BENZIMIDAZOLE DERIVATIVE AS ANTITUMOR DRUG AGAINST EXPERIMENTALLY INDUCED LUNG CARCINOMA

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Most cancer drugs used in a clinical setting are insufficiently effective and insufficiently safe. This prompts the search for novel substances to fight cancer. The aim of this study was to explore the effects of dihydrobromide 2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo[1,2-a] benzimidazole (RU-185) on the growth and metastasis of experimentally induced transplantable Lewis lung carcinoma (LLC). Fifty-five C57/Bl6 male mice (weight 18–20 g) were subcutaneously inoculated with LLC cells. The tested substance (0.5 ml) was administered intragastrically at 50, 220, and 500 mg/kg (groups 1, 2 and 3, respectively) once a day for 10 days starting at 48 h after inoculation. The control group received normal saline. Intragastric administration of the tested substance resulted in significantly longer survival in group 2 only (162.3%) and in the significant reduction of tumor size on day 1 after treatment in all groups. After the end of treatment, tumor sizes in groups 2 and 3 were 3.4 and 1.3 times smaller, respectively, on day 7 and 2.2. and 1.3 times smaller, respectively, on day 14 than in the control group ($p < 0,05$). The growth delay rate was sustained in group 2 by day 14 after the end of treatment; tumor regression was observed in 20% of the animals. The number of metastases in the lungs was lower in groups 1 and 2 than in the control group (2.6 and 3.1-fold, respectively), and the metastasis inhibition was 68.1% and 80%, respectively. The tested substance RU-185 has an anticancer effect in mice: it results in longer survival, slower growth of the primary tumor and fewer lung metastases of Lewis lung carcinoma.

Keywords: Lewis lung carcinoma, dihydrobromide 2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo[1,2-a] benzimidazole, antitumor activity, antimetastatic activity, intragastric administration.

Funding: synthesis of the tested compound was supported by the Russian Ministry of Science and Higher Education under the state assignment for the Southern Federal University, 2020, Project FENW-2020-0031 (0852-2020-0031). *In vivo* experiments were part of the state assignment *Study of antitumor activity of pharmacological substances in vivo and in vitro* (121031100253-3).

Author contributions: Komarova EF proposed the design, conducted the experiment and wrote the draft version of the manuscript; Zhukovskaya ON synthesized the tested compound and edited the manuscript; Lukbanova EA conducted the experiment and contributed to writing the manuscript; Yengibaryan MA edited the manuscript; Vashenko LN proposed the concept and design for the study, edited the manuscript; Kharagezov DA contributed to writing the manuscript; Pozdnyakova VV performed statistical analysis; Ushakova ND proposed the concept and design for the study; Shatova YuS prepared the list of references and edited the manuscript; Przhedetsky YuV performed technical editing.

Compliance with ethical standards: the study was approved by the Ethics Committee of National Medical Research Center for Oncology (Protocol № 18 dated September 10, 2015); the experiment complied with the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes.

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Received: 01.06.2021 **Accepted:** 15.06.2021 **Published online:** 25.06.2021

DOI: 10.24075/brsmu.2021.031

ПРОИЗВОДНОЕ БЕНЗИМИДАЗОЛА КАК ПРОТИВООПУХОЛЕВОЕ СРЕДСТВО В ОТНОШЕНИИ ЭКСПЕРИМЕНТАЛЬНОЙ ЗЛОКАЧЕСТВЕННОЙ ОПУХОЛИ ЛЕГКОГО

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Значительное число применяемых в клинике противоопухолевых средств недостаточно эффективно и безопасно, что обусловливает поиск новых лекарственных субстанций. Цель работы — изучить влияние дигидробромида 2-(3,4-дигидроксифенил)-9-диэтиламиноэтилимидазо[1,2-а]бензимидазола (РУ-185) на рост и метастазирование перевиваемой экспериментальной опухоли легкого Льюис (LLC). LLC прививали 55 мышам-самкам C57/Bl6 массой 18–20 г подкожно. Внутрижелудочное (0,5 мл в сут.) введение препарата начинали через 48 ч после перевивки опухоли 1 раз в сутки 10 дней в разовых дозах 50, 220, 500 мг/кг (группы 1, 2 и 3 соответственно). Мышам контрольной группы вводили физиологический раствор. При внутрижелудочном введении субстанции происходило достоверное увеличение продолжительности жизни животных только в группе 2 (162,3%), а также значимое уменьшение объемов опухоли уже на 1-е сутки после окончания лечения. На 7-е и 14-е сутки от момента окончания лечения размеры опухоли в группах 2 и 3 были снижены по сравнению с контрольной группой в 3,4 и 1,3 раза (на 7-е сутки) и в 2,2 и 1,3 раза (на 14-е сутки) соответственно ($p < 0,05$). Индекс торможения роста опухоли сохранился в группе 2 к 14-м суткам после окончания лечения и у 20% животных отмечен регресс опухоли. Число метастазов в легких в группах 1 и 2 было снижено относительно контроля в 2,6 и 3,1 раза соответственно, а индекс ингибирования метастазирования составил 68,1 и 80% соответственно. Исследованный РУ-185 оказывает противоопухолевое действие, что выражено в увеличении продолжительности жизни животных, снижении скорости роста первичной опухоли, а также частоты развития и количества легочных метастазов экспериментальной эпидермоидной карциномы легкого Льюис мышей.

Ключевые слова: эпидермоидная карцинома легких Льюис, дигидробромид 2-(3,4-дигидроксифенил)-9-диэтиламиноэтилимидазо[1,2-а]бензимидазола, противоопухолевая активность, антиметастатическая активность, внутрижелудочное введение

Финансирование: синтез исследуемого соединения осуществляли при финансовой поддержке Министерства науки и высшего образования Российской Федерации (государственное задание в области научной активности, Южный федеральный университет, 2020, проект FENW-2020-0031 (0852-2020-0031). Исследования *in vivo* проводили в рамках государственного задания «Изучение противоопухолевой активности фармакологических субстанций *in vivo* и *in vitro*» (121031100253-3).

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Соблюдение этических стандартов: исследование одобрено этическим комитетом ФГБУ «РНИОИ» МЗ РФ (протокол № 18 от 10 сентября 2015 г.); все манипуляции с животными, в том числе выведение из эксперимента, осуществляли в соответствии с этическими принципами, установленными Европейской конвенцией по защите позвоночных животных, используемых для экспериментальных и других научных целей.

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Статья получена: 01.06.2021 **Статья принята к печати:** 15.06.2021 **Опубликована онлайн:** 25.06.2021

DOI: 10.24075/vrgmu.2021.031

Numerous studies of mechanisms underlying tumor growth and progression are laying the groundwork for the discovery of new therapeutic targets [1–3]. Development of novel antineoplastic and antimetastatic targeted therapies is in progress. Still, a lot of anticancer medications used in the clinical setting cannot boast sufficient efficacy or safety. This makes the search for novel anticancer drugs a priority field of experimental medicine.

DNA is the main target of many antineoplastic and antimetastatic drugs from various classes and chemical groups with different mechanisms of action. Studies have shown that 3H-triazolo[1,5-a]benzimidazole, the parent compound for tricyclic benzimidazole-based systems, effectively binds to the ADP site of checkpoint kinase 2 and inhibits this enzyme. Since checkpoint kinase 2 plays the definitive role in the activation of signal transduction pathways participating in cellular response to DNA damage, its inhibition in tumor cells is expected to block DNA repair and trigger apoptosis [4]. In addition, the anticancer activity of benzimidazole derivatives is associated with their effects on other cellular targets involved in DNA repair. For example, they are capable of inhibiting poly(ADP-ribose) polymerase (PARP-1 and -2), the key enzyme of the DNA repair system, and potentiating the cytotoxicity of DNA damaging agents [5]. Simpler monocyclic imidazole-based compounds can block effective DNA replication through electrostatic interactions, intercalation and groove binding [6].

Another important target for anticancer drugs is tubulin; by binding to this protein, anticancer drugs prevent its participation in some processes critical for cell division, including tubulin polymerization and depolymerization. For example, tubulin can be inhibited by benzimidazole derivatives that disrupt microtubule assembly [7]. Some benzimidazole derivatives are characterized by good pharmacokinetics and can overcome multidrug resistance in many cell lines. For instance, benzimidazole-2-urea derivatives are potent β-tubulin inhibitors: according to the literature, they exert a cytotoxic effect on human NCI-H460, Colo205, K562, A431, HepG2, Hela, and MDA-MB-435S cells [8].

The cytotoxic effect of benzimidazole derivatives on A549 (human lung adenocarcinoma) cells in hypoxic conditions is linked to the activation of their caspase-dependent apoptosis [9]. It is reported that one of structurally complex benzimidazole derivatives inhibits oncogenic kinases MEK1 and PI3K [10].

The aim of this study was to investigate the effect of 2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo[1,2-a] benzimidazole dihydrobromide (RU-185) on the growth and metastasis of LLC cells.

METHODS

The experiment was conducted on 55 male C57Bl/6 mice weighing 18–20 g. The animals were purchased from Andreevka breeding facility (Moscow region).

Cancer was modelled using transplantable Lewis lung carcinoma cells characterized by 100% spontaneous spread to the lungs. The cells were obtained from the tumor bank of the Laboratory for Combination Therapy of Tumors (Research Institute of Experimental Diagnostics and Therapy of Tumors of Blokhin National Medical Research Center of Oncology). The cells were maintained and subcutaneously transplanted following standard protocols.

The tested compound RU-185 was synthesized at the Research Institute of Physical and Organic Chemistry, Southern Federal University, from 1-diathylaminethyl-2-aminobenzimidazole by quaternization with 3,4-dimethoxyphenacylbromide followed by cyclization of the produced quaternary salt in the presence of 48% boiling hydrobromic acid, which was accompanied by O-demethylation [11].

The compound was dissolved in normal saline. The animals were divided into 3 groups. The tested compound was administered to the animals intragastrically via a nasogastric tube, at 50 mg/kg (group 1), 220 mg/kg (group 2) and 500 mg/kg (group 3), which equals to 1/40, 1/8 and 1/4 of LD_{50}, once a day for 10 days. Treatment was initiated 48 after inoculation with LLC cells (Table 1). The control group consisted of mice with transplantable LLC and received normal saline (placebo) intragastrically in the same volumes following the same regimen.

On day 26 after inoculation, the mice were sacrificed in a CO_2 chamber and subsequently necropsied. The antineoplastic and antimetastatic activities of the compound were studied according to the guidelines from [12]. The antineoplastic and antimetastatic activities were estimated using standard parameters, such as tumor volume, survival time (T/C%) calculated as the ratio of mean survival time in the treatment group to that in the control group, and the number of metastases. Based on the obtained estimates, tumor growth inhibition index (TGI%) and metastasis inhibition index (MII%) were calculated [12].

Prior to the experiment, LD_{50} for intragastrically administered RU-185 was calculated. The obtained value (1,980,4 mg/kg) corresponded to Category 4 of GHS criteria for acute toxicity. According to criteria described in [13], the compound can be classified as moderately hazardous (Class 3).

Statistical analysis was conducted in STATISTICA 12.0 (StatSoft Inc.; USA). Normality of distribution was tested using the Shapiro-Wilk and Kolmogorov-Smirnov tests. For mean values, the significance of differences between independent samples was determined using Student's *t*-test. Differences were considered significant at $p \leq 0.05$.

RESULTS

The antitumor effects of intragastrically administered RU-185 are analyzed in Table 2. At the studied doses, RU-185 had different effects on survival times in the groups. A significant

Table 1. The design of the experiment

Basic parameters	Groups			
	Experimental			Control
	1	2	3	
Number of animals in group	18	18	19	10
Treatment	2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo[1,2-a]benzimidazole dihydrobromide			Normal saline
Dose, mg/kg	50	220	500	
Treatment duration	10 days			
Volume administered	0.5 ml a day			
Route of administration	Intragastric via a nasogastric tube			

Table 2. Effects of intragastrically administered 2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo[1,2-a]benzimidazole dihydrobromide on LLC growth

Dose, mg/kg	T/C, %	Tumor volume (cm^3), M ± *m* (TPO, %)		
		Day after end of treatment		
50	94.3	2.34 ± 0.42	8.63 ± 1.3[1,2]	10.4 ± 0.52
220	162.3	0.41 ± 0.3[1,2]	2.04 ±0.5[1,2]	4.5 ± 0.1[1,2] (55.0) – 80% of animals 0 (100) – 20% of animals
500	112.9	1.08 ± 0.45[1,2] (30.1)	5.21 ± 1.21.2 (22.1)	7.4 ± 0.3[1,2] (28.6)
Control	0	1.56 ± 1.4	6.7 ± 0.4	9.8 ± 0.7

Note: 1 — differences are significant relative to the control group ($p < 0.05$); 2 — differences are significant relative to the subgroups of the experimental group ($p < 0.05$).

increase in survival time was observed only in group 2 (T/C = 162.3%). In group 3, survival time was longer than in the control group, but T/C did not differ significantly between these two groups. By contrast, survival time was shorter in group 1 than in the control group.

The dynamics of primary tumor growth was assessed based on tumor volume on days 1, 7 and 14 after the end of treatment. The volume of the primary tumor differed between the groups as early as day 1 after inoculation. Moderate and high doses of RU-185 (groups 2 and 3, respectively) resulted in the reduction of tumor volume relative to the control group indicated by the TGI index. However, significant changes in tumor volume at this time was observed only in group 2. In group 1, the tumor was progressing and its size exceeded 1.5 times the tumor size in the control group ($p < 0.05$).

Measurements of tumor volumes on days 7 and 14 after the end of treatment revealed the dynamics of tumor growth relative to the first days of therapy in all groups. For example, tumor volume in group 1 was larger than in the control group, whereas tumor volume in groups 2 and 3 was 3.4 and 1.3 times smaller (day 7) and 2.2 and 1.3 times smaller (day 14) than in the control group, respectively ($p < 0.05$). The value of the TGI index suggested the significant efficacy of the tested compounds at 220 mg/kg; tumor growth inhibition was observed on day 14 after the end of treatment. Importantly, tumor regression confirmed by necropsy was noted among 20% of the animals in this group (Table 2).

Interestingly, the intragastric administration of the tested compound had an antimetastatic effect against LLC (Table 3).

This effect manifested as the pronouncedly reduced rate of metastasis and fewer lung metastases in groups 1 and 2: the number of lung metastases in these groups was 2.6 and 3.1 times lower, respectively, in comparison with that in the control group, and MII was 68.1% and 80%, respectively. In group 3, administration of high doses of the tested compound resulted in the inhibition of metastasis.

Thus, we conclude that intragastrically administered RU-185 exhibited antitumor activity against experimentally induced Lewis lung carcinoma, inhibiting its growth and metastasis. At 220 mg/kg, RU-185 increased mean survival time and caused tumor regression in 20% of the animals by day 14 after the beginning of treatment. The most pronounced antitumor and antimetastatic effect of the studied benzimidazole derivative was observed at 220 mg/kg. Reduction in the number of lung metastases and the metastatic rate (the metastasis inhibition index) was observed at all tested doses, indicating the pronounced antimetastatic effect of RU-185 against the spread of LLC to the lungs.

DISCUSSION

Earlier studies investigating the effects of intragastrically administered RU-185 on the growth of transplantable subcutaneous B16 melanoma showed that the compound had a greater inhibiting effect on metastasis to the lungs than on the growth of the primary tumor [14, 15]. However, our study has demonstrated a pronounced antitumor effect on both primary LLC and its metastases. Perhaps, the antitumor effect of the studied compound against the primary tumor can be explained by differences in the phenotypic characteristics of melanoma and lung carcinoma [16, 17]. Pronounced inhibition of metastatic spread to the lungs suggests that there are common factors that determine the adaptation of cancer cells to the metastatic niche and the growth of metastases in a given metabolic environment, predicating the mechanism of action of the tested compound [18]. The metastatic proteome and transcriptome of the tumor are dynamically modulated by the metabolome. Metabolome-induced signal cascades can modulate tumor aggression and metastatic spread via different pathways involved at each stage of the metastatic cascade [19]. However, further research is needed to support the hypothesis about the possible mechanism underlying the antitumor effect of the tested compound.

CONCLUSION

RU-185 administered intragastrically at 220 mg/kg once a day exerts antitumor activity reflected in the significant increase in survival time, slower primary tumor growth, the reduced rate of metastasis and the reduced number of metastases of

Table 3. Effects of intragastrically administered 2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo[1,2-a]benzimidazole dihydrobromide on LLC spread

Dose, mg/kg	Number of mts per mouse	MII, %
50	12.3 ± 1.0[1,2]	68.1 ± 2.1[1,2]
220	10.3 ± 0.6[1,2]	80.0 ± 3.1[1,2]
500	27.5 ± 0.92	13.9 ± 1.1
Control	32.2 ± 1.2	–

Note: 1 — differences are significant relative to the control group ($p < 0.05$); 2 — differences are significant relative to the subgroups of the experimental group ($p < 0.05$).

experimentally induced epidermal LLC in a mouse model. The antimetastatic effect of the compound against transplantable LLC is observed at 50 and 500 mg/kg. Identification of metabolic mechanisms underlying the antitumorigenic and antimetastatic effects of RU-185 will help to detect its therapeutic targets and make it a candidate drug against lung cancer.

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