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Research Article

ANTI-TUMOR ACTIVITY OF RADIOPHARMACEUTICAL MEDICATION BASED ON BIOSPECIFIC ANTIBODIES TO TUMOR-ASSOCIATED STROMA ELEMENTS AND ^{177}LUTECIUM

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Radiopharmaceutical targeted medication based on biospecific antibodies to tumor-associated stroma elements and ^{177}lutecium (^{177}Lu-DOTA-anti-CTLA4-GITR) potential anti-tumor activity was studied in two courses: one-time administration and two injections with a considerable lag. Subcutaneously transplanted experimental colonic carcinoma (AKATOL; cell line — CT26 EGFP) with high expression of green fluorescent protein (eGFP) and additional expression of target tumor-associated stroma molecules — CTLA4 and GITR was used as a model in BALB/c male mice. The experimental radiopharmaceutical targeted medication proved to possess high pharmacologic activity against the tumor under study. It was apparent in valid increase of experimental animals' mean lifespan, tumor debut latent period inhibition and clinically valid tumor growth rate slowdown. Double administration of ^{177}Lu-DOTA-anti-CTLA4-GITR proved to be more effective than one-time one, however neither of them managed to yield statistically valid difference in safety levels.

Keywords: biospecific antibodies to CTLA4 and GITR with ^{177}Lu radionuclide; colonic adenocarcinoma; colorectal cancer; CT26; tumor-associated stroma; mice.

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Научная статья

АНАЛИЗ ПРОТИВООПУХОЛЕВОЙ АКТИВНОСТИ РАДИОФАРМАЦЕВТИЧЕСКОГО ЛЕКАРСТВЕННОГО ПРЕПАРАТА НА ОСНОВЕ БИСПЕЦИФИЧЕСКИХ АНТИТЕЛ К ЭЛЕМЕНТАМ ОПУХОЛЬ-АССОЦИИРОВАННОЙ СТРОМЫ И ИЗОТОПА ЛЮТЕЦИЯ 177

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Для цитирования: Трашков А.П., Гаглоева Т.Д., Будько А.И., Петровский А.Н., Тимаева О.И., Цыган Н.В., Станжевский А.А., Васильев А.Г., Майстренко Д.Н., Сергунова К.А., Сысоев Д.С., Шатик С.В., Антуганов Д.О., Коневега А.Л. Анализ противоопухолевой активности радиофармацевтического лекарственного препарата на основе биспецифических антител к элементам опухоль-ассоциированной стромы и изотопа лютеция 177 // Педиатр. – 2022. – Т. 13. – № 6. – С. 35–44. DOI: https://doi.org/10.17816/PED13635-44

Цель – провести исследование по оценке потенциальной противоопухолевой активности таргетного радиофармацевтического лекарственного препарата ^{177}Lu-DOTA-anti-CTLA4-GITR при двух курсах введения: однократно и два раза со значительным интервалом.

Материалы и методы. В качестве модели опухолевого процесса использовали субкутанно трансплантированную самцам мышей линии BALB/c экспериментальную аденокарциному толстой кишки (АКАТОЛ; клеточная линия – CT26 EGFP) с высокой экспрессией зеленого флуоресцентного белка (eGFP) и дополнительной экспрессией целевых молекул-мишеней опухоль-ассоциированной стромы – CTLA4 и GITR.

Результаты. Показано, что тестируемый радиофармацевтический лекарственный препарат обладает высокой фармакологической эффективностью в отношении оцениваемого новообразования. Это проявлялось в достоверном увеличении средней продолжительности жизни подопытных животных, ингибировании латентного периода развития опухоли и клинически значимом торможении ее роста.

Заключение. Курсовое применение ^{177}Lu-DOTA-anti-CTLA4-GITR в сравнительном аспекте оказалось более эффективным. При этом статистически значимых отличий по уровню безопасности использования между оцениваемыми курсами применения препарата не установлено.

Ключевые слова: биоспецифическое антитело к CTLA4 и GITR с радионуклидом ^{177}Lu; экспериментальные исследования; опухоль; аденокарцинома толстой кишки; колоректальный рак; CT26; опухоль-ассоциированная строма; мыши.

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BACKGROUND

The intensive development of immunology, structural biology, and radiochemistry and the creation of effective biotechnological and radiopharmaceutical production facilities according to GMP standards have formed the prerequisites for the development and introduction into clinical practice of fundamentally novel classes of radiopharmaceutical medicinal agents (RPMAs) based on highly selective targeting molecules, usually of an immunobiological nature, and radionuclides with different emission spectra [18, 19]. The use of targeted RPMAs, especially preparations based on radionuclides that are sources of α- or β-radiation, furthers broad prospects for malignant neoplasm treatment that are not very susceptible to traditional antitumor treatment types, primarily due to the very selective localization in the area of the tumor process of a large number of radioactive elements that have a nonselective cytopathological action [6, 10, 13, 15]. This greatly increases the variability of the treatment approach and its efficiency. Moreover, the targeted nature of the RPMA mechanism of action indirectly protects intact organs and tissues of the body, reducing the systemic toxic effect of the drug [3, 9, 11].

Various immunobiological drugs with targeted action have long been successfully used in the treatment of a large number of diseases, including cancer [2, 4, 5, 14, 16, 18]. Nevertheless, the RPMA range is becoming more extensive every year, while technologies for the development and production of drugs and their components (carrier molecules, radionuclides, chelating complexes, auxiliary compounds) are being improved.

This study aimed to investigate the antitumor activity of a new RPMA based on the ^{177}Lu isotope and a complex target carrier, a bispecific antibody that combines membrane glycoprotein 4 associated with cytotoxic T-lymphocytes (CTLA4) and membrane protein, tumor necrosis factor receptor (GITR). The technique's distinctiveness is determined precisely by the antibody properties, which is able to bind selectively to conservative (not subject to tumor progression) target molecules of the neoplasm microenvironment. The ability of RPMA to interact specifically with the targets of the tumor stroma enables theoretically to consider the drug as a therapeutic agent against malignant tumors of various initial histological types and localizations.

MATERIALS AND METHODS

The study was performed on 15 male laboratory BALB/c mice, obtained from a specialized nursery for laboratory animals of the Federal Research Center Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences (ICG SB RAS). The mice were quarantined for 14 days and then transferred to the main department of the vivarium. The maintenance of mice, feeding, and maintaining the microclimate in the vivarium corresponded to the rules in force in global and Russian practice [1]. The experiment was approved by the Commission on Bioethics of the National Research Center Kurchatov Institute, Petersburg Nuclear Physics Institute (conclusion no. 04/1-KPB21, dated April 16, 2021).

The RPMA being tested, ^{177}Lu-DOTA-anti-CTLA4-GITR, was developed by the A.M. Granov Russian Scientific Center for Radiology and Surgical Technologies of the Ministry of Health of Russia. The drug was a clear solution, 1 ml of which contained 0.1 mg of the target antibody; ^{177}Lu activity was at least 1.5 MBq.

To model the tumor process, a clone of experimental mouse colon adenocarcinoma (cell line CT26 EGFR) from the collection of the NRC Kurchatov Institute, Petersburg Nuclear Physics Institute, was used. The pathogenesis of the tumor assessed during the study is as close as possible to the clinical presentation of the target disease of colorectal cancer in humans. The tumor has a high growth rate, significant invasive potential, and satisfactory intensity of metastasis both by lymphogenous (the main method) and hematogenous (mainly to the liver) mechanisms and is widely used in fundamental and preclinical experiments [7, 12, 20, 21]. Malignant cells were transplanted to experimental animals at a dose of 10^6 cells per individual by injection into the subcutaneous tissue on the right side. Tumor material was taken for study from donor animals from the second passage of the neoplasm, after pathomorphological and immunohistochemical evaluation of the tumor. The tumor tissue has been shown to contain a satisfactory level of target molecules for therapy. Previously, in the preliminary studies, we revealed that the test drug ^{177}Lu-DOTA-anti-CTLA4-GITR accumulates in the tissue of the neoplasm under evaluation [8, 17].

Three experimental groups were formed:

- Group 1 ($n = 5$): With assessment of the main parameters of growth and development of a tumor in mice with a transplanted tumor
- Group 2 ($n = 5$): With assessment of the antitumor activity (functional suitability) of the tested drug after a single injection
- Group 3 ($n = 5$): With an assessment of the antitumor activity (functional suitability) of the test drug after duplicate injection (interval of 7 days).

Considering the rate of development of experimental colon adenocarcinoma in mice, therapy was performed according to two schemes:

1. A single application of the test drug 48 h after neoplasm transplantation at a dose of 5 MBq/mouse (group 2).

2. Double (course) application of the test drug 48 and 216 h after neoplasm transplantation at a dose of 5 MBq/mouse (total dose 10 MBq/mouse; group 3).

We believe that early prescription of therapy (before the emergence of a clearly visible and palpable primary tumor node) is justified by assessment of the drug effect on the formation of the tumor microenvironment and duration of the latent period of development and of the possibility of suppression by treatment with ^{177}Lu-DOTA-anti-CTLA4-GITR tumor micrometastases.

The test drug efficiency was evaluated with a conventional method. The following indicators were analyzed:

- Duration of the latent period of the transplanted tumor development (days before the emergence of the primary tumor node, palpation)
- Tumor node growth dynamics with calculation of tumor growth inhibition indices (mm^3,%)
- Average life expectancy with the calculation of the increase in life expectancy (days,%)

The size of the primary tumor node was assessed by measuring in three mutually perpendicular sizes; the effect of tissue edema in the peritumoral area was not considered.

Tumor growth inhibition (TGI) was obtained using the following equation:

$$TGI\ (\%) = [(V_{control} - V_{experiment}) / Control] \cdot 100\%$$

where V is the tumor volume in group 1 and the experimental group, respectively. The clinically significant level of difference was at least 50%.

The lifespan increment (LSI) was calculated as follows:

$$LSI\ (\%) = [ALS_{experiment} - ALS_{control}] / ALS_{control}] \cdot 100\%$$

where ALS is the average lifespan of animals in group 1 and the experimental group, respectively. The clinically significant level was not <25%.

Statistical analysis of the study results was performed using the SPSS program (USA). The data obtained are presented as Me $[Q_1–Q_3]$ (median and quartile range). The nature of the distribution of the variants in the groups was tested using the Kolmogorov–Smirnov method. These samples were compared using the Mann–Whitney U-test, since the distribution of the variants in the sample sets was different from normal. A probability of at least 95% ($p < 0.05$) was considered a significant level of difference, which is the standard in biomedical research.

RESULTS AND DISCUSSION

Transplantation of tumor cells from experimental colon adenocarcinoma to BALB/c mice was successful in all cases studied.

Table 1 shows the results of the effect of CT26 EGFR therapy with the test drug on the duration of the latent period of neoplasm development recorded in the test “determining the time of emergence of the primary tumor node.”

According to the data, the applied radionuclide therapy had a significant influence on the early stages of neoplasm formation, inhibiting tumor growth. Nonetheless, no significant differences were found in the time of registration of the primary tumor node of colon adenocarcinoma between the groups of mice that received the drug once or twice ($p > 0.05$), although more pronounced suppression of the tumor in the latent period was noted during the course of administration of the study drug. The estimated indicator was statistically significantly higher in group 3 than in group 1 by an average of 5 days (Table 1; $p = 0.015$).

The analysis results of the influence of the drug under study on the growth dynamics of the primary tumor node are presented in Table 2 and Figs. 1 and 2.

Inhibition of the latent period of neoplasm development with the use of the test drug contributed significantly to a later and slower increase of the tumor node. The inhibition of tumor growth was more pronounced during the course application of ^{177}Lu-DOTA-anti-CTLA4-GITR compared to its single administration to experimental animals.

Table 1 / Таблица 1

The effect of ^{177}Lu-DOTA-anti-CTLA4-GITR upon the time of primary palpable tumor node emergence in BALB/c mice with transplanted CT26 EGFR (days since the moment of tumor transplantation; *Me* [Q_1–Q_3])
Влияние препарата ^{177}Lu-DOTA-anti-CTLA4-GITR на время появления первичного пальпируемого опухолевого узла у мышей линии BALB/c с трансплантированной CT26 EGFR (сутки от момента трансплантации новообразования; *Me* [Q_1–Q_3])

Experimental groups / Обследуемые группы		
Group 1 (Control) / Группа 1 (Контроль)	Group 2 / Группа 2	Group 3 / Группа 3
19 [16–21]	24 [18–25]	24 [24–27]*

*Difference from mean values in group 1 are valid, $p < 0,05$. *Отличие от средних показателей группы 1 достоверно на принятом уровне значимости, $p < 0,05$.

Table 2 / Таблица 2

The effect of ^{177}Lu-DOTA-anti-CTLA4-GITR upon the dynamics of primary tumor node growth in BALB/c mice with transplanted CT26 EGFR, mm^3, *Me* [Q_1–Q_3]
Влияние препарата ^{177}Lu-DOTA-anti-CTLA4-GITR на динамику роста опухолевого узла у мышей линии BALB/c с трансплантированной CT26 EGFR, мм^3, *Me* [Q_1–Q_3]

Day / Сутки	Experimental groups / Обследуемые группы			TGI / ТРО
	Group 1 / Группа 1	Group 2 / Группа 2	Group 3 / Группа 3	
20	12 [7–15]	3 [3–3]*	–	Group 2 / Группа 2 — 75%
22	24 [12–45]	11 [4–18]	–	Group 2 / Группа 2 — 54%
24	108 [96–144]	30 [17–45]*	6 [4–9]*	Group 2 / Группа 2 — 72% Group 3 / Группа 3 — 94%
26	216 [180–324]	84 [44–150]*	24 [18–30]*	Group 2 / Группа 2 — 61% Group 3 / Группа 3 — 89%
28	765 [594–936]	216 [140–360]*	51 [18–90]*	Group 2 / Группа 2 — 72% Group 3 / Группа 3 — 93%
30	–	432 [342–513]	138 [39–252]	–
32	–	693 [610–756]	396 [180–516]	–
34	–	898 [756–1040]	732 [336–1040]	–
36	–	–	1248 [1033–1632]	–

Note. TGI — tumor growth inhibition; clinically significant level, >50 %. *Difference from mean values in control group are valid, $p < 0.05$. *Примечание*. ТРО — торможение роста опухоли; клинически значимый уровень отличий, >50 %. *Отличие от показателей контрольной группы достоверны на принятом уровне значимости, $p < 0,05$.

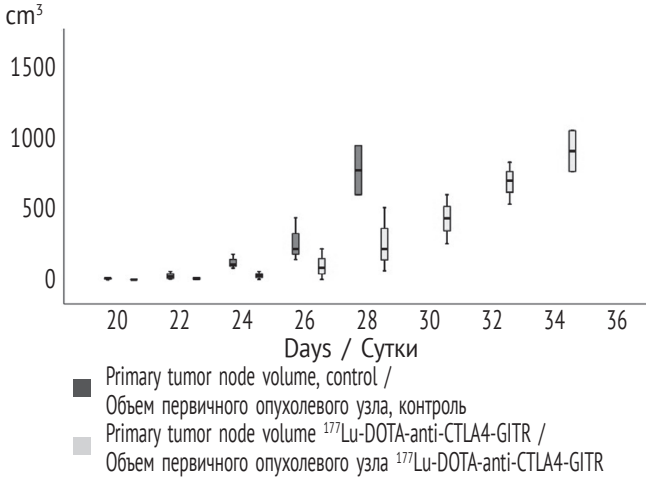

Fig. 1. The effect of one-time introduction of ^{177}Lu-DOTA-anti-CTLA4-GITR upon the dynamics of primary tumor node growth in BALB/c mice with transplanted CT26 EGFR

Рис. 1. Влияние однократного применения ^{177}Lu-DOTA-anti-CTLA4-GITR на динамику роста опухолевого узла у мышей линии BALB/c с трансплантированной CT26 EGFR

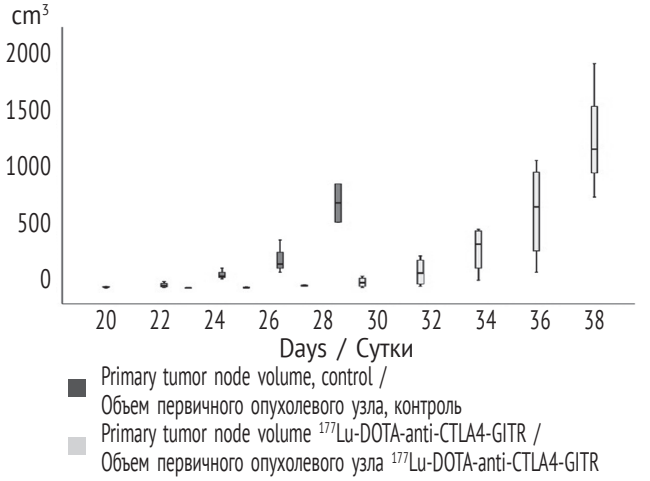

Fig. 2. The effect of course introduction of ^{177}Lu-DOTA-anti-CTLA4-GITR upon the dynamics of primary tumor node growth in BALB/c mice with transplanted CT26 EGFR

Рис. 2. Влияние курсового применения ^{177}Lu-DOTA-anti-CTLA4-GITR на динамику роста опухолевого узла у мышей линии BALB/c с трансплантированной CT26 EGFR

Table 3 / Таблица 3

The effects of ^{177}Lu-DOTA-anti-CTLA4-GITR radiopreparation upon mean lifespan of BALB/c male mice with с трансплантированной CT26 EGFR, day, *Me* [Q_1–Q_3]

Влияние препарата ^{177}Lu-DOTA-anti-CTLA4-GITR на среднюю продолжительность жизни мышей линии BALB/c с трансплантированной CT26 EGFR, сутки, *Me* [Q_1–Q_3]

Experimental groups / Обследуемые группы			LSI, % / УПЖ, %
Group 1 / Группа 1	Group 2 / Группа 2	Group 3 / Группа 3	
28 [24–29]	34 [25–36]	38 [36–38]*	Group 2 / Группа 2 21% Group 3 / Группа 3 36 %

Note. LSI — lifespan increment, clinically valid level of difference, >25%. *Difference from control group values are valid, $p < 0.05$.
Примечание. УПЖ — увеличение продолжительности жизни; клинически значимый уровень отличий, >25 %. *Отличие от показателей контрольной группы достоверны на принятом уровне значимости, $p < 0,05$.

Inhibition of the latent period of the tumor process and clinically significant inhibition of the tumor node in the treatment of experimental colon adenocarcinoma in mice with the test drug resulted in increased average life expectancy in mice with transplanted colon adenocarcinoma. Table 3 reveals the results of the analysis of this indicator.

A considerable increase in life expectancy, 10 days on average, was noted in the group of mice that received the test drug than in the group of mice that did not receive the treatment ($p = 0.047$). Concurrently, a clinically significant level was reached. The life expectancy of mice in group 2 (single application of the test drug) did not significantly differ from either the control values or the values obtained in the group of mice that received the test drug twice (Table 3).

CONCLUSIONS

1. The therapeutic targeted radiopharmaceutical drug ^{177}Lu-DOTA-anti-CTLA4-GITR had high pharmacological efficacy against the neoplasm being assessed, transplanted mouse colon adenocarcinoma (cell line CT26 EGFR). This was manifested in a significant increase in the average life expectancy of the experimental animals, inhibition of the latent period of tumor development, and clinically significant inhibition of its growth.

2. The course application of ^{177}Lu-DOTA-anti-CTLA4-GITR was comparatively more effective than a single administration in experimental animals.

3. The results of the study of the antitumor activity of ^{177}Lu-DOTA-anti-CTLA4-GITR indicate the need for preclinical and prospective subsequent clinical studies of this drug in oncology.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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