ORIGINAL STUDY ARTICLE
DOI: https://doi.org/10.36233/0507-4088-251

Mutations in human cytymegalovirus (Orthoherpesviridae: *Herpesvirales: Cytomegalovirus: Cytomegalovirus humanbeta 5*) *UL97* gene lead to increase in viremia duration and poor antiviral response in recipients of allogeneic hematopoietic stem cells

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Abstract

Introduction. Human cytomegalovirus (Orthoherpesviridae: *Herpesvirales: Cytomegalovirus: Cytomegalovirus humanbeta 5*) (HCMV) is one of the most commonly detected viruses in recipients of allogeneic hematopoietic stem cell (allo-HSCT) transplants. However, the emergence of resistance to antiviral drugs such as ganciclovir (GCV) poses a challenge in managing these patients.

This study **aims** to investigate the prevalence and impact of mutations in the HCMV UL97 gene associated with resistance to GCV on the course of infection among allo-HSCT patients.

Materials and methods. The study examined the association between UL97 mutations and the clinical course of HCMV infection in allo-HSCT patients. Genetic sequencing was performed to identify mutations, and their impact on viral replication and resistance to GCV was assessed.

Results and discussion. Six mutations were identified (D490A, T502A, C592G, C592F, E596G, C603W). C592G, C592F, E596G, and C603W are associated with resistance to antiviral drugs, while D490A and T502A described for the first time. When comparing patients with wild-type and those carrying the mutant variant, several parameters of peripheral blood were significantly lower in the former group. The median time to peak viral load following allo-HSCT, duration of viremia, and rate of virological response to high-dose therapy also differed significantly between the two groups.

Conclusion. It was shown that approximately one third (4 out of 14) of allogeneic stem cell transplant recipients had mutations associated with resistance to GCV. Patients carrying the mutant variant of HCMV had longer viremia and took longer to achieve a negative virological test result after starting high-dose therapy. Performing genotyping may help make more evidence-based therapeutic decisions.

Keywords: *human cytomegalovirus (HCMV); hematopoietic stem cells (HSCs) transplantation; viral chemoresistance; ganciclovir (GCV); antiviral therapy*

For citation: Tikhomirov D.S., Demin M.V., Serikova A.A., Biderman B.V., Sudarikov A.B., Tupoleva T.A. Mutations in human cytomegalovirus (Orthoherpesviridae: *Herpesvirales: Cytomegalovirus: Cytomegalovirus humanbeta 5*) UL97 gene lead to increase in viremia duration and poor antiviral response in recipients of allogeneic hematopoietic stem cells. *Problems of Virology* (*Voprosy Virusologii*). 2024; 69(5): 449–458. DOI: https://doi.org/10.36233/0507-4088-251 EDN: https://elibrary.ru/vrdyiz

Funding. This study was not supported by any external sources of funding.

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the National Medical Research Center for Hematology of the Ministry of Health of Russia (Protocol No. 160 dated December 23, 2021).

ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
DOI: https://doi.org/10.36233/0507-4088-251

Мутации в гене *UL97* цитомегаловируса (Orthoherpesviridae: *Herpesvirales: Cytomegalovirus: Cytomegalovirus humanbeta 5*) увеличивают продолжительность виремии и снижают противовирусный ответ у реципиентов аллогенных гемопоэтических стволовых клеток

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Резюме

Введение. Цитомегаловирус (Orthoherpesviridae: *Herpesvirales: Cytomegalovirus: Cytomegalovirus humanbeta 5*) (ЦМВ) является одним из наиболее распространенных вирусов, детектируемых у реципиентов аллогенных гемопоэтических стволовых клеток (алло-ГСК). При этом возможность развития резистентности вируса к противовирусным препаратам, таким как ганцикловир (GCV), создает сложности при проведении противовирусной терапии (ПВТ). Настоящее исследование позволяет обосновать необходимость внедрения новых диагностических подходов для улучшения результатов лечения у реципиентов алло-ГСК.
Цель исследования – изучение распространенности и влияния мутаций в гене *UL97* ЦМВ, ассоциированных с устойчивостью к действию GCV, на характер течения инфекции у реципиентов алло-ГСК.
Материалы и методы. В исследование вошли 14 реципиентов алло-ГСК с подозрением на устойчивую ЦМВ-инфекцию. Проводили амплификацию участка гена *UL97* методом гнездовой полимеразной цепной реакции, осуществляли секвенирование по Сэнгеру, последовательности сравнивали со штаммом Merlin (дикий тип).
Результаты и обсуждение. Выявлено 6 мутаций (D490A, T502A, C592G, C592F, E596G и C603W), из которых 4 (C592G, C592F, E596G и C603W) ранее были описаны как ассоциированные с устойчивостью к действию противовирусных препаратов, а D490A и T502A обнаружены впервые. При сравнении параметров пациентов – носителей вируса дикого типа и носителей мутантного варианта, установлено, что основные показатели периферической крови у первых были достоверно ниже. Медиана срока наступления пика вирусной нагрузки после трансплантации алло-ГСК, продолжительность виремии и скорость вирусологический ответа на ПВТ также имели достоверные различия в исследуемых группах.
Заключение. Показано, что почти у 1/3 (4 из 14) реципиентов алло-ГСК выявлены мутации, ассоциированные с устойчивостью к действию GCV. У реципиентов – носителей мутантного варианта ЦМВ наблюдались более длительные виремия и срок получения отрицательного результата вирусологического исследования после начала ПВТ. Проведение генотипирования может способствовать принятию более обоснованного терапевтического решения.

Ключевые слова: *цитомегаловирус (ЦМВ) человека; трансплантация гемопоэтических стволовых клеток (ТГСК); вирусная резистентность; ганцикловир (GCV); противовирусная терапия (ПВТ)*

Для цитирования: Тихомиров Д.С., Демин М.В., Серикова А.А., Бидерман Б.В., Судариков А.Б., Туполева Т.А. Мутации в гене *UL97* цитомегаловируса (Orthoherpesviridae: *Herpesvirales: Cytomegalovirus: Cytomegalovirus humanbeta 5*) увеличивают продолжительность виремии и снижают противовирусный ответ у реципиентов аллогенных гемопоэтических стволовых клеток. *Вопросы вирусологии*. 2024; 69(5): 449–458. DOI: https://doi.org/10.36233/0507-4088-251 EDN: https://elibrary.ru/vrdyiz

Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.
Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.
Этическое утверждение. Исследование проводилось при информированном согласии пациентов. Протокол исследования одобрен Этическим комитетом ФГБУ «Национальный медицинский исследовательский центр гематологии» Минздрава России (Протокол № 160 от 23.12.2021).

Introduction

Infection caused by human cytomegalovirus (Orthoherpesviridae: *Herpesvirales: Cytomegalovirus: Cytomegalovirus humanbeta 5*) (HCMV) poses a serious threat to immunosuppressed individuals, which can include HIV-infected people (especially in the AIDS stage), patients with tumor diseases, and organ or tissue recipients [1–3]. For specific antiviral therapy, the following drugs that inhibit various viral enzymes are used: viral DNA polymerase – pUL54 (ganciclovir (GCV), cidofovir and foscarnet), viral phosphotransferase – pUL97 (maribavir), viral terminal enzyme complex (letermovir) [4, 5]. However, in the Russian Federation, as well as abroad, due to the limited number of antiviral drugs authorized for use, the drug of choice is GCV or its prodrug – valganciclovir [6–8]. GCV phosphorylated by the viral enzyme is an analog of deoxyguanosine nucleotide, which accumulates in HCMV-infected cells and prevents virus replication by terminal incorporation into the growing viral DNA strand [9, 10].

However, the use of GCV for a long time and in suboptimal doses may contribute to the selection of drug-resistant mutant strains of HCMV, the replication of which is not blocked in the presence of the active substance of the drug [11]. According to the literature, mutations associated with resistance to GCV are localized in the *UL97* and *UL54* genes. In the *UL97* gene, mutations occur more frequently in codons 460, 520 and 590–607 [4, 12], not disrupting the virus life cycle but reducing the affinity of the enzyme for GCV [13].

Despite the advances in the prevention and treatment of HCMV infection, its resistance to the effect of antiviral drugs still raises concerns on the part of specialists. Previously, data on the prevalence of drug-resistant HCMV mutants in patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT) were presented and possible algorithms of antiviral treatment in such situations were proposed [14, 15]. Nevertheless, the data on the influence of such mutations on the course of infection and on the survival rate of patients are extremely scarce. The question of the feasibility of routine screening for mutations during antiviral therapy is also unclear. Thus, further research on this topic is extremely relevant and important for modern medical science, including the development of personalized medicine.

The aim of the study was to investigate the prevalence and impact of mutations in the *UL97* gene of HCMV associated with resistance to ganciclovir on the course of infection in recipients of allogeneic hematopoietic stem cells (allo-HSC).

Materials and methods

Patients and samples

The study was conducted with informed consent of the patients. The study protocol was approved by the Ethical Committee of the National Medical Research Center of Hematology of the Ministry of Health of Russia (Protocol No. 160 of 23.12.2021).

Allo-HSC recipients with signs of persistent HCMV infection in the post-transplantation period were included in the study. The presence of high viral load in blood, more specifically 1000 or more copies of genome-equivalent per 10 thousand nucleus-containing blood cells, for 2 weeks or more against the background of antiviral therapy was considered as a sign of such form of infection. Totally 14 allo-HSC recipients meeting these criteria were included into the study. In all recipients, hematopoietic stem cells (HSC) concentrate was used as a transplant source [16], and the majority (12 out of 14) underwent partially compatible allo-HSCT.

Mutations were searched for in the fragment of *UL97* gene of HCMV, codons from 420 to 630, by Sanger sequencing. A blood sample of the patient with the highest viral load was analyzed. Next, we collected and analyzed clinical and laboratory data of recipients for the period of 2 months before detection of high viral load and 2 months after detection. The characteristics of allo-HSC recipients are presented in **Table 1**.

Table 1. Characteristics of allo-HSC recipients included in the study
Таблица 1. Характеристики реципиентов алло-ГСК, включенных в исследование

Parameter Параметр	Value Величина
Total patients, abs. Всего пациентов, абс.	14
Gender, male/female Пол, мужчины/женщины	5/9
Median age, years (range) Медиана возраста, лет (диапазон)	40 (28–65)
The main diagnosis Основной диагноз	Number of patients, *n* Число пациентов, *n*
acute myeloid leukemia острый миелоидный лейкоз	7
acute lymphoblastic leukemia острый лимфобластный лейкоз	3
aplastic anemia апластическая анемия	1
primary myelofibrosis первичный миелофиброз	1
diffuse B-large cell lymphoma диффузная В-крупноклеточная лимфома	1
follicular lymphoma фолликулярная лимфома	1
Type of transplantation Вид трансплантации	Number of patients, *n* Число пациентов, *n*
related partially compatible родственная частично-совместимая	7
unrelated partially compatible неродственная частично-совместимая	4
unrelated fully compatible неродственная полностью совместимая	2
related fully compatible родственная полностью совместимая	1

All but one patient received GCV or valganciclovir as antiviral therapy on average from day 1 or day 3 after peak viral load was detected. None of the patients included in the study died during the follow-up period.

Amplification by nested-PCR to obtain product for subsequent sequencing

Amplification by nested polymerase chain reaction (nested-PCR) was performed using Genta PCR Master Mix reagents from Genterra (USA). For the first round of nested-PCR the following amplification mixture was used per one tube: deionized water (8 μL), Genta PCR Master Mix (5 μL), Forward and Reverse 1 primers solution (**Table 2**) 1 μL each (primer concentration 100 pmol/mL), DNA sample – 10 μL. The total volume of the mixture for the first round of nested-PCR was 25 μL.

Amplification program for the first round of nested-PCR:
– 95 °C (5 min) initial melting temperature;
– 32 cycles: 95 °C (10 s), 55 °C (40 s), 72 °C (1 min);
– final elongation – 72 °C (5 min).

Amplification mixture for the second round of amplification: the product of the first round of amplification (1 μL), a solution of forward (Forward) and reverse (Reverse 2) primers (Table 2) 1 μL each (primer concentration 100 pmol/mL), Genta PCR Master Mix (5 μL), 17 μL of deionized water. The total volume of the mixture for the second round of nested-PCR was 25 μL.

Amplification program for the second round of nested-PCR:
– 95 °C (5 min) initial melting temperature;
– 5 cycles: 95 °C (10 s), 64 °C (10 s), 72 °C (30 s);
– 25 cycles: 95 °C (10 s), 60 °C (15 s);
– final elongation – 72 °C (5 min).

Sanger DNA sequencing

The presence of nested-PCR products was confirmed by electrophoresis in 2% agarose gel for further sequencing using the BrilliantDye version 1.1, cyclic sequencing kit manufactured by NimaGen (The Netherlands). Sequencing was performed on a Nanofor 05 instrument. To exclude false-positive results, both sense and antisense DNA chains were sequenced independently and the results were checked for concordance. The data obtained during sequencing were analyzed using the Sequencing Analysis 5.31 computer program.

In the next step of data analysis, the obtained nucleotide sequences were compared with the reference sequence of the *UL97* gene of the Merlin strain (GenBank accession No: AY446894.2), which is considered to be a wild-type strain, using the Benchling platform (https://www.benchling.com).

Statistical analysis

Statistical analysis was performed using statistical software (Minitab for Windows, version 22.1; Minitab LLC.). Fisher's exact test was used to compare categorical variables between groups of patients who were carriers of the mutant strain and the wild-type strain. The Mann-Whitney *U*-criterion was used to compare constant variables in the study groups. Factorial ANOVA was used to assess the strength of the influence of the studied factors on the researched traits. The level of statistical significance was taken as $p < 0.05$.

Results

Prevalence of mutations in the UL97 HCMV gene in allo-HSC recipients with an episode of persistent infection

Six mutations (D490A, T502A, C592G, C592F, E596G and C603W) were detected in HCMV DNA samples isolated from the blood of 5 of 14 patients. Four of these have been previously described in the literature (C592G [17], C592F [18], E596G [19] and C603W [20]) as mutations associated with virus resistance to antiviral drugs. The remaining mutations (D490A and T502A) have not been previously reported in the literature. In one patient, two mutations were detected simultaneously, and both of them had GCV resistance phenotype (C592G and C603W). The results are summarized in **Table 3**.

There was no association of the fact of mutation detection with the main diagnosis and type of allo-HSCT. In one patient (Wt_9), the peak viral load was observed 28 days before allo-HSCT. In almost all wild-type virus carriers the maximum viral load was observed at early terms after allo-HSCT (up to 100+ days). In the overwhelming majority of patients – carriers of mutant variant of the virus, on the contrary, this peak was fixed at terms more than 100 days after allo-HSCT.

Comparison of clinical and laboratory data of patients – carriers of wild-type and mutant variants of the virus

To evaluate the influence of mutations on the character of the course of infection, the patients were divided into two groups. Wild-type virus carriers were included in the Wt group and mutant virus carriers were included in the Mt group (**Table 4**). The clinical and laboratory data of patients 2 months before the onset of maximal viral load and 2 months later were collected and analyzed.

Further, peripheral blood parameters, duration of viremia and time of virological response to antiviral therapy were analyzed. The data are presented in **Tables 5, 6**.

The main parameters of peripheral blood of wild-type virus recipients and carriers were significantly lower than in carriers of the mutant variant of the virus.

The median time of peak viral load onset after allo-HSCT, the duration of viremia and the rate of virological response to antiviral therapy were not significantly different in the studied groups.

Table 2. Primers used for nested-PCR and sequencing

Таблица 2. Праймеры, использованные для nested-PCR и секвенирования

Primer name Название праймера	Sequence (5'-3') Последовательность олигонуклеотидов (5'-3')
Forward	ACAACGTCACGGTACATCGA
Reverse 1	GTCGTAGTCCAAACTCGAGA
Reverse 2	CGACACGAGGACATCTTGG

Table 3. Identified mutations in the HCMV genome and the timing of the onset of viral load peaks in all patients

Таблица 3. Выявленные мутации в геноме ЦМВ и сроки наступления пиков вирусной нагрузки у всех пациентов

Patient code Код пациента	The main diagnosis Основной диагноз	Allo-HSCT type Вид алло-ТГСК	Mutation Наличие мутации	Onset of the peak viral load after allo-HSCT, days Срок наступления пика вирусной нагрузки после алло-ТГСК, сут
Mt_1	Acute myeloid leukemia ОМЛ	R, PC Р, ЧС	C592G C603W	+118
Mt_2	Follicular lymphoma ФЛ	UR, FC НР, ПС	E596G	+152
Mt_3	Acute myeloid leukemia ОМЛ	UR, FC НР, ПС	C592F	+405
Mt_4	Acute lymphoblastic leukemia ОЛЛ	UR, FC НР, ПС	D490A	+314
Mt_5	Acute myeloid leukemia ОМЛ	UR, PC НР, ЧС	T502A	+18
Wt_1	Acute lymphoblastic leukemia ОЛЛ	UR, PC НР, ЧС	Not detected Не обнаружена	+167
Wt_2	Acute myeloid leukemia ОМЛ	UR, PC НР, ЧС	Not detected Не обнаружена	+70
Wt_3	Aplastic anemia АА	R, FC Р, ПС	Not detected Не обнаружена	+23
Wt_4	Acute myeloid leukemia ОМЛ	R, PC Р, ЧС	Not detected Не обнаружена	+39
Wt_5	Primary myelofibrosis ПМФ	R, PC Р, ЧС	Not detected Не обнаружена	+50
Wt_6	Diffuse B-large cell lymphoma ДВККЛ	R, PC Р, ЧС	Not detected Не обнаружена	+63
Wt_7	Acute lymphoblastic leukemia ОЛЛ	R, PC Р, ЧС	Not detected Не обнаружена	+16
Wt_8	Acute myeloid leukemia ОМЛ	R, PC Р, ЧС	Not detected Не обнаружена	+60
Wt_9	Acute myeloid leukemia ОМЛ	R, PC Р, ЧС	Not detected Не обнаружена	-28

Note. UR – unrelated allo-HSCT; PC – partially compatible allo-HSCT; R – related allo-HSCT; FC – fully compatible allo-HSCT.

Примечание. АА – апластическая анемия; ДВККЛ – диффузная В-клеточная крупноклеточная лимфома; ОЛЛ – острый лимфобластный лейкоз; ОМЛ – острый миелоидный лейкоз; ПМФ – первичный миелофиброз; ФЛ – фолликулярная лимфома; НР – неродственная алло-ТГСК; ЧС – частично-совместимая алло-ТГСК; Р – родственнная алло-ТГСК; ПС – полностью совместимая алло-ТГСК.

Table 4. Demographic characteristics of patients

Таблица 4. Демографические характеристики пациентов

Parameter Параметр	All patients Все пациенты	Group Wt Группа Wt	Group Mt Группа Mt	*p*
Number of patients, abs. Число пациентов, абс.	14	9	5	
Gender, male/female Пол, муж/жен	5/9	4/5	1/4	NS
Median age (range) Медиана возраста (диапазон)	40 (28–65)	42 (28–65)	43 (39–52)	NS

Note. NS – the difference is not significant.

Примечание. NS – разница незначима.

The obtained results raised some doubts because they contradicted the data of the literature [14]. New groups were formed for analysis: a patient with the previously undescribed T502A mutation was excluded from the group of patients with resistance mutations (the parameters of this patient differed dramatically from patients carrying the resistance mutation). After reassignment of patients to the groups described above, the analy-

Table 5. The main indicators of peripheral blood of patients
Таблица 5. Основные показатели периферической крови пациентов

Parameter Параметр	All patients Все пациенты	Group Wt Группа Wt	Group Mt Группа Mt	*p*
Hemoglobin, g/l, average ± SD Гемоглобин, г/л, среднее ± SD	83,2 ± 15,6	82,4 ± 16,3	85,0 ± 14,3	0,036
Platelets, thousand/μl, average ± SD Тромбоциты, тыс/мкл, среднее ± SD	92,0 ± 68,7	73,5 ± 55,5	127,7 ± 77,3	< 0,001
Leukocytes, thousand/μl, average ± SD Лейкоциты, тыс/мкл, среднее ± SD	2,9 ± 2,4	2,7 ± 2,5	3,5±2,0	< 0,001

Note. Here and in tables 6, 7: SD – standard deviation.

Примечание. Здесь и в табл. 6, 7: SD – стандартное отклонение.

Table 6. Duration of viremia and time of onset of virological response to antiviral therapy in patients
Таблица 6. Длительность виремии и срок наступления вирусологического ответа на ПВТ у пациентов

Parameter Параметр	All patients Все пациенты	Group Wt Группа Wt	Group Mt Группа Mt	*p*
Median time of onset of peak viral load after allo-HSCT, days (range) Медиана срока наступления пика вирусной нагрузки после алло-ТГСК, сут (диапазон)	69 (1–405)	50 (1–167)	152 (18–405)	0,083
Duration of viremia, days, average ± SD Продолжительность виремии, сут, среднее ± SD	37,7 ± 29,1	25,8 ± 16,6	61,6 ± 35,6	0,075
Virological response* to antiviral therapy, days, average ± SD Вирусологический ответ* на ПВТ, сут, среднее ± SD	19,3 ± 19,4	13,0 ± 11,1	35,0 ± 28,2	0,102

Note. * – Mt_2 patient data was not taken into account (did not receive antiviral therapy).

Примечание. * – данные пациента Mt_2 не учитывали (не получал ПВТ).

Table 7. Comparison of patient indicators in newly formed groups
Таблица 7. Сравнение показателей пациентов во вновь образованных группах

Parameter Параметр	Group Wt_new Группа Wt_new	Group Mt_new Группа Mt_new	*p*
Number of patients, abs. Число пациентов, абс.	10	4	
Hemoglobin, g/l, average ± SD Гемоглобин, г/л, среднее ± SD	82,7 ± 16,3	84,7 ± 13,5	0,036
Platelets, thousand/μl, average ± SD Тромбоциты, тыс/мкл, среднее ± SD	77,7 ± 57,2	127,9 ± 81,1	< 0,001
Leukocytes, thousand/μl, average ± SD Лейкоциты, тыс/мкл, среднее ± SD	2,7 ± 2,5	3,5 ± 2,0	< 0,001
Median time of onset of peak viral load after allo-HSCT, days (range) Медиана срока наступления пика вирусной нагрузки после алло-ТГСК, сут (диапазон)	46 (1–167)	233 (118–405)	0,013
Duration of viremia, days, average ± SD Продолжительность виремии, сут, среднее ± SD	24,2 ± 16,7	75,0 ± 22,2	0,007
Virological response to antiviral therapy, days, average ± SD Вирусологический ответ на ПВТ, сут, среднее ± SD	12,5 ± 10,7	44,3 ± 25,9	0,029

sis was repeated, the results of which are presented in **Table 7**.

Discussion

A distinction should be made between refractory and resistant HCMV infection. Thus, refractory is a clinical definition based on the criteria of response to antiviral therapy, while resistant HCMV infection is a concept based on the laboratory detection of drug-resistant genotype or mutations that are responsible for resistance to antiviral drugs [21].

The frequency of detection of refractory forms of HCMV infection among organ and tissue recipients is quite high. According to the latest data, it ranges from 5 to 12% among

solid organ recipients [22, 23]. In HSC recipients, this index varies depending on many factors, among which the compatibility of the recipient and donor according to the leukocyte antigen (HLA) system takes an important place. Thus, in HLA-compatible allo-HSCT from both related and unrelated donors the frequency of resistance is about 8% [23], and in high-risk patients with partially compatible allo-HSCT – 14.5% [24].

In the present study, mutations in the CMV *UL97* gene were detected in 5 of 14 allo-HSC recipients with evidence of resistant CMV infection. Among the mutations, the following were detected: D490A, T502A, C592G, C592F, E596 and C603W. Four of these (C592G, C592F, E596G and C603W) are known mutations associated with resistance of the virus to antiviral drugs. The remaining two mutations have not been previously described in the literature. In one patient, two mutations were detected simultaneously, both being resistance mutations (C592G and C603W).

Analysis and comparison of clinical and laboratory data of patients carrying mutant and non-mutant *UL97* variants of the virus allowed to reveal a significant difference in the main peripheral blood parameters (hemoglobin, platelets and leukocytes). These indices were significantly higher in recipients with the mutant variant. However, when comprehensively comparing the data, it became evident that this phenomenon was related not to the presence of the mutation as such, but to the time of its detection. Thus, in case of wild-type strain high viral load on the average was observed at earlier terms after allo-HSCT than in mutant strain carriers (50 days vs. 152 days). In the first case, in the majority of patients at this term the final transplant engraftment and complete restoration of hematopoiesis at the expense of the donor have not yet occurred.

In contrast, the average duration of viremia, the rate of onset of virological response to antiviral therapy, and the median time to peak viral load had no significant difference. This phenomenon was unexpected. It would be logical to assume that the presence of a GCV resistance mutation should increase the duration of viremia and delay the onset of antiviral response to antiviral therapy. To explain this phenomenon, we further analyzed the data of recipients with mutations not previously described in the literature.

The patient with T502A mutation differed strikingly from other carriers of the mutant strain by clinical and laboratory data, namely: high viral load was recorded only 18 days after allo-HSCT, the duration of viremia was 8 days, and antiviral response was observed on the 8th day of antiviral therapy. Thus, it can be hypothesized that the T502A mutation in the *UL97* gene of HCMV is probably not associated with GCV resistance. Consequently, this patient should have been considered as a carrier of a variant virus without the resistance mutation and assigned to the group of patients with wild-type virus (Wt_new group).

Clinical and laboratory data of the patient with D490A mutation, on the contrary, indicated probable resistance to GCV: high viral load was recorded on the 314th day after allo-HSCT, the duration of viremia was 45 days, and the antiviral response occurred on the 16th day after initiation of antiviral therapy. Such a difference between the duration of viremia and duration of antiviral therapy can be explained by the fact that the viral load in this patient before the peak was in the area of low values, and their condition did not require antiviral treatment. The data obtained suggest that the D490A mutation is associated with GCV resistance. However, confirmation of this fact requires further research. Thus, the above-mentioned patient should have been left in the group of carriers of the mutant variant of the virus, and the group should have been renamed to Mt_new.

After redistribution of patients into the newly formed groups, a significant difference was obtained for all studied parameters (Table 7). The obtained data provide additional grounds to suggest that the T502A mutation is probably not associated with GCV resistance, while the D490A mutation, on the contrary, is associated. Thus, the detection rate of GCV resistance mutations among allo-HSC recipients was 4 of 14 (28.6%).

Within the framework of the present study and taking into account previously published data [14, 15], it can be stated that the emergence of GCV resistant virus can lead to a change in the course of HCMV infection. The results obtained in the course of the study confirm the relevance and practical significance of the identification of mutations associated with resistance to antiviral drugs.

Research limitation

When evaluating the results obtained, it should be taken into account that the Sanger sequencing method used in this study to search for mutations has limitations. For example, it does not allow detection of DNA sequences with a proportion of less than 10%. Other laboratory methods, such as next-generation sequencing (NGS), are more sensitive, which confirms the relevance of a similar study putting them to use [25]. GCV resistance mutations can also be localized in the *UL54* gene encoding DNA polymerase. Viruses carrying such mutations may be cross-resistant to other antiviral drugs [26].

Conclusion

The data obtained during the present study are consistent with the results of previous studies and expand the ideas about the influence of mutations associated with resistance to antiviral drugs on the course of HCMV infection in HSC recipients [7, 15]. It was shown that almost 1/3 (4 out of 14) of allo-HSC recipients with signs of stable HCMV infection have mutations associated with resistance to GCV action. D490A, a mutation with such potential, was found and described for the first time. Recipients who are carriers of the mutant variant of HCMV had longer viremia and a longer period of negative virological results after the start of antiviral therapy.

Nevertheless, at the moment, standardized algorithms for mutation diagnosis have not been approved either in the Russian Federation or abroad, despite the fact that such proposals have been put forward repeatedly [7, 15, 27]. Genotyping and search for mutations in

case of non-response to antiviral therapy is extremely relevant. Information about a specific mutation and its characteristics can contribute to making a more informed therapeutic decision.

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Contribution: Demin M.V. – research concept and design, conducting experiments, collecting, analyzing and interpreting data, preparing the text of the article; Serikova A.A. – conducting experiments, collecting data; Tikhomirov D.S. – analyzing and interpreting data, preparing the text of the article; Biderman B.V. – technical support, analyzing and interpreting data; Sudarikov A.B. – approval of the final version of the article for publication; Filatov F.P. – consulting on general issues, text editing; Tupoleva T.A. – approval of the final version of the article for publication.

Received 17 July 2024
Accepted 10 September 2024
Published 31 October 2024

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Поступила 17.07.2024
Принята в печать 10.09.2024
Опубликована 31.10.2024