well as during the relapses.
5. "Flaraxin" is the phytogenic drug; it belongs to the low-toxic compounds, according to the toxicological evaluation and clinical effect it excels the known antineoplastic drugs both home-produced and foreign.
6. Taking into account the results of the clinical trials, we consider the tumors to be advisably cured with "Flaraxin".

Chairman of the Commission,
Associate Professor of the Oncology Department,
Candidate of Medical Sciences *Signature* I. P. Loboda

Seal: *Ministry of Healthcare of the Ukrainian Soviet Socialist Republic*
Kiev Scientific-Research Institute for Pharmacology and Toxicology

Stamp: *True*
Secretary
Signature

Цей переклад з української та російської мов на англійську мову виконано мною, перекладачем **Ачкасовим Сергієм Володимировичем _____.**

This document is translated by ***Sergiy Volodymyrovych Achkasov***, from Ukrainian and Russian into English *Signature*

Місто Харків, Україна

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