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EXPLORING THE INTRAVENOUS COMBINATION OF D-ISOASCORBIC ACID (D-VC) AND ARSENIC TRIOXIDE IN ADVANCED/METASTATIC MALIGNANCIES

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ABSTRACT

Background: Addressing the therapeutic challenges associated with Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) mutant cancers remains a significant focus in oncology. The combined intravenous administration of the D-isomer of vitamin C (D-VC) (dextro-rotatory isomer of ascorbic acid) and arsenic trioxide (ATO) is proposed as a potential approach for achieving an anti-tumor effect in Colorectal cancer (CRC) with KRAS-mutant tumor cells. ATO enhances the oxidative effect of vitamin C (VC), and the combination of both drugs provides effective eradication of KRAS-mutant cancer cells. A potent synergistic effect of the VC and ATO combination has been observed about KRAS-mutant cancer cells.

Purpose: This clinical trial aims to assess the tolerability and safety of intravenous administration of D-VC along with ATO in patients with advanced/metastatic malignancies who have exhausted standard therapy.

Methods and Patients: This single-center Phase I clinical trial evaluated the tolerability and safety of D-VC when administered intravenously alone or in sequential administration with ATO. The target group for the Phase I exploratory clinical trial includes 10 patients with advanced/metastatic malignant neoplasms who have exhausted standard therapy.

Results: The administration of the drug followed the treatment regimen according to the ap-proved study protocol. After a single intravenous infusion of D-VC in escalating doses of 0.05 g/kg - 0.1 g/kg - 0.15 g/kg - 0.3 g/kg all patients felt satisfactory, and no subjective intolerance to the investigational drug was reported. The main functional and laboratory parameters remained within normal values recorded at the start of the study. The maximum tolerated dose of D-VC was determined to be 0.3 g/kg, and this dose was chosen as the baseline for the second stage of the study, where D-VC (0.3 g/kg) was administered alongside ATO (0.15 mg/kg).

Conclusions: Our findings showed favorable safety and well-tolerated profiles and provided the recommended dose for high-dose D-VC in combination with ATO.

Keywords: Cancer, KRAS, arsenic trioxide (ATO), vitamin C enantiomer D (D-VC), Phase I and Phase II clinical trials

INTRODUCTION

Colorectal cancer (CRC) is a major cause of cancer-related deaths worldwide, with more than 150,000 new cases and 50,000 deaths reported annually globally [1,2]. The development and progression of CRC are influenced by a combination of genetic factors, environmental risk factors, and lifestyle choices. Genetic dysregulation of metabolic enzymes plays a role in CRC pathogenesis. Notably, genetic mutants, such as Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS), have been found to contribute to global metabolic reprogramming in CRC [3]. KRAS mutant cancers are highly aggressive and often associated with poor outcomes. Addressing the therapeutic challenges associated with KRAS mutant cancers remains a significant focus in oncology. In this context, the combined intravenous administration of the D-isomer of vitamin C (D-VC) (dextro-rotatory isomer of ascorbic acid) and arsenic trioxide is proposed as a potential approach for achieving an antitumor effect in CRC with KRAS-mutant tumor cells. ATO enhances the oxidative effect of VC, and the combination of both drugs provides effective eradication of KRAS-mutant cancer cells. A potent synergistic effect of the VC and ATO combination has been observed in relation to KRAS-mutant cancer cells [4].

The conducted study of the pharmacodynamic effects of D-VC confirmed the previously suggested hypothesis that the selective effect in cancer cells may be associated with increased glucose consumption mediated by significant expression of GLUT1 - glucose transporter [5]. It is hypothesized that within the body, VC is oxidized to dehydroascorbate (DHA), which is actively taken up by cancer cells through GLUT1 due to its structural similarity to glucose. Inside the cell, DHA is reduced back to VC through the oxidation of glutathione (GSH). As a result, significant depletion of DHA in KRAS mutant cells leads to the development of oxidative stress [6].

During the investigation of the pharmacodynamic effects of ATO/D-VC on immunodeficient mice with the AK192 xenograft model and the HCT116 cell line xenograft, it was determined that the combination of oxidizing agents ATO/D-VC resulted in a reduction in tumor volume compared to the control (placebo) [4,7]. According to our study, the combination of ATO and D-VC resulted in a catastrophic oxidative stress and cell death in KRAS mutant cells under natural conditions. Our research demonstrated that the combined treatment of ATO/D-VC more effectively suppressed tumor growth in the AK192 xenograft model compared to the HCT116 cell line xenograft (average tumor weight was 3.57 and 3.4 times lower than the control group, respectively) [4,7].

The antitumor potential of arsenic trioxide (ATO) is well-established in the treatment of acute pro-myelocytic leukemia. However, its application for solid tumors has been limited by dose-related toxicity and unfavorable pharmacokinetics.

In a comprehensive study by Subbarayan et al [8], the out-

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comes of clinical trials using ATO, both as a single agent and in combination settings, in patients with solid tumors were summarized. The article also explores potential additional mechanisms by which ATO could serve as a chemosensitizer in combination therapy [8].

Significantly, ATO enhances the oxidative effects of VC (vitamin C), and the combination of both drugs demonstrates efficacy in eliminating KRAS-mutant cancer cells. A remarkable synergistic effect has been observed with the combination of VC and ATO against KRAS-mutant cancer cells [9]. While the individual administration of ATO, VC, or D-VC alone showed weak and partial tumor suppression, the combined treatment of ATO and D-VC exhibited a substantially more cytotoxic effect on potent KRAS-mutant colorectal cancer cells.

Our preclinical studies have established that ATO and D-VC act synergistically, selectively induce cytotoxic oxidative stress in mutant KRAS cancer cells [4,7]. The synergistic cytotoxic effect induced by the combination of ATO and D-VC suggests that the high level of oxidative stress in KRAS mutant cancer cells affects redox-sensitive cellular systems, including vulnerable mitochondrial oxidative phosphorylation (OXPHOS) systems. It may occur through a two-step process: firstly, the high dose of D-VC depletes GSH and inhibits the anti-oxidant defense of cells and secondly, ATO effectively targets thiol-reactive groups in cellular proteins, particularly the mitochondrial OXPHOS complexes. Direct oxidation of thiol-reactive proteins within the OXPHOS complexes likely leads to uncontrolled suicidal mitochondrial production of reactive oxygen species.

Therefore, the proposed combination of drugs can effectively inhibit the growth of KRAS mutant cells by generating high concentrations of reactive oxygen species, which induce apoptosis and suppress angiogenesis. It is hypothesized that in this combination of oxidative agents, D-VC serves as the primary component, while ATO acts as an auxiliary agent. Arsenic trioxide enhances the oxidative stress induced by ascorbic acid, ultimately leading to targeted cell death of KRAS-mutant cancer cells.

The volume and content of the preclinical research materials have been deemed sufficient by the National Center for Drug Expertise of the Republic of Kazakhstan for approval to proceed with Phase I clinical trials.

The main objectives of present clinical trial are evaluation of the tolerability and safety of D-isoascorbic acid (D-VC) through single intravenous administration as monotherapy and sequential administration with arsenic trioxide (ATO) in patients with advanced/metastatic malignant neoplasms who have exhausted standard therapy; as well as an assessment of the safety and tolerability of D-isoascorbic acid through multiple intravenous administrations with arsenic trioxide in patients with advanced/metastatic malignant neoplasms. These objectives are crucial in establishing the appropriate dosage, administration schedule, and potential therapeutic benefits of D-VC and its combination with ATO in patients with advanced/metastatic malignant neoplasms.

PATIENTS AND METHODS

This protocol has been developed in accordance with the provisions of the standard protocol: recommendations for interventional trials according to the order of the Minister of Health of the Republic of Kazakhstan No. QR DSM-248/2020 dated December 11, 2020, «Approval of the Rules for Conducting Clinical Trials of Medicines and Medical Devices, Clinical Laboratory Tests of Medical Devices for In Vitro Diagnostics, and Requirements for Clinical Bases and the Provision of the State Service for Issuing Permission to Conduct a Clinical Trial and/or Pharmacological and Medicinal Product Testing, Medical Devices» [18].

The study is an exploratory investigation. It is an interventional study, with Phase 1 focusing on the safety and tolerability of the investigational drug D-VC in two groups, first group – 6 patients and second group – 4 patients considering a 20% dropout rate.

The clinical research protocol has been submitted and approved by the local ethical committee of the Kazakh Scientific Research Institute of Oncology and Radiology. Prior to participation, written informed consent were obtained from the patients.

Characteristics of the study drug.

D-isoascorbic acid (D-VC) (Nur-may Pharmacy, Almaty, Kazakhstan)

The drug D-VC (erythorbic acid) is an enantiomer of D ascorbic acid. To carry out a clinical study, a dosage form of D-VC was prepared as the main glucose-dependent oxidative drug for the treatment of colorectal cancer. The pharmaceutical development of the dosage form of D-VC was carried out, the active pharmaceutical substance (APS) was tested for compliance with the international pharmacopeias USP 43-NF 38 Erythorbic Acid, and the guaranteed quality preservation period (shelf life) was determined at 2 years.

The D-VC drug was administered in doses from 0.05 g/kg to 0.3 g/kg intravenously, diluted with saline.

Arsenic Trioxide (ATO)

ATO Injection 10mg/10mL (GLS PHARMA LIMITED, New Delhi, India)

ATO is an FDA-approved chemotherapy agent for the treatment of solid cancers and leukemia.

In our clinical study, it was used as an adjuvant drug to enhance oxidative stress caused by D-VC, ultimately leading to targeted death of KRAS mutant cancer cells.

ATO was administered to patients intravenously at a dose of 0.15 mg/kg according to the drug instructions.

Study design, participants and setting

The study is being conducted at the Department of Chemotherapy of the Kazakh Scientific Research Institute of Oncology and Radiology (KazNIIO&R) since February 2023, where patients were being enrolled into specific treatment groups. The target group for the Phase I exploratory clinical trial includes the minimum number of patients necessary to make judgements about the safety and tolerability of the investigational drug D-VC (8-10 patients, considering a 20% probability of dropouts from the study) with advanced/metastatic malignant neoplasms who have exhausted standard therapy.

Inclusion Criteria: informed consent to participate in the study; Patients diagnosed with advanced/metastatic malig-

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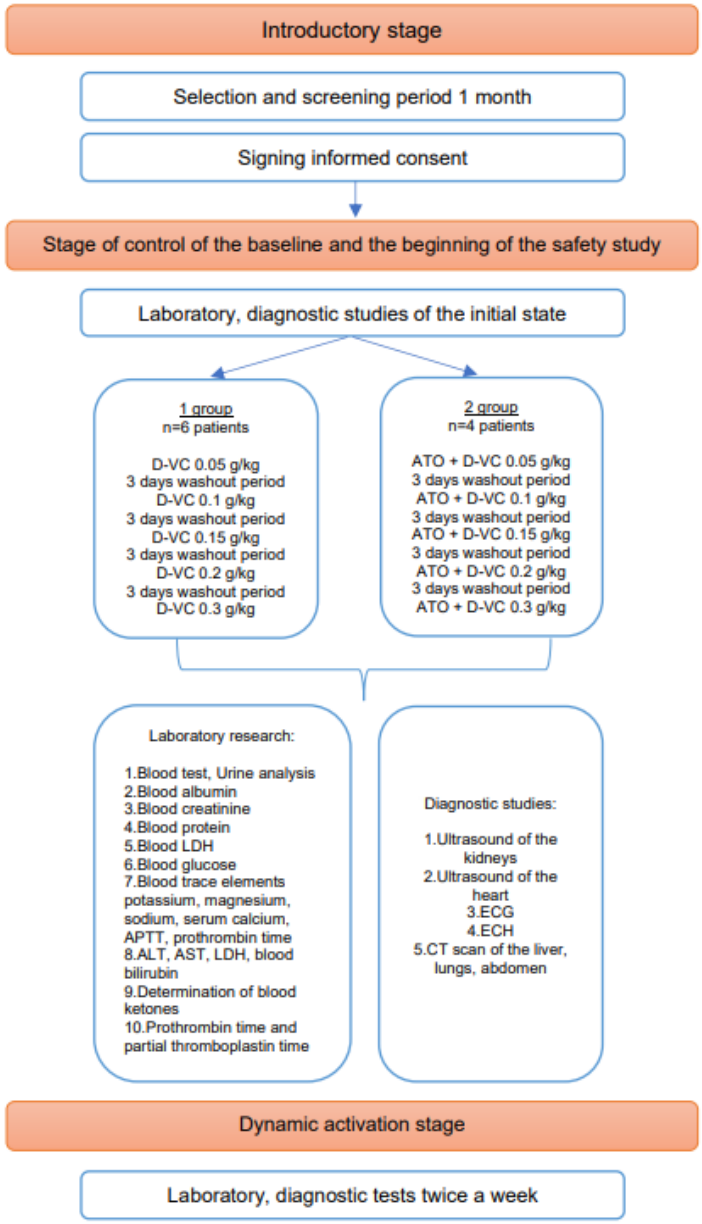


Figure 1. Phase I Study Design Scheme

nant neoplasms who have undergone at least 3 lines of standard therapy, including targeted drugs;

Exclusion Criteria: age below 18 years; pregnancy and lactation; patients with an auto-immune disease or a medical diagnosis requiring systemic immunosuppression; decompensated diabetes mellitus; renal insufficiency and urolithiasis; diabetes mellitus; thrombophlebitis or a predisposition to thrombosis; severe lung disease, dyspnea at rest, pleural effusion; cardiovascular insufficiency, left ventricular ejection fraction <40%; grade 1 sensory neuropathy of any etiology; uncontrolled infections.

All enrolled patients were undergoing laboratory tests (complete blood count, urine analysis, biochemical analyses including albumin, creatinine, protein, glucose, ALT, AST, bilirubin, ketones, microelements: potassium, magnesium, sodium, serum calcium, activated partial thromboplastin time, prothrombin time) and diagnostic investigations (ultrasound of the kidneys and heart, ECG, echocardiography, CT of the liver, lungs, abdominal cavity).

Stages of the study and treatment regimen.

The clinical study was conducted sequentially in two stages. Patients who meet the inclusion criteria were sequentially enrolled in the 1st and 2nd groups (Figure 1).

Abbreviations: D-VC, D-isoascorbic acid; ATO, arsenic trioxide; LDH, Lactate Dehydrogenase; APTT, Activated Partial Thromboplastin Time; ALT, Alanine transaminase; AST, Aspartate Transferase; ECG, electrocardiogram; ECH, Echocardiogram; CT, Computer tomography

Stage 1: Patients (n = 6) received a single intravenous administration of D-VC as a solution for intravenous infusions at a dose of 0.05 g/kg/day (at least 6 patients), followed by a 3-day washout period. If the tolerability and safety were satisfactory, the administration of D-VC was increased to a dose of 0.1 g/kg/day, followed by another 3-day washout period. Likewise, the dose of D-VC was increased to 0.15 g/kg/day, and further to the maximum tolerated dose of 0.3 g/kg/day, with a mandatory washout period. After the completion of Stage 1, an intermediate analysis of the safety and tolerabil-

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ity of D-VC were conducted. Based on the satisfactory tolerability and safety of D-VC (as determined by the intermediate analysis results of Stage 1), the decision to proceed to Stage 2 was made by the investigator in consultation with the sponsor.

Stage 2: Patients (n = 4) received a single intravenous administration of D-VC as a solution for intravenous infusions at a dose of 0.05 g/kg, 2 hours after a single intravenous administration of arsenic trioxide (ATO) at a dose of 0.15 mg/kg. This will be followed by a 3-day washout period. As in the first stage, if tolerability and safety were satisfactory, the dose of D-VC was increased at a dose of 0.1 g/kg, 0.15 g/kg and 0.3 g/kg, observing a washout period. The dose of ATO did not change and was 0.15 mg/kg.

Based on the analysis of tolerability and safety, a decision was made regarding the dose selection (maximum tolerated dose of D-VC in combination with ATO) for the multiple ad-ministrations in Phase II.

Data safety and monitoring

The safety of the investigational drug is assessed as a medical risk for the subject in the clinical study through laboratory tests (including clinical biochemistry and hematology), vital signs assessment, monitoring of adverse events (diseases, symptoms, and complaints), and other specific safety tests (e.g., electrocardiogram, ophthalmological examination).

Patients were closely monitored on a continuous basis during the dose escalation phase of the study. Bayesian rule was used for toxicity control (calculating the probability that a toxic effect was caused by the administration of the investigational drug), allowing for the gradual updating of the probability of an event as new observations or information become available.

RESULTS

The first phase of the clinical study

The first phase of the clinical study was conducted as planned in two stages:

a) intravenous administration of D-VC in escalating doses, starting with a single dose of 0.05 g/kg and ending with a single dose of 0.3 g/kg with a washout period of 3 days between doses;

b) Two hours after the intravenous administration of ATO at a stable dose of 0.15 mg/kg, D-VC was administered in escalating doses, starting with a single dose of 0.05 g/kg and ending with a single dose of 0.3 g/kg with a washout period of 3 days between doses. The maximum investigational dose of D-VC was limited to the maximum tolerated dose of D-VC established in a sub chronic (3-month) experiment in rats and recalculated for humans using the following formula: maximum tolerated dose in rats (NOAEL) 2 g/kg x conversion factor 0.162 = 0,324 g/kg.[8,9] In the study, the value of the maximum dose was planned at 0.3 g/kg.

The first stage of Phase I of the study included 6 patients. All patients were females aged between 45 and 75 years with malignant neoplasms who had exhausted standard FOLFOX (combination of leucovorin, 5-fluorouracil, and oxaliplatin) and FOLFIRI (combination of leucovorin, fluorouracil, and irinotecan) therapies. All data is presented in the Table 1.

The administration of the drug followed the treatment regimen according to the approved study protocol. After a single intravenous infusion of D-VC in escalating doses of 0.05 g/kg - 0.1 g/kg - 0.15 g/kg - 0.3 g/kg, all patients felt satisfactory, and no subjective intolerance to the investigational drug was reported. The main functional and laboratory parameters remained within normal values recorded at the start of the study. The maximum tolerated dose of D-VC was determined to be 0.3 g/kg, and this dose was chosen as the baseline for the second stage of the study, where D-VC (0.3 g/kg) was administered alongside ATO (0.15 mg/kg).

The second stage of the clinical study

The second stage of the study involved a single intravenous administration of D-VC in combination with a single intravenous ATO dose of 0.15 mg/kg (administered 2 hours prior to D-VC). D-VC was administered in escalating doses of 0.05 g/kg - 0.1 g/kg - 0.15 g/kg - 0.3 g/kg alongside ATO. The study includes 4 patients who completed the first stage (D-VC monotherapy).

During the second stage of the study, it was established that all patients tolerated the combined administration of D-VC + ATO satisfactorily, even with an increase in D-VC dose from 0.05 g/kg to 0.3 g/kg. No cases of intolerance were observed in any dosing regimen. Adverse events were observed in 2 patients when administered a dose of D-VC 0.3 g/kg + ATO 0.15 mg/kg, while in 1 patient they occurred within 24 hours after administration with symptoms of dyspepsia, hepatolienal syndrome, in 1 patient short-term phenomena of asthenic syndrome were noted. Laboratory analysis also was change according to the ATO instruction.

The maximum tolerated dose of D-VC for intravenous administration alongside the licensed dose of ATO can be considered as 0.3 g/kg. This dosing regimen is planned to be used in the second phase of the current clinical study: 0.3 g/kg D-VC + 0.15 mg/kg ATO for intravenous administration once daily for 14 days

Abbreviations: D-VC, D-isoascorbic acid; ATO, arsenic trioxide; AE/SAE, adverse effects/secondary adverse effects

Table 1. Summary information of the patients I phase clinical study

ID patient	Sex	Diagnosis	1 stage of treatment D-VC g/kg	AE/SAE	2 stage of treatment D-VC g/kg + ATO 0.15 mg/kg	AE/SAE
BR0101	female	Malignant neoplasm of the sigmoid colon, IV Stage	intake doses 0.05, 0.1, 0.15, 0.2, 0.3	No AE/SAE	refuse	Not applicable

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BR0102	female	Malignant neoplasm of the upper outer quadrant of the breast, IV Stage	intake doses 0.05, 0.1, 0.15, 0.2, 0.3	No AE/SAE	intake doses D-VC 0.05+ATO, 0.1+ATO, 0.15+ATO, 0.2+ATO, 0.3+ATO	24 hours after administration with symptoms of dyspepsia, hepatolienal syndrome
BR0103	female	Malignant neoplasm of the gastric cardia, III Stage	intake doses 0.05, 0.1, 0.15, 0.2, 0.3	No AE/SAE	intake doses D-VC 0.05+ATO, 0.1+ATO, 0.15+ATO, 0.2+ATO, 0.3+ATO	short-term phenomena of asthenic syndrome were noted
BR0104	female	Malignant neoplasm of the endometrium of the uterine body, II Stage	intake doses 0.05, 0.1, 0.15, 0.2, 0.3	No AE/SAE	refuse	Not applicable
BR0105	female	Malignant neoplasm of the sigmoid colon, II stage	intake doses 0.05, 0.1, 0.15, 0.2, 0.3	No AE/SAE	intake doses D-VC 0.05+ATO, 0.1+ATO, 0.15+ATO, 0.2+ATO, 0.3+ATO	No AE/SAE
BR0106	female	Malignant neoplasm of the rectum, IV Stage	intake doses 0.05, 0.1, 0.15, 0.2, 0.3	No AE/SAE	intake doses D-VC 0.05+ATO, 0.1+ATO, 0.15+ATO, 0.2+ATO, 0.3+ATO	No AE/SAE

DISCUSSION

This randomized phase 1 clinical trial showed that high-dose D-VC with ATO have a favorable safety and tolerability profiles. The study's proven safety of using a relatively high dose of D-VC (0.3 g/kg) for intravenous infusion in combination with intravenous administration of a standard dose of ATO (0.15 mg/kg) creates the basis for moving to a phase 2 clinical trial of the effectiveness of this combination in patients with colorectal cancer who have a KRAS mutation. The safety profile of high-dose D-VC in the current study was consistent with the safety profile of vitamin C in various tumor types [10,11]. Taken together, the results of this phase 1 clinical trial provide compelling evidence to justify moving to a larger clinical trial combining high-dose vitamin C with chemotherapy for patients with KRAS-mutant meta-static colorectal cancer.

Based on our hypothesis that D-VC selectively induces oxidative stress, we explored the combination of D-VC with another oxidizing drug to enhance its cytotoxic impact on cancer cells. Our findings demonstrate that the combination of the oxidizing agent ATO with D-VC exerts a potent cytotoxic effect on KRAS mutant pancreatic and colorectal cancer cells. Over the past decade, there has been a significant increase in the number of clinical studies investigating high-dose VC as a treatment for various oncological diseases, both as monotherapy and in combination therapy. A large number of studies have demonstrated promising anticancer activity of vitamin C (VC) at high millimolar concentrations (~1-20 mM) in preclinical models of various types of cancer [1]. The most extensively studied cancers in relation to the use of high-dose vitamin C include leukemia, colorectal cancer, melanoma, pancreatic cancer, and prostate cancer [2]. Notable examples of progress in pre-clinical research on vitamin C (VC) are studies focusing on difficult-to-treat tumors driven by the KRAS, such as KRAS-mutant colorectal cancer [3,10]. Based on previous preclinical studies, the authors of the aforementioned clinical trials utilized elevated doses of VC (5-10 mM) in KRAS-mutant CRC both in vitro and in vivo. They demonstrated that VC can exert its effects by reducing adenosine triphosphate (ATP) levels and glucose transporter 1 (GLUT-1), as well as dissipating the mitochondrial membrane potential, thereby increasing the sensitivity of KRAS-mutant CRC cells to chemotherapy. However, the underlying mechanism of its antitumor action remains insufficiently understood.

The main idea is that a clinical study is being conducted to evaluate the use of high doses of D-VC in combination with ATO (a different drug) for antitumor activity in patients with oncological diseases, including colorectal cancer with KRAS mutations. The administration of ATO, VC, or D-VC alone resulted in only weak and partial suppression of the tumor, but the combination of ATO and D-VC had a significantly more cytotoxic effect on KRAS-mutant CRC cells. This finding demonstrates that the combination of ATO and D-VC is a highly promising candidate as a targeted therapy for CRC. The study builds upon promising results from previous clinical trials that investigated the use of high doses of ascorbic acid and aims to assess the potential efficacy and safety of high doses of D-VC in combination with ATO for treating oncological diseases. It's important to note that while some clinical trials have shown potential benefits of combining high-dose VC with other treatments, not all trials have yielded significant advantages over standard treatments alone [11,12]. The efficacy of such combinations can vary depending on the specific cancer type, patient characteristics, treat-

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ment protocols, and other factors.

Several pioneering studies have demonstrated the efficacy of pharmacological VC in improving the survival of patients with advanced cancer [5]. On the contrary, two randomized double-blind controlled trials did not demonstrate any benefits of VC in the context of advanced malignant cancer [17]. Therefore, the route of administration is crucial for achieving therapeutic effects of high-dose VC, and only intravenous administration leads to sufficiently high concentrations in plasma and urine to potentially exert anticancer activity [18].

Recently, it has been demonstrated that intravenous administration of VC can selectively kill colorectal cancer cells with KRAS or BRAF mutations by targeting GAPDH [10]. VC is believed to induce the death of cancer cells through a ROS-, AMPK-, and MAPK-dependent mechanism [19]. The cytotoxic action of VC is likely mediated through a glucose-dependent oxidative effect, which confers selectivity in the destruction of highly malignant KRAS-mutant CRC cells. It is important to emphasize that the presumed mechanism of the anticancer effect of vitamin C can be attributed not only to the synthetic L-isomer of vitamin C (LVC) but also to D-VC.

In 1993, an original study was published describing the direct cytotoxic effects of both VC and D-VC on rapidly proliferating malignant cancer cells [16]. Similarly, a potent cytotoxic effect of D-VC against KRAS-mutant cancer cells in cell culture was demonstrated later as well [4]. D-VC, also known as erythorbic acid, is a common food additive and a non-toxic antioxidant. The lower toxicity of D-VC compared to VC is expected, as it has been reported to be more rapidly eliminated from the human body [21].

The available evidence supports a high likelihood of having an antitumor effect for both VC and D-VC. ATO has been utilized in the treatment of acute pro-myelocytic leukemia, but its use in solid tumors has been limited due to dose-dependent toxicity and unfavorable pharmacokinetics. However, promising results have been observed in the treatment of refractory/recurrent CRC resistant to 5-fluorouracil. Therefore, the com-bination of high-dose VC and ATO may hold potential for the treatment of refractory/recurrent CRC that does not respond to standard protocols involving 5-fluorouracil. The anticancer effects of VC and ATO may synergistically target tumor cells, providing a new perspective in the treatment of this type of cancer.

The main mechanism of the antitumor effect of ATO is the induction of reactive oxygen species (ROS)-dependent apoptosis. The action of ATO leads to an oxidant-antioxidant imbalance in cells, which can contribute to the formation of various ROS, such as H2O2, superoxide ($O2^{-}$•), nitric oxide (•NO), hydroxyl (HOO•), dimethylarsinyl ((CH3)2AsOO•), and dimethylarsenic ((CH3)2As•) radicals, causing oxidative stress [1]. Initially, during the planning of the clinical study, we relied on promising results of using ascorbic acid in the form of the levorotatory isomer LVC (corresponding to natural ascorbic acid) in high doses (up to 75 g of ascorbic acid intravenously per day) in clinical trials involving patients with oncological diseases, including colorectal cancer with KRAS mutations [10,15]. Considering the higher prooxidant potential of the levorotatory isomer of ascorbic acid (D-VC) and the possibility of potentiation of the cytotoxic effects of D-VC when combined with ATO, we anticipate that the use of high doses of D-VC in combination with the licensed dose of ATO for antitumor activity will be effective and safe.

CONCLUSION

Based on the results of phase I, the maximum tolerated dose of the study drug D-VC was determined at a dosage of 0.3 g/kg when administered sequentially with ATO. Our findings showed favorable safety profiles and provided the recommended dose for high-dose D-VC in combination with ATO. Although the current dose of D-VC and dosing schedule in combination with ATO have been shown to be well tolerated, we intend to continue the phase 2 study with more days of infusion, which could provide more information in this area.

This is the first clinical trial evaluating the tolerability and safety of intravenous administration of D-Isoascorbic Acid in combination with Arsenic Trioxide for patients with advanced/metastatic malignancies who have exhausted standard therapy.

The research hypothesis is that the combined intravenous administration of D-Isoascorbic Acid and Arsenic Trioxide is well-tolerated and safe for patients with advanced/metastatic malignancies who have exhausted standard therapy.

AUTHOR CONTRIBUTIONS

Conceptualization — B.A.Yermekbaeva; Methodology and study design — B.A.Yermekbaeva, U.Y. Kairov; Investigation and data collection — B.A.Yermekbaeva, A.M. Kukanova; Analysis and interpretation of results — Y B.A.Yermekbaeva; Writing and manuscript preparation — B.A.Yermekbaeva, D.A. Begimbetova, A.K. Makishev.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ИЗУЧЕНИЕ КОМБИНАЦИИ ВНУТРИВЕННОГО ВВЕДЕНИЯ D-ИЗОАСКОРБИНОВОЙ КИСЛОТЫ (D-VC) И ТРИОКСИДА МЫШЬЯКА ПРИ ЗАПУЩЕННЫХ/МЕТАСТАТИЧЕСКИХ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЯХ

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АННОТАЦИЯ

Актуальность: Решение терапевтических проблем, связанных с мутантным раком, связанным с вирусным гомологом онкогена саркомы крысы Кирстен (KRAS), остается важным направлением в онкологии. Комбинированное внутривенное введение D-изомера витамина C (D-VC) (правого изомера аскорбиновой кислоты) и триоксида мышьяка (ATO) предлагается в качестве потенциального подхода для достижения противоопухолевого эффекта при колоректальном раке (CRC) с опухолевыми клетками, мутантными по KRAS. ATO усиливает окислительный эффект витамина C (VC), а комбинация обоих препаратов обеспечивает эффективное уничтожение раковых клеток, мутантных по KRAS. В отношении раковых клеток, мутировавших по KRAS, наблюдался мощный синергетический эффект комбинации VC и ATO.

Цель: Данное клиническое исследование направлено на оценку переносимости и безопасности внутривенного введения D-VC наряду с ATO у пациентов с распространенными/метастатическими злокачественными новообразованиями, которые исчерпали стандартную терапию.

Методы и пациенты: В этом одноцентровом клиническом исследовании I фазы оценивались переносимость и безопасность D-VC при однократном внутривенном введении или при последовательном введении с ATO. Целевая группа для исследовательского клинического исследования I фазы включает 10 пациентов с распространенными/метастатическими злокачественными новообразованиями, у которых закончилась стандартная терапия.

Результаты: Введение препарата проводилось в соответствии со схемой лечения в соответствии с утвержденным протоколом исследования. После однократной внутривенной инфузии D-VC в возрастающих дозах 0,05 г/кг - 0,1 г/кг - 0,15 г/кг - 0,3 г/кг все пациенты чувствовали себя удовлетворительно, и о субъективной непереносимости исследуемого препарата не сообщалось. Основные функциональные и лабораторные показатели оставались в пределах нормальных значений, зафиксированных в начале исследования. Было определено, что максимально переносимая доза D-VC составляет 0,3 г/кг, и эта доза была выбрана в качестве базовой для второго этапа исследования, на котором D-VC (0,3 г/кг) вводился одновременно с ATO (0,15 мг/кг).

Выводы: Наши результаты показали благоприятный профиль безопасности и хорошей переносимости и позволили получить рекомендуемую дозу для приема высоких доз D-VC в комбинации с OTO.

Ключевые слова: Рак, KRAS, триоксид мышьяка (ATO), энантиомер D витамина C (D-VC), фаза I и фаза II клинических испытаний.

ДАМЫҒАН / МЕТАСТАЗДЫҚ ҚАТЕРЛІ ІСІКТЕРДЕ D-ИЗОАСКОРБИН ҚЫШҚЫЛЫ (D-VC) МЕН МЫШЬЯК ТРИОКСИДІНІҢ КӨКТАМЫР ІШІНЕ ЕНГІЗУ КОМБИНАЦИЯСЫН ЗЕРТТЕУ

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АҢДАТПА

Өзектілігі: Кирстен егеуқұйрық саркома онкогенінің (KRAS) вирустық гомологымен байланысты мутантты қатерлі ісікке байланысты терапевтік мәселелерді шешу онкологияның маңызды бағыты болып қала береді. С витаминінің (D-VC) d-изомерін (аскорбин қышқылының оң жақ изомері) және мышьяк триоксидін (ATO) біріктірілген көктамыр ішіне енгізу kras мутантты ісік жасушалары бар колоректальды қатерлі ісікте (CRC) ісікке қарсы әсерге қол жеткізудің әлеуетті тәсілі ретінде ұсынылады. ATO С витаминінің (VC) тотығу әсерін күшейтеді және екі препараттың комбинациясы kras мутантты рак клеткаларын тиімді өлтіруді қамтамасыз етеді. KRAS арқылы мутацияланған рак клеткаларына қатысты VC және ATO комбинациясының күшті синергетикалық әсері байқалды.

Мақсаты: бұл клиникалық зерттеу стандартты терапияны таусылған жалпы/метастатикалық қатерлі ісіктері бар емделушілерде ATO-мен бірге d-VC көктамыр ішіне енгізудің төзімділігі мен қауіпсіздігін бағалауға бағытталған.

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Әдістер мен пациенттер: бұл бір орталықты I фазалық клиникалық зерттеу d-Vc төзімділігі мен қауіпсіздігін бір рет көктамыр ішіне енгізгенде немесе ato-мен дәйекті енгізгенде бағалады. I фазалық зерттеу клиникалық зерттеуінің жұмыс тобына стандартты терапиядан өткен жалпы/метастатикалық қатерлі ісіктері бар 10 пациент кіреді.

Нәтижелері: препаратты енгізу бекітілген зерттеу хаттамасына сәйкес емдеу схемасына сәйкес жүргізілді. 0,05 г/кг-0,1 г/кг - 0,15 г/кг - 0,3 г/кг дозада бір реттік көктамыр ішіне d - VC инфузиясынан кейін барлық пациенттер қанағаттанарлық сезінді және зерттелетін препараттың субъективті төзімсіздігі туралы хабарланған жоқ. Негізгі функционалдық және зертханалық көрсеткіштер зерттеудің басында тіркелген қалыпты мәндер шегінде қалды. D-VC-нің максималды төзімді дозасы 0,3 г/кг екендігі анықталды және бұл доза зерттеудің екінші кезеңі үшін негіз ретінде таңдалды, онда D-VC (0,3 г/кг) ATO-мен (0,15 мг/кг) бір мезгілде енгізілді.

Қорытындылар: біздің нәтижелер қолайлы қауіпсіздік профилін және жақсы төзімділікті көрсетті және D-VC жоғары дозаларын OTO-мен бірге қабылдау үшін ұсынылған дозаны алуға мүмкіндік берді.

Түйін сөздер: қатерлі ісік, KRAS, мышьяк триоксиді (ATO), C дәрумені D энантиомері (D-VC), I фаза және II фаза клиникалық зерттеулер.