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ORIGINAL ARTICLE

A BENZIMIDAZOLE DERIVATIVE AS AN EFFECTIVE ANTITUMOR AGENT IN TERMS OF SYNGENEIC LUNG TUMORS AND MELANOMA TREATMENT

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ABSTRACT

Purpose of the study. Evaluation of the effect of the benzimidazole derivative dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole (RU-185) on the growth of Lewis lung epidermoid carcinoma and B16-F10 melanoma when administered intragastrically.

Materials and methods. For the experiment, we used female C57Bl/6j mice, which were inoculated subcutaneously with syngeneic tumors: Lewis lung carcinoma (LLC) and B16-F10 melanoma. RU-185 was administered intragastrically to animals in a volume of 0.3 ml for 10 days, 1 time per day. For both tumors, depending on single doses of the substance for administration, groups were divided: 1st and 4th – 50 mg/kg, 2nd and 5th – 220 and 3rd and 6th – 500 mg/kg. The control groups were injected intragastrically with physiological saline in the same volumes and according to the same scheme. The following parameters were assessed: tumor volume, increase in life expectancy (T/S, %) and tumor growth inhibition index (TGI, %).

Results. For animals with LLC in the 2nd group there is an increase in the indicator of life expectancy (T/S 162.3 %), and in the 3rd group there is a tendency to an increase in the T/S indicator. On the 1st day after the end of treatment in the 2nd and 3rd groups TGI was 73.0 % and 30.1 %, respectively ($p < 0.05$). On the 7th and 14th days after the end of the use of RU-185 in the 2nd and 3rd groups the volume of tumors is 3.5 and 1.4 times less (on the 7th day) and 2.3 and 1.3 times (on the 14th day), respectively than in the control group ($p < 0.05$). At a dose of 220 mg/kg, complete regression of LLC tumors was shown in 20 % of animals.

With the growth of B16-F10, the life expectancy of all groups did not differ. Intergroup differences in the dynamics of tumor growth are provided. Highlighted changes were found in the 5th group (on the 14th day after the end of the administration of RU-185, TGI was 48.7 %).

Conclusion. The investigated chemical substance dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole showed antitumor efficacy against syngeneic tumors: Lewis lung epidermoid carcinoma and B16-F10 melanoma when administered intragastrically which leads to further testing of RU-185 as a potential drug for the treatment of malignant neoplasms.

Keywords:
dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole, Lewis lung carcinoma, melanoma B16-F10, antitumor efficacy, intragastric administration

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ПРОИЗВОДНОЕ БЕНЗИМИДАЗОЛА КАК ЭФФЕКТИВНОЕ ПРОТИВООПУХОЛЕВОЕ СРЕДСТВО В ЛЕЧЕНИИ СИНГЕННЫХ ОПУХОЛЕЙ ЛЕГКОГО И МЕЛАНОМЫ

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РЕЗЮМЕ

Цель исследования. Оценка влияния производного бензимидазола дигидробромид-2-(3,4-дигидроксифенил)-9-диэтиламино-этилимидазо-[1,2-a] бензимидазола (РУ-185) на рост эпидермоидной карциномы легкого Льюиса и меланомы B16-F10 при внутрижелудочном применении.

Материалы и методы. Для эксперимента использовали мышей линии C57Bl/6j самок, которым подкожно прививали сингенные опухоли: эпидермоидная карцинома легких Льюис (LLC) и меланома B16-F10. РУ-185 вводили внутрижелудочно животным в объеме 0,3 мл в течении 10 дней 1 раз в сутки. Для обеих опухолей в зависимости от разовых доз субстанции для введения выделены группы: 1-я и 4-я – 50 мг/кг, 2-я и 5-я – 220 и 3-я и 6-я – 500 мг/кг. Контрольным группам внутрижелудочно вводили физиологический раствор в аналогичных объемах и по той же схеме. Оценивали показатели: объем опухоли, увеличение продолжительности жизни (Т/С, %) и индекс торможения роста опухоли (ТРО, %).

Результаты. Для животных с LLC во 2-й группе отмечается увеличение показателя продолжительности жизни (Т/С 162,3 %), а в 3-й показана тенденция к повышению показателя Т/С. В 1-е сутки после окончания лечения во 2-й и 3-й группах ТРО составил 73,0 % и 30,1 % соответственно ($p < 0,05$). На 7-е и 14-е сутки после окончания применения РУ-185 во 2-ей и 3-ей группах объемы опухолей меньше в 3,5 и 1,4 раза (на 7-е сутки) и 2,3 и 1,3 раза (на 14-е сутки) соответственно, чем в контрольной группе ($p < 0,05$). В дозе 220 мг/кг показана полная регрессия опухолей LLC у 20 % животных. При росте B16-F10 продолжительность жизни во всех группах не различалась. Показаны межгрупповые различия динамики роста опухоли. Выраженные изменения обнаружены в 5-й группе (на 14-е сутки после окончания введения РУ-185 ТРО составил 48,7 %).

Заключение. Исследованная химическая субстанция дигидробромид-2-(3,4-дигидроксифенил)-9-диэтиламино-этилимидазо-[1,2-a] бензимидазола показала противоопухолевую эффективность в отношении сингенных опухолей: эпидермоидной карциномы легкого Льюиса и меланомы B16-F10 при внутрижелудочном введении, что обусловливает проведение дальнейших испытаний РУ-185 как потенциального препарата терапии злокачественных новообразований.

Ключевые слова:
дигидробромид-2-(3,4-дигидроксифенил)-9-диэтиламино-этилимидазо-[1,2-a] бензимидазола, эпидермоидная карцинома легких Льюиса, меланома B16-F10, противоопухолевая эффективность, внутрижелудочное введение

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INTRODUCTION

The search for targets for the treatment of malignant neoplasms, despite numerous developments in modern oncology, is still relevant [1–3]. The identified targets require the study of various means of influencing. Chemical substances, in particular benzimidazole derivatives, can be useful and effective for therapeutic purposes in practical oncology.

By it's structure, benzimidazole is a heterocyclic compound in which benzene and imidazole rings are connected. The antitumor efficacy of imidazoles has long been known, some of which, for example, dacarbazine, temozolomide, zoledronic acid, mercaptopurine, nilotinib, tipifarnib, etc., are used in oncological practice in the treatment of various oncological diseases [4]. This antitumor effect of imidazoles is due to their ability to easily bind to protein molecules and destroy them, and in high concentrations directly inhibit the synthesis of the main components of the cell membrane [5].

The potential antitumor effect of benzimidazole is also due to the similarity of it's structure with natural nucleotides, and therefore cell DNA is an important target for them. Thus, triazolobenzimidazole is able to inhibit check point kinase 2, which plays an important role in the cell's response to DNA damage, and therefore has an antitumor effect [6]. The benzimidazole derivative 2-[(R)-2-Methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide can inhibit DNA repair by inhibiting poly (ADP-ribose) polymerase (PARP)-1 and –2 [7].

The effect of benzimidazole derivatives on the microtubule protein tubulin has been shown, in which it's polymerization and depolymerization are disrupted [8]. The inhibitor of β-tubulin is benzimidazole-2-urea – it's cytotoxic effect against an extensive panel of tumor cells has been shown [9; 10]. The participation of some benzimidazole derivatives benzimidazole-4,7-diones in the activation of caspase-dependent apoptosis on the lung adenocarcinoma cell line was found [11].

The purpose of the study: to evaluate the effect of benzimidazole derivative dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole (RU-185) on the growth of Lewis lung epidermoid carcinoma and melanoma B16-F10 with intragastric use.

MATERIALS AND METHODS

Mice of the C57Bl/6j female line weighing 20–22 grams were used for the experiment. The animals were obtained from the Andreevka vivarium of the FSBIC of biomedical technologies of FMABA Russia (Moscow region) with a veterinary certificate. The study was conducted according to the principles of humane treatment of animals in scientific research in accordance with the European Convention.

Table 1. Study design

	Groups/ Number of animals	Supplement drug	Doses mg/kg	V, ml	Way of supplementation	Duration of supplementation
LLC	1st 12 mice	dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo-[1,2-a] benzimidazole	50	0.3 ml	I/g	10 days
	2nd 12 mice		220			
	3rd 12 mice		500			
	Control 12 mice	Normal saline	-			
B16-F10	4th 12 mice	dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo-[1,2-a] benzimidazole	50			
	5th 12 mice		220			
	6th 12 mice		500			
	Control 1 12 mice	Normal Saline	-			

Note: LLC – Lewis lung epidermoid carcinoma, B16-F10 – melanoma, I/g – intragastric.

Syngenic tumors were used: Lewis epidermoid lung carcinoma (LLC) and melanoma B16-F10. The tumors were inoculated in mice subcutaneously in a standard way.

The design of the experiment is presented in Table 1. The investigated chemical substance dihydrobromide 2-(3,4-dihydroxyphenyl)-9-diethylaminoethylimidazo-[1,2-a] benzimidazole (RU-185) (RF patent No. 2391979) was dissolved in saline solution and administered intragastrically to animals using a nasogastric probe in a volume of 0.3 ml. The mode of administration was 10 days daily, 1 time per day.

The choice of doses to study the antitumor effect is due to the value of the semi-lethal toxicity of LD50, which was determined with a single intragastric administration to outbred mice (LD50 was 1860.4 mg/kg) [12]. For both tumors, depending on single doses of the substance for administration, groups were divided: 1st and 4th – 50 mg/kg, 2nd and 5th – 220 and 3rd and 6th – 500 mg/kg. The control groups, which consisted of animals with transplanted tumors B16-F10 and LLC, were intragastrically injected with saline solution in similar volumes and according to the same scheme. Both the surviving and fallen animals underwent necropsy within 2 hours after death.

The study of the antitumor activity of the substance was carried out in accordance with regulatory documents [13; 14], the following indicators were evaluated: tumor volume, increase in life expectancy (T/S, %), calculated as the ratio of the average life expectancy of animals subjected to therapy to control indicators, and the tumor growth inhibition index (TGI, %) was calculated.

The normality of the distribution of features was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov criteria. Median and interquartile range were calculated for quantitative data. The statistical significance of the differences between the groups was assessed using the Mann-Whitney criterion, and in dynamics using the Wilcoxon criterion. The signifi-

Table 2. The impact of PY-185 on LLC and B16-F10 growth dynamics

Group number (Single dose, mg/kg)	T/S, %	Tumor volume (cm^3), Me [25-75] (TGI, %) The day after treatment termination		
		1	7	14
LLC				
1st (50)	94.3	2.3 [1.9–2.7][2]	8.6 [7.8–9.2][1,2]	10.3 [9.9–10.9][2] (**14.8**)
2nd (220)	162.3	0.4 [0.2–0.7][1,2] (**73.0**)	2.1 [1.9–2.3][1,2] (**70.0**)	4.5 [4.1–5.0][1,2] (**55.0**) – 80 % abdomen 0 (**100**) – 20 % abdomen
3rd (500)	112.9	1.1 [0.8–1.4][1,2] (**30.1**)	5.2 [4.8–5.5][1,2] (**22.1**)	7.4 [6.9–8.0][1,2] (**28.6**)
Control	0	1.6 [1.1–2.1]	6.7 [6.3–7.1]	9.8 [9.3–10.2]
B16-F10 Melanoma				
4th (50)	96. 2	0.4 [0.1–0.9]	2.7 [2.3–3.1]	5.9 [5.3–6.1]
5th (220)	131.1	0.4 [0.2–0.7]	2.6 [2.3–2.9] (**4**)	2.4 [1.9–2.7][1,2] (**48.7**)
6th (500)	103.1	0.4 [0.1–0.9]	2.1 [1.8–2.4][2] (**20.4**)	4.5 [3.9–4.9][2] (**4.5**)
Control		0.3 [0.1–0.7]	2.7 [2.1–3.4]	4.7 [3.9–5.1]

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

cance level for the methods used was set as $p \leq 0.05$. Statistical data processing was carried out using the STATISTICA 12.0 program.

RESEARCH RESULTS AND DISCUSSION

The use of RU-185 in tumor-bearing animals with LLC caused a change in life expectancy and tumor size in experimental groups (Table 2). Thus, it was found that when a single dose of 220 mg/kg (group 2) was administered, an increase in life expectancy (T/S 162.3 %) was noted. In the group of animals administered a dose of 500 mg/kg (group 3), a tendency to increase the T/S index was shown, which has insignificant differences with the animals of the control group. In group 1, the life expectancy indicator was reduced in comparison with the control.

The study of the growth dynamics of the subcutaneous tumor node LLC with the use of RU-185 revealed differences in the study groups. On the 1st day after the end of treatment in the 2nd and 3rd groups, the tumor growth inhibition index indicated a decrease in the size of the primary focus and amounted to 73.0 % and 30.1 %, respectively ($p < 0.05$) (Table 2). On the 7th and 14th days after the end of the use of RU-185 in the 2nd and 3rd groups, tumor volumes were statistically significantly less by 3.5 and 1.4 times (on the 7th day) and 2.3 and 1.3 times (on the 14th day), respectively, than in the control group ($p < 0.05$). When applying a dose of 220 mg/kg, a complete regression of LLC tumors was shown in 20 % of animals, which was confirmed by the results of necropsy. At the same time, there was a tendency to tumor growth in group 1, but no statistically significant differences were found in comparison with the control group.

When analyzing the study results of the subcutaneous melanoma B16-F10 growth, we've shown that the life expectancy of all experimental groups didn't differ from the control group ($p > 0.05$) (Table 2). The T/S index in tumor-bearing animals with melanoma B16-F10 when using RU-185 was 96.2, 131.1 and 103.1 %, respectively, in groups 4, 5 and 6.

Analysis of the dynamics of tumor growth in 16 showed intergroup differences. In the group with a single dose of RU-185 50 mg/kg, the administration of the substance did not affect the growth of the subcutaneous node, the tumor size indicators at all stages were similar to the control group. The most pronounced changes were shown in the group with a single dose of 220 mg/kg. So, on the 14th day after the end of the administration of RU-185, the TGI index was 48.7 %, which indicates a decrease in tumor size compared to the control group (by 2 times at $p < 0.05$).

CONCLUSION

The studied chemical substance dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole (RU-185) showed antitumor efficacy against syngenic transplantable tumors: Lewis lung epidermoid carcinoma and melanoma B16-F10. It was shown that with intragastric administration of the substance in a single dose of 220 mg/kg for 10 days, a significant decrease in the size of tumors was noted. In animals with melanoma B16-F10, a significant decrease in tumor volume occurs on the 14th day after the end of the administration of the substance. Unlike melanoma, in animals with epidermoid lung carcinoma at a dose of 220 mg/kg, RU-185 has a pronounced inhibition of the growth of the subcutaneous tumor node already on the first day after the end of the use of the substance.

We explain the differences in the effectiveness of the substance under study by the peculiarities of metabolic phenotypes of tumors. Metabolic phenotypes of melanoma demonstrate dynamism between glycolysis and oxidative phosphorylation, which gives an advantage in the survival of tumor cells and in the formation of chemoresistance [15; 16]. Moreover, simultaneous activation of both oxidative phosphorylation and glycolysis (metabolic symbiosis) is vital for the progression of melanoma [15; 16]. At the same time, the metabolism of lung cancer cells is characterized by the activation of glucose oxidation enzymes, which indicates it's glycolytic phenotype [17]. Along with the activation of glycolysis for lung cancer, an increase in the intensity of other glucose-related processes, such as gluconeogenesis, the tricarboxylic acid cycle, has been shown [17].

Thus, the revealed antitumor efficacy of dihydrobromide-2-(3,4-dihydroxyphenyl)-9-diethylamino-ethylimidazo-[1,2-a] benzimidazole determines further testing of RU-185 as a potential drug for the treatment of malignant neoplasms. However, further studies are needed to identify the mechanism of it's antitumor action.

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