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Investigation of toxicological properties and optimal therapeutic doses of compound T1084 with anti-tumor activity

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Antiangiogenic therapy, despite its effectiveness, is limited by systemic toxicity, the development of organism resistance, and high treatment costs. In this regard, the development of new, safer, and more effective antiangiogenic agents is a relevant task in modern oncology.

The aim. Assessment of toxicological characteristics and experimental substantiation of the optimal range of therapeutic doses of an NOS/PDK inhibitor (compound T1084) for enteral administration.

Materials and methods. The study was conducted on 118 BALB/c mice and 79 F1 hybrids (CBA×C57BL/6j). The acute toxicity of compound T1084 was studied following a single enteral administration. Cumulative effects were assessed using the Lim method with parenteral administration. The optimal range of anti-tumor doses was investigated on a model of Ehrlich's solid carcinoma therapy with subchronic enteral administration of compound T1084 at doses of 200–400 mg/kg.

Results. Parameters of acute toxicity for compound T1084 upon enteral (intragastric) administration were established: LD_{10} — 2031 mg/kg, LD_{16} — 2100 mg/kg, LD_{50} — 2356±15 mg/kg, LD_{84} — 2644 mg/kg. According to toxicological studies, compound T1084, when administered enterally, belongs to hazard class III (moderately hazardous substances) according to GOST 12.1.007–76 and class V according to GOST 32419–2022 for the EAEU. A 5-fold decrease in the toxicity of T1084 was revealed with enteral administration compared to parenteral administration. The absence of cumulative properties in T1084 was established, which allows for prolonged courses of this compound. On the Ehrlich's carcinoma therapy model, a dose-dependent anti-tumor effect was shown: at 200 mg/kg, tumor growth inhibition (TGI) was 15–20%; 300 mg/kg — 28–31%; 400 mg/kg — 30–35%. The absence of significant differences between doses (300 and 400 mg/kg) with more favorable tolerability allowed the selection of 300 mg/kg as the optimal dose.

Conclusion. The obtained data substantiate the promise of preclinical development of an oral dosage form of T1084 for long-term therapy in oncology, including in adjuvant treatment regimens.

Keywords: anti-tumor agents; isothiouronium derivatives; acute toxicity; cumulative effect; optimal doses

Abbreviations: MNs — malignant neoplasms; NO — nitric oxide; NOS — nitric oxide synthase; eNOS — endothelial nitric oxide synthase; iNOS — inducible nitric oxide synthase; DCA — dichloroacetate; PDKs — pyruvate dehydrogenase kinases; ESC — Ehrlich's solid carcinoma; CC — cervical cancer; TGI — tumor growth inhibition.

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Исследование токсикологических свойств и оптимальных терапевтических доз соединения Т1084 с противоопухолевой активностью

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Антиангиогенная терапия, несмотря на свою эффективность, ограничена системной токсичностью, развитием резистентности организма и высокой стоимостью лечения. В связи с этим разработка новых, более безопасных и эффективных антиангиогенных средств является актуальной задачей современной онкологии.

Цель. Оценка токсикологических характеристик и экспериментальное обоснование оптимального диапазона терапевтических доз NOS/PDK-ингибитора (соединение Т1084) при энтеральном применении.

Материалы и методы. Исследование выполнено на 118 мышах линии BALB/c и 79 гибридах F1 (CBA×C57BL/6j). Острую токсичность соединения Т1084 изучали при однократном энтеральном введении. Кумулятивное действие оценивали по методу Лима при парентеральном введении. Оценку диапазона оптимальных противоопухолевых доз проводили на модели терапии солидной карциномы Эрлиха при субхроническом энтеральном введении соединения Т1084 в дозах 200–400 мг/кг.

Результаты. Установлены параметры острой токсичности для соединения Т1084 при энтеральном (внутрижелудочном) введении: $ЛД_{10}$ — 2031 мг/кг, $ЛД_{16}$ — 2100 мг/кг, $ЛД_{50}$ — 2356±15 мг/кг, $ЛД_{84}$ — 2644 мг/кг. По данным токсикологических исследований соединение Т1084 при энтеральном применении относится к III классу опасности (умеренно опасные вещества) по ГОСТ 12.1.007–76 и V классу по ГОСТ 32419–2022 для ЕАЭС. Выявлено 5-кратное снижение токсичности Т1084 при энтеральном применении по сравнению с парентеральным введением. Установлено отсутствие кумулятивных свойств у Т1084, что позволяет применять это соединение продолжительными курсами. На модели терапии карциномы Эрлиха показан дозозависимый противоопухолевый эффект: при 200 мг/кг торможение роста опухоли (ТРО) составило15–20%; при 300 мг/кг — 28–31%; при 400 мг/кг — 30–35%. Отсутствие значимых различий между дозами (300 и 400 мг/кг) при более благоприятной переносимости позволило выбрать дозу 300 мг/кг как оптимальную.

Заключение. Полученные данные обосновывают перспективность доклинической разработки пероральной лекарственной формы Т1084 для длительной терапии в онкологии, в том числе в схемах адъювантного лечения.

Ключевые слова: противоопухолевые средства; производные изотиуронии; острая токсичность; кумулятивное действие; оптимальные дозы

Список сокращений: ЗНО — злокачественные новообразования; NO — оксид азота; NOS — синтаза оксида азота; eNOS — эндотелиальная синтаза оксида азота; iNOS — индуцибельная синтаза оксида азота; DCA — дихлорацетат; PDK — киназы пируватдегидрогеназы; СКЭ — солидная карцинома Эрлиха; РШМ-5 — рак шейки матки; ТРО — торможение роста опухоли.

INTRODUCTION

Malignant neoplasms (MNs) remain a leading cause of mortality and disability in the Russian Federation, being the second most frequent cause of death after cardiovascular diseases. According to official data, 698,693 cases of MN[1] were newly diagnosed in 2024, with the number of cancer patients continuing to grow steadily each year. Despite the progress made in early diagnosis and treatment methods, the problem of effective therapy for many common and metastatic forms of cancer remains relevant. In modern anti-tumor therapy regimens, anti-angiogenic drugs, which act by suppressing tumor tissue vascularization [1, 2], play an important role. However, the clinical use of these drugs is limited by several factors, including

[1] Kaprin AD, Starinsky VV, Shakhzadova AO. The state of oncological care for the Russian population in 2024. Moscow: Herzen Moscow Medical Research Institute – branch of the NMITS of Radiology; 2025. 275 p. Russian

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insufficient therapeutic efficacy, the development of systemic side effects, and high treatment costs [3, 4]. Furthermore, tumor cells have the ability to adapt to hypoxic conditions by activating alternative metabolic pathways and developing resistance to therapy [5]. These circumstances underscore the importance of searching for and developing new anti-angiogenic agents with good tolerability and the ability to overcome therapeutic resistance.

The discovery in the 1980s–1990s of the role of nitric oxide (NO) as a universal signaling molecule significantly expanded the understanding of tumor angiogenesis mechanisms [6, 7]. NO/eNOS signaling plays a key role in tumor angiogenesis [8]. Under the influence of pro-angiogenic factors (VEGF, bFGF, etc.), endothelial NO synthase (eNOS) expression is activated in endothelial cells, leading to a sustained increase in NO production. The resulting NO acts as a pleiotropic mediator, initiating a cascade of events necessary for new vessel formation. These include: relaxation of vascular smooth muscle cells (vasodilation), increased vascular wall permeability through remodeling of endothelial junctions, and stimulation of endothelial cell migration and proliferation [9]. Collectively, these processes ensure the formation of a functional vascular network that nourishes tumor tissue. A logical consequence of these discoveries was the strategy of pharmacologically suppressing angiogenesis by non-specific inhibition of endogenous NO synthesis with chemical NOS inhibitors. In the laboratory of radiation pharmacology of the Medical Radiological Research Center named after A.F. Tsyb, anti-angiogenic activity was demonstrated for a number of thioamidine NOS inhibitors—N,S-substituted isothiouronium derivatives. In particular, studies have shown that competitive inhibitors of iNOS/eNOS from the isothiouronium class, when administered parenterally chronically at safe doses (1/9–1/5 LD_{16}), suppress the growth and metastasis of solid mouse tumors [10]. However, as with pharmacopoeial anti-angiogenic drugs, prolonged use of NOS inhibitors is accompanied by neoplasm adaptation and the development of therapeutic resistance [11].

A significant number of modern studies are dedicated to finding ways to overcome hypoxic resistance that arises during anti-angiogenic therapy. One of the most studied agents used for these purposes is the structural analog of pyruvate, sodium dichloroacetate (DCA)—the only pyruvate dehydrogenase kinase inhibitor that has completed Phase I and II clinical trials [12, 13]. DCA reactivates the pyruvate dehydrogenase complex, switching tumor cell metabolism from aerobic glycolysis to oxidative phosphorylation, which is accompanied by the accumulation of reactive oxygen species to a level sufficient to cause a toxic effect in the tumor cell [14].

The ability of thioamidine NOS inhibitors (weak bases) to form salts with strong acids, particularly with dichloroacetic acid, has opened up the possibility of creating hybrid molecules. The implementation of this combination led to the synthesis of compound T1084 (1-isobutanoyl-2-isopropylisothiourea dichloroacetate), which combines NOS- and PDK-inhibiting fragments in its structure. In the resulting molecule, NOS inhibition contributes to a vasoconstrictor effect and suppression of angiogenesis [10], while PDK blockade disrupts the metabolic adaptation of tumor cells to hypoxic conditions, inducing their apoptosis [15]. Due to this bifunctional action, compound T1084, when administered parenterally at a safe dose of 70.7 mg/kg (1/4 LD_{10}), not only suppresses the growth of experimental tumors (Ehrlich's carcinoma, cervical cancer (RShM-5), B-16 melanoma) but also prevents the development of hypoxic resistance in neoplasms [16], and enhances the antitumor effects of single and fractionated γ-irradiation [17].

As the compound T1084 has demonstrated pronounced antitumor activity upon parenteral administration (1–2 week course), extrapolating such a regimen to clinical application requires selecting a route and method of administration optimal for long-term therapy. The widespread use of oral dosage forms in standard adjuvant regimens (capecitabine for breast cancer, temozolomide for gliomas, tyrosine kinase inhibitors for various solid tumors, etc.)[2,3,4] confirms that the enteral route is preferred for prolonged treatment. Oral administration allows for outpatient therapy, eliminates the need for invasive procedures, reduces the risk of infectious complications, and lessens the psychological burden on patients [18], which is particularly important for long-term adjuvant treatment courses. In this regard, preclinical studies of T1084 are focused on developing an oral dosage form of this compound.

THE AIM. To investigate the toxicological characteristics and experimentally substantiate the

[2] Clinical Guidelines "Breast Cancer". Ministry of Health of the Russian Federation. Available from: https://cr.minzdrav.gov.ru/preview-cr/379_4. Russian
[3] Clinical Guidelines "Glioblastoma". Ministry of Health of the Russian Federation. Available from: https://cr.minzdrav.gov.ru/recomend/652
[4] Clinical Guidelines "Lung Cancer". Ministry of Health of the Russian Federation. Available from: https://cr.minzdrav.gov.ru/preview-cr/30_5

optimal antitumor therapeutic doses of the NOS/PDK inhibitor T1084 upon enteral administration.

MATERIALS AND METHODS

Object of study

The object of study is an antitumor bifunctional agent based on 1-isobutanoyl-2-isopropylisothiourea dichloroacetate (compound T1084), which was theoretically substantiated and synthesized in the laboratory of radiation pharmacology at the Medical Radiological Research Center (MRRC; Obninsk). The structure of the compounds was confirmed by elemental analysis (C, H, N) on an EA 1108 analyzer (Carlo Erba Instruments, Italy) and 1H, 13C NMR spectroscopy on an AVANCE AV 300 Fourier spectrometer (Bruker, Germany). The purity of T1084 was controlled by thin-layer, high-performance liquid, and gas chromatography, and melting point [16]. Thin-layer chromatography was performed on Silufol UV-254 plates in a benzene–ethanol–triethylamine (9 : 1 : 0.1) system. HPLC studies were conducted on a Hitachi Chromaster HPLC System (Hitachi High-Tech Corp., USA). Melting point was measured on a PTP-M automatic heating system (LOIP, Russia).

Laboratory animals

The studies were performed on 118 male Balb/c mice and 79 female F1 (CBAxC_{57}Bl/6j) mice aged 3–4 months and weighing 22–25 g. The laboratory animals were obtained from the nursery of the Scientific Center for Biomedical Proteins and were housed in the vivarium of the MRRC under conditions compliant with sanitary and epidemiological rules for housing experimental biological clinics (vivariums)[5]. The mice were housed in T-3 cages with sterile wood bedding, 5–10 animals per cage, with free access to water and standard complete feed PK-120-1 (Laborator-Korm LLC, Russia). The cages were located in a room at a temperature of 18–20°C, humidity of 40–70 %, and natural lighting. Animals without signs of health deviations were selected for the studies. All animal work was approved by the Bioethics Committee of the National Medical Research Center of Radiology (protocol No. 1-D-00041, dated October 20, 2023). Upon completion of the studies, experimental animals were euthanized in accordance with bioethical norms using a CO_2 euthanizer (Aw-Tech, Russia).

[5] SP 2.2.1.3218-14. Sanitary and epidemiological requirements for the establishment, equipment and maintenance of experimental biological clinics (vivariums); approved by Resolution No. 51 of the Chief State Sanitary Doctor of the Russian Federation dated August 29, 2014; Moscow: Rospotrebnadzor; 2014. 23 p. Russian

Acute toxicity of T1084 upon enteral administration

The acute toxicity of compound T1084 was assessed after a single enteral (intragastric, ig) administration using a two-stage protocol. In the first stage (preliminary), the approximate LD_{50} was determined in 10 Balb/c mice using the Deichmann and Leblanc method[6]. In the second stage (detailed), 48 Balb/c mice were divided into 7 groups (6–12 animals each) and received doses above and below the approximate LD_{50} (in the dose range of 2000–3000 mg/kg). Compound T1084 was administered intragastrically as a 10 % solution, freshly prepared in water for injection (Dalchimpharm OJSC, Russia). Steel curved gastric tubes (GK Vivarium, Russia) were used for administration. Acute toxicity parameters (LD_{10}, LD_{16}, LD_{50}, and LD_{84}) were calculated using Litchfield and Wilcoxon probit analysis[7]. Animals were observed continuously for the first 4–6 hours after administration, and then daily for 14 days. During these periods, the general condition of the animals was visually assessed based on a combination of clinical signs (behavior, appetite, motor activity, coat condition).

Cumulative action of T1084 upon parenteral administration

The cumulative action of T1084 was assessed upon parenteral administration (intraperitoneal, ip) of the compound according to the method of Lima et al. in accordance with the guidelines for preclinical studies[8]. The method is based on recording mortality rates with stepwise dose increases every four days, starting from 0.1 LD_{50} up to 0.75 LD_{50}. The study design was developed based on previously established parameters of acute toxicity of T1084 after single parenteral administration to mice and is presented in Table 1 [15]. In the experiment, 60 male Balb/c mice were divided into 6 groups (n = 10) according to the number of doses and time points studied. After each administration stage, one group was set aside for mortality assessment, and the remaining animals continued administration according to the study scheme (Table 1). Compound T1084 was administered ip to the animals as 0.4–2.5 % solutions prepared using water for injection.

[6] Deichmann WB, LeBlanc TJ. Determination of the approximate lethal dose with about six animals. J Ind Hyg Toxicol. 1943;25:415–417.
[7] Litchfield JT Jr, Wilcoxon F. A simplified method of evaluating dose-effect experiments. J Pharmacol Exp Ther. 1949;96(2):99–113.
[8] Mironov AN. Guidelines for conducting preclinical studies of medicines. Part 1. Moscow: Grif and K; 2012. 944 p. Russian

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Precise toxicometric parameters (LD_{10}, LD_{16}, LD_{50}, and LD_{84}) were calculated using Litchfield and Wilcoxon probit analysis[9]. The cumulative index (Kk) was determined as the ratio of the cumulative LD_{50} upon repeated administration to the LD_{50} upon single administration.

Experimental evaluation of the optimal antitumor dose range of T1084

The experimental evaluation of the optimal dose range of T1084 was conducted on a model of solid Ehrlich's carcinoma (SEC) therapy in 79 female F1 ($CBAxC_{57}Bl/6j$) mice. The tumor was transplanted by subcutaneous injection into the thigh of 2.5×10^6 cells in 0.2 mL of medium 199 (Pan-Eco, Russia). On the 7 day after transplantation, when the tumor nodules reached reliably measurable sizes (100–150 mm^3), the animals were divided into 5 groups (control and 4 experimental) of 17–21 individuals each. From this day until the 21 day of tumor growth, mice in the experimental groups received compound T1084 daily ig at doses of 200–400 mg/kg (2–4 % solutions), and mice in the control group received a daily ig injection of 0.9 % sodium chloride solution.

The antitumor effect was assessed morphometrically by the dynamics of relative tumor volumes and growth inhibition in accordance with the methodology described in [16]. Standard parameters of variation statistics were calculated for the experimental data, and their values are presented graphically as M ± SD. The significance level of intergroup differences in the evaluated indicators was determined using non-parametric criteria with the Kruskal-Wallis ANOVA test and the post-hoc Mann-Whitney U-test according to the Holm-Bonferroni multiple comparison procedure. Differences were considered significant at $p < 0.05$. Statistical calculations were performed using the Statistica 10.0 software package (StatSoft Inc., USA).

RESULTS

Acute toxicity upon enteral administration

In the acute toxicity test, it was established that the clinical picture of intoxication after a single intragastric administration of compound T1084 was dose-dependent. At doses of 2000–2300 mg/kg, intoxication in animals was weakly expressed and manifested in the first minutes after administration as reduced motor activity, lying down, and weak response to external stimuli. With an increase in dose to 2300–3000 mg/kg, toxic effects were more pronounced and appeared within 10–20 minutes after administration of the compound, including tachypnea, respiratory arrhythmia, ataxia, tremor, and clonic seizures. Lethal outcomes at toxic doses were recorded within the first 20–60 min after administration of compound T1084. In surviving animals, signs of intoxication began to regress after 2 hours, with complete disappearance of neurological symptoms by 4–5 hours of observation. In the long-term period (24 hours and throughout the subsequent 14 days), surviving mice did not differ visually from the control group of intact animals in their general condition, which, overall, indicated the absence of residual toxic effects and restoration of bodily functions.

The data on the lethal effect of compound T1084 after single intragastric administration to BALB/c mice, obtained in the two stages of the study, are presented in Table 2.

Using the Litchfield and Wilcoxon probit analysis method, toxicometric parameters of T1084 upon intragastric administration were established, which are presented in Table 3. The LD_{50} of the studied compound was 2356 ± 15 mg/kg, which corresponds to Hazard Class III (moderately hazardous substances) according to GOST 12.1.007-76 (LD50 upon gastric administration—from 151 mg/kg to 5000 mg/kg) and Class V according to GOST 32419-2022 for EAEU ($2000 < LD_{50} < 5000$ mg/kg, ig).

Cumulative effect of compound T1084 upon parenteral administration

The study of the cumulative effect of T1084 allowed for the assessment of its subchronic application. Upon prolonged parenteral administration of T1084 in increasing doses, the first signs of intoxication and cases of animal death were recorded on the 15 day of the experiment after reaching a cumulative dose of 1296.2 mg/kg. Cumulative doses and mortality rates are presented in Table 4.

Toxicometric parameters of T1084, determined by the Litchfield and Wilcoxon probit analysis method, are presented in Table 5. It was established that the LD_{50} upon repeated parenteral administration of T108 mg/kg was 2227 ± 15 mg/kg. The calculated cumulative coefficients significantly exceeded unity for all lethality levels, indicating the absence of cumulative properties in the multitarget compound T1084.

[9] Litchfield JT Jr, Wilcoxon F. A simplified method of evaluating dose-effect experiments. J Pharmacol Exp Ther. 1949;96(2):99–113.

Table 1 — Scheme for studying the cumulative properties of the multitarget compound T1084 in BALB/c mice

Groups, days of administration	Number of animals		Doses administered	
	Per group	Remaining for subsequent doses	Fraction of LD_{50}	Upon parenteral administration (mg/kg)
1–4	10	60	0.1	44.7
5–8	10	50	0.15	67.1
9–12	10	40	0.22	98.3
13–16	10	30	0.34	152.0
17–20	10	20	0.5	223.5
21–24	10	10	0.75	335.3

Table 2 — Toxicity assessment of compound T1084 after single enteral (ig) administration to Balb/c mice

T1084 doses, mg/kg	Died mice / number of mice in group
First stage of study (preliminary)	
2000	0 / 2
2300	1 / 2
2600	2 / 2
3000	2 / 2
3500	2 / 2
Second stage of study (detailed)	
2000	0 / 6
2125	1 / 6
2375	4 / 8
2500	9 / 12
2750	7 / 8
3000	8 / 8

Note: Increasing the sample size in the region close to LD_{50} improves the accuracy of toxicometric parameter calculation and reduces the standard error.

Table 3 — Acute toxicity parameters of T1084 after single enteral (ig) administration to Balb/c mice

Compound	LD_{10}		LD_{16}		LD_{50}		LD_{84}	
	mg/kg	mM/kg	mg/kg	mM/kg	mg/kg	mM/kg	mg/kg	mM/kg
T1084 i.v.	2031	6.40	2100	6.61	2356 ± 15	7.40	2644	8.33

Table 4 — Cumulative doses and mortality rates of male BALB/c mice receiving parenteral injections of T1084

Groups, days of administration	Test doses, administered over 4 days		Planned maximum cumulative doses		Number of deaths/ number in group	Individual cumulative doses causing death	
	mg/kg	fraction of LD_{50}	mg/kg	fraction of LD_{50}		mg/kg	fraction of LD_{50}
1–4	44.7	0.10	178.8	0.4	0/10	–	–
5–8	67.1	0.15	447.0	1.0	0/10	–	–
9–12	98.34	0.22	840.6	1.88	0/10	–	–
13–16	152.0	0.34	1448.6	3.24	1/10	1296.2	2.90
17–20	223.5	0.50	2342.6	5.24	0/10	–	–
21–24	335.3	0.75	3683.8	8.24	5/10 7/10 10/10	2581.1 2677.5 3012.8	5.78 5.99 6.74

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Table 5 — Toxicity of T1084 after prolonged parenteral administration to male BALB/c mice in increasing doses

Compound	Toxicity indicators, mg/kg			
	LD_{10}	LD_{16}	LD_{50}	LD_{84}
T1084 ig, once*	302	330	448±13	608
T1084 ig, multiple	1410	1562	2227±15	3174
K_{cum}	4.67	4.73	4.97 (3.77 ÷ 6.97)	5.22

Note: * parameters of acute toxicity of T1084 with parenteral administration, obtained earlier [16]; K_{cum}, accumulation coefficient.

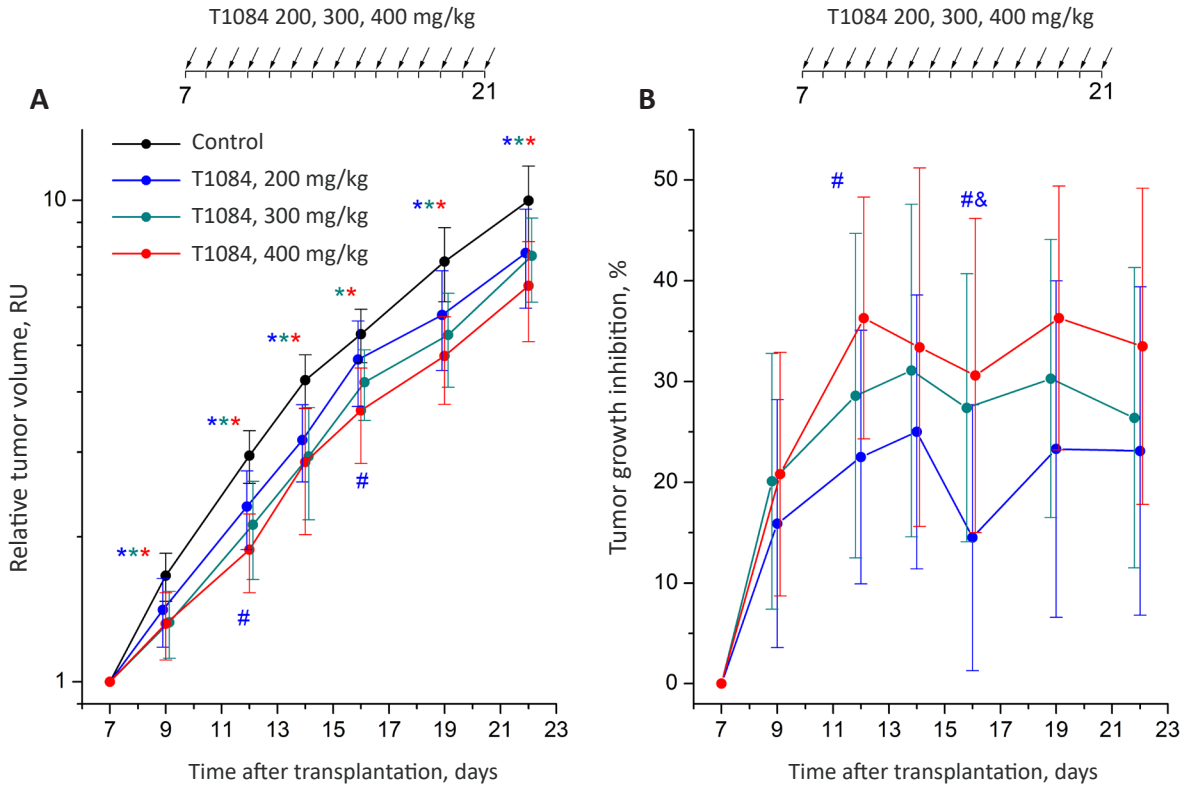

Figure 1 — Effect of T1084 compound administered chronically enterally at doses of 200–400 mg/kg on the growth of solid Ehrlich carcinoma in female F1 (CBA×C57BL6j) mice.

Note: A, tumor growth curves in animal groups. Values for each mouse are normalized to the tumor volume before the start of interventions. Graphical deviations correspond to SD (n = 17–21). * statistically significant differences between experimental groups and control (symbol color corresponds to the compared curve): Control/T1084 200 mg/kg (p = 0.008344, p = 0.000180, p = 0.000042, p = 0.004452, p = 0.004880), Control/T1084 300 mg/kg (p = 0.000330, p = 0.000040, p = 0.000045, p = 0.000290, p = 0.000040, p = 0.001005), Control/T1084 400 mg/kg (p = 0.000156, p < 0.000001, p = 0.000120, p = 0.004456, p = 0.000006, p = 0.000012); # between groups T1084 400 mg/kg and T1084 200 mg/kg (p = 0.002109, p = 0.032400). B, dynamics of tumor growth inhibition (TGI) in animal groups; & statistically significant differences between groups T1084 300 mg/kg and T1084 200 mg/kg (p = 0.046870); # statistically significant differences between groups T1084 400 mg/kg and T1084 200 mg/kg (p = 0.002109, p = 0.003270).

Experimental evaluation of the optimal dose range of T1084 in a mouse model of Ehrlich carcinoma therapy

The conducted study on a model of Ehrlich carcinoma therapy established that the compound T1084, administered subchronically via intragastric instillation (14 injections), exerted a statistically significant antitumor effect at all observation stages (p < 0.05) (Fig. 1 A, B). The intensity of these effects was dose-dependent. At the minimum tested dose (200 mg/kg), a generally weak antitumor effect was observed, accompanied by a 15–20 % inhibition of tumor growth. Increasing the dose to 300 mg/kg enhanced the antitumor activity of T1084: the effect was more pronounced and stable, maintaining a significant level throughout all observation periods (p = 0.0003–0.001). At this dose, T1084 inhibited tumor growth by 28–31 %. The level of antitumor effects of T1084 at this dose was comparable to the efficacy of parenteral administration of this compound at a dose of 70.7 mg/kg, as established in earlier studies [16]. Further increasing the dose of T1084 to 400 mg/kg

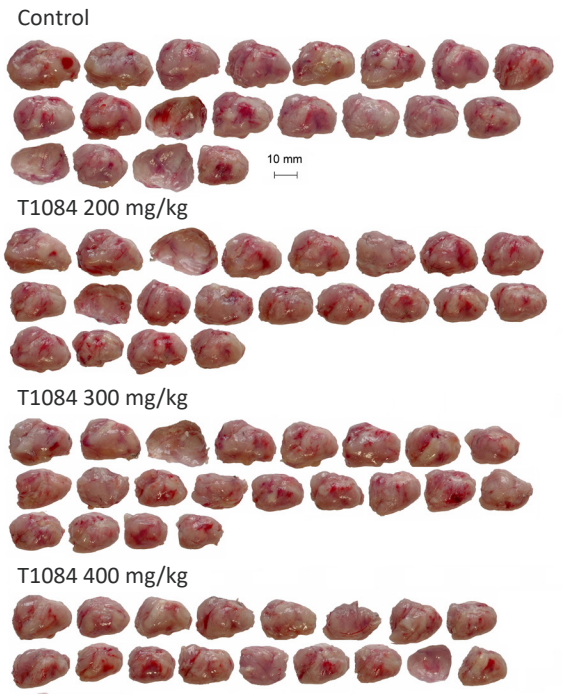

Figure 2 — Macroscopic appearance of solid Ehrlich carcinoma tumor nodules excised from mice in experimental groups on the 22 day of growth.

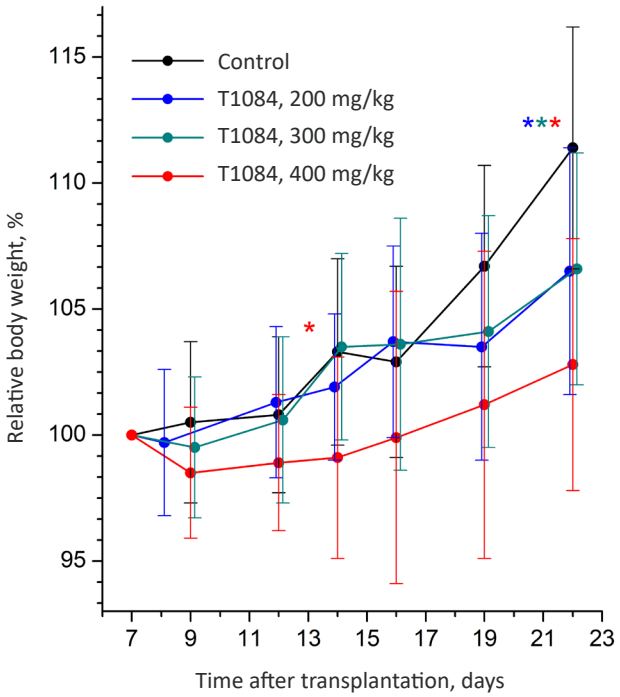

Figure 3 — Effect of T1084 compound administered chronically enterally at doses of 200–400 mg/kg on the dynamics of relative body weight in tumor-bearing mice.
Note: * statistically significant differences between experimental groups and control ($p < 0.05$).

did not result in a significant increase in antitumor efficacy: the maximum tumor growth inhibition was 30–35 %, which did not significantly differ from the rates obtained with T1084 at a dose of 300 mg/kg.

Macroscopic evaluation of tumor nodules excised on the 22 day after transplantation (Fig. 2) confirmed the dose-dependent nature of the compound's antitumor action: in groups of mice receiving T1084 at doses of 300 mg/kg and 400 mg/kg, the tumor nodules were visually smaller than in the control group, but, overall, showed little difference between them.

Evaluation of therapy tolerability based on body weight dynamics showed (Fig. 3) that at doses of 200 mg/kg and 300 mg/kg, a slight (3–5 %) decrease in body weight gain was observed, which was recorded only at later observation stages (days 19–23). At these doses, the observed decrease in body weight gain was not life-threatening for the animals. With an increase in the T1084 dose to 400 mg/kg, changes in this parameter became more noticeable and were recorded earlier. By the end of the experiment, the body weight of mice in this group was approximately 10 % less than that of control and experimental animals, which could most likely be interpreted as an initial sign of T1084 toxicity.

Considering the comparable antitumor efficacy of doses 300 and 400 mg/kg (TGI 26.4–31.5 % and 30–36 % respectively) with a more favorable tolerability profile, the optimal therapeutic dose of T1084 for intragastric administration is 300 mg/kg. Further increasing the dose of T1084 to 400 mg/kg proved to be inexpedient: no significant enhancement of the antitumor effect was observed, but signs of compound toxicity were already evident.

DISCUSSION

More than half a century has passed since J. Folkman's fundamental discovery (1971) of the role of angiogenesis in tumor progression [19] and the emergence of the first anti-angiogenic drug, bevacizumab (2004) [20]. During this time, the arsenal of anti-angiogenic agents has significantly expanded, and their clinical use has become routine practice for oncologists. However, as numerous studies [21–23] indicate, the initial expectations for anti-angiogenic therapy have not been met. The efficacy of monotherapy with anti-angiogenic agents remains moderate, and survival improvements in combination regimens rarely exceed a few months [24]. The main obstacle to achieving a sustained clinical response, according to many researchers [25–27], is the rapid development of tumor resistance to the hypoxic microenvironment induced by anti-angiogenic treatment.

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A possible way to increase the stability and efficacy of anti-angiogenic cancer therapy may be the use of anti-vascular drugs in combination with hypoxia-oriented cytotoxins, which primarily target hypoxic tumor cells. The idea of combining these agents found experimental confirmation in the work of J.H. Baker et al., where the combined use of the NOS inhibitor L-NNA with the bioreductive hypoxic toxin tirapazamine led to an enhanced antitumor effect [28]. In our own studies, the promise of this strategy was confirmed with the use of a NOS inhibitor from the class of N,S-substituted isothiouronium derivatives and sodium dichloroacetate. The combined use of these agents not only enhanced the antitumor effect but also blocked the development of hypoxic resistance in Ehrlich carcinoma (TGI 50–55 % throughout the observation period) [29]. The obtained results formed the basis for creating a new bifunctional molecule, T1084, based on these compounds, combining anti-angiogenic (NOS-inhibiting) and hypoxia-oriented cytotoxic (PDK-inhibiting) activity.

Most modern anti-angiogenic drugs, particularly tyrosine kinase inhibitors, are intended for course-based oral administration in the treatment regimens for many common oncological diseases [30]. The multi-target anti-angiogenic compound T1084 developed by us showed its efficacy with course-based parenteral administration [16]; however, its activity via the enteral route of administration remained unstudied. In this regard, the aim of the present work was to conduct a toxicological evaluation and provide experimental justification for the optimal therapeutic dose of T1084 for enteral administration. The established parameters of acute toxicity of T1084 upon intragastric administration (LD_{50} 2356 ± 15 mg/kg) correspond to Class III (moderately hazardous substances) and Class V hazard[10,11]. Comparison of these parameters with previously obtained data for parenteral administration of T1084 (LD_{50} 447 mg/kg) revealed a significant, 5-fold reduction in the toxic effect of T1084 upon intragastric administration compared to its intraperitoneal administration. This difference may be due to peculiarities of the compound's absorption and metabolism in the gastrointestinal tract [31]. Such a dependence of toxicity on the route of administration is a favorable factor for the development of an oral dosage form of T1084, as it allows for a reduction in the risk of systemic side effects while maintaining therapeutic efficacy. The obtained results are generally consistent with literature data on the more favorable safety profile of oral drug forms [32, 33].

An important result of the work is the experimental confirmation of the absence of cumulative toxicity in T1084. The obtained cumulative value (4.97) significantly exceeds unity and indicates not only the absence of accumulation of toxic effects but also the development of an adaptive response of the organism upon repeated administration of the compound in increasing doses. The absence of cumulative toxicity is an important advantage of T1084 and favorably distinguishes the developed compound from many classical cytostatic and anti-angiogenic agents, the use of which is limited by the development of cumulative dose-dependent toxic effects [34]. For example, cumulative cardiotoxicity is known for tyrosine kinase inhibitors (sunitinib, sorafenib), which limits the duration of therapy and requires careful monitoring of the cardiovascular system function [35, 36]. For bevacizumab and other anti-VEGF agents, cumulative effects such as proteinuria, arterial hypertension, and coagulation disorders are characteristic, which increase with prolonged use [37]. The conducted assessment of the cumulative properties of T1084 indicates a low risk of toxic effect accumulation with repeated use of this agent, and the results obtained in this study open prospects for the use of T1084 in long-term adjuvant therapy regimens.

In the Ehrlich carcinoma model, the optimal therapeutic dose of T1084 for enteral administration was established as 300 mg/kg. At a dose of 200 mg/kg, the antitumor effect of T1084 was insufficiently effective (TGI 15–20 %). Increasing the dose to 300 mg/kg was accompanied by a significant increase in antitumor activity (TGI 28–31 %), whereas further increase to 400 mg/kg did not lead to a substantial enhancement of the effect (TGI 30–35 %) but caused the development of initial signs of toxicity. It is important to note that the tumor growth inhibition (28–31 %) achieved with enteral administration at a dose of 300 mg/kg is practically comparable to the efficacy of parenteral administration of T1084 at a dose of 70.7 mg/kg, which confirms the preservation of T1084's activity upon oral administration. For comparison, when switching from intravenous to oral administration of etoposide, its efficacy can decrease by 20–40 % due to variable drug bioavailability [38]. In the case of T1084, there is practically no loss of efficacy.

When recalculating the optimal therapeutic dose of T1084 for other animal species and humans

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(considering body surface area)[12], the equivalent doses were: for rats—150 mg/kg, for rabbits—75 mg/kg, for humans—24 mg/kg (1700 mg/person for a body weight of 70 kg). The obtained data form the necessary foundation for transitioning to the next stages of preclinical development of this agent, intended for adjuvant therapy of oncological diseases (evaluation of specific activity and pharmacokinetics).

Study Limitations

This work has several limitations that should be considered when interpreting the results. The acute toxicity of T1084 was assessed in only one animal species (male BALB/c mice), whereas according to the methodology of preclinical studies, a complete toxicological characterization requires studies in two animal species (mice and rats) of both sexes, with an assessment of possible sex-related differences in sensitivity to the compound. Cumulative effects were studied with parenteral, not enteral, administration; pharmacokinetic parameters (bioavailability, metabolism, tissue distribution) were not evaluated. The indicated limitations define the directions for further research on T1084, but do not diminish the significance of the obtained results.

[12] Deichmann W.B., LeBlanc T.J. Determination of the approximate lethal dose with about six animals.J Ind Hyg Toxicol. 1943;25:415–417.

CONCLUSION

In the conducted toxicological studies, the LD50 value for the multitargeted antitumor agent based on 1-isobutanolyl-2-isopropylisothiourea dichloroacetate (compound T1084) upon enteral administration was determined to be 2356 ± 15 mg/kg. This value corresponds to hazard class III according to GOST 12.1.007-76 (moderately toxic substances) and hazard class V according to GOST 32419-2022 for the EAEU. A significant reduction in toxicity was demonstrated with enteral administration of T1084 compared to parenteral administration of this compound. The absence of cumulative effects for T1084 was experimentally confirmed, which justifies its subchronic use in adjuvant therapy regimens without the risk of toxic effect accumulation. On the model of solid Ehrlich's carcinoma, the optimal enteral therapeutic dose of 300 mg/kg was established, providing a pronounced antitumor effect (tumor growth inhibition of 28–31 %) with satisfactory therapy tolerability.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Anna A. Shitova — conceptualization, investigation, data analysis, visualization, writing—original draft, writing—review & editing; Marina V. Filimonova, Alexandr S. Filimonov — conceptualization, data analysis, visualization, writing—original draft, writing—review & editing; Daria I. Filatova, Ekaterina A. Prosovskaya — investigation, writing—original draft; Olga V. Soldatova, Vitaly A. Rybachuk, Aleksandr O. Kosachenko, Kirill A. Nikolaev, Alexander Yu. Gorbachev — investigation, data analysis, validation; Olga S. Izmesteva — data analysis, visualization. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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