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USE OF SODIUM DICHLOROACETATE FOR CANCER TREATMENT: A SCOPING REVIEW

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Abstract

In recent years, drug repurposing (DR) has gained significant attention as a promising strategy for identifying new therapeutic uses of existing drugs. One potential candidate for DR in cancer treatment is sodium dichloroacetate (DCA), which has been shown to alter tumor metabolism and decrease apoptosis resistance in cancer cells. In this paper, we present a scoping review of the use of DCA for cancer treatment in adult patients, aiming to identify key research gaps in this area. This scoping review aims to explore the existing scientific literature to provide an overview of the use of DCA (any dose, frequency, or route of administration) in adults with cancer.

A comprehensive literature search of the medical databases MEDLINE/PubMed, LILACS, EPISTEMONIKOS, the Cochrane Library, and ClinicalTrials was performed. We included publications reporting on adult patients diagnosed with any type of cancer treated with sodium dichloroacetate in combination or not with other drugs. All types of study design were included.

A total of 12 articles were included, most of them were case reports. We found a high degree of heterogeneity between them. The most frequent adverse events in the evaluated studies were asthenia, reversible toxicity, and an increase in liver enzymes. Effectiveness was difficult to evaluate.

We conclude that there is insufficient evidence to affirm that treatment with DCA in cancer patients is effective or is safe.

Key words: dichloroacetic acid, neoplasms, adverse reactions

Resumen

Uso de dicloroacetato de sodio para el tratamiento del cáncer en pacientes adultos: una revisión

El reposicionamiento de fármacos (RF) es un enfoque terapéutico reciente que se presenta como una estrategia prometedora para identificar nuevos usos terapéuticos de fármacos existentes. Un candidato potencial para RF en el tratamiento del cáncer es el dicloroacetato de sodio (DCA), el cual ha mostrado la capacidad de alterar el metabolismo tumoral y disminuir la resistencia a la apoptosis de células tumorales. La presente es una revisión (*scoping review*) del uso del DCA para el tratamiento del cáncer en pacientes adultos, que tiene como objetivo identificar brechas de investigación claves en esta área. Esta revisión pretende explorar la literatura científica existente, para proporcionar una visión general del uso del DCA (cualquier dosis, frecuencia o vía de administración) en individuos adultos con cáncer.

Se llevó a cabo una búsqueda exhaustiva de la literatura en las bases médicas de datos MEDLINE/PubMed, LILACS, EPISTEMONIKOS, the Cochrane Library y ClinicalTrials. Se incluyeron publicaciones que informaban sobre pacientes adultos diagnosticados con cualquier tipo de cáncer, tratados con DCA, en combinación o no con otros fármacos. Dichos estudios presentaban distintos tipos de diseño.

Se incluyó un total de 12 artículos, la mayoría de los cuales fueron reportes de casos. Se encontró un alto grado de heterogeneidad entre los mismos. Los eventos adversos más frecuentes fueron astenia, toxicidad reversible y aumento de las enzimas hepáticas, siendo la efectividad terapéutica difícil de evaluar.

Concluimos que existe evidencia insuficiente para afirmar que el tratamiento con DCA en pacientes con cáncer es efectivo y/o seguro.

Palabras clave: ácido dicloroacético, neoplasias, reacciones adversas

KEY POINTS
Current knowledge

- The use of sodium dichloroacetate (DCA) in cancer treatment has been explored, especially because of its modulating activity on cellular metabolism after the inhibition of pyruvate dehydrogenase kinase. However, the lack of controlled clinical studies has left doubts about its effectiveness and safety.

Contribution of the article to current knowledge

- Despite promising preclinical evidence, results from clinical studies and case reports show a lack of conclusive evidence on the efficacy and safety of DCA in cancer treatment. The heterogeneity of the studies and the presence of adverse events, such as peripheral neuropathy, highlight the need for additional controlled investigations.

In recent years, drug repurposing (DR) has become a valuable strategy for identifying new therapeutic uses for approved drugs. This approach is particularly appealing given the high cost and lengthy timelines associated with traditional drug discovery processes. In oncology, DR has a long history dating back to the development of the first chemotherapy drugs, chlorambucil (Leukeran®) and busulfan (Myleran®), which were derived from 'mustard gas' used during the I World War. Advances in our understanding of the chemical structures and mechanisms of action of drugs have made it possible to repurpose drugs for different types of diseases, even when they were not originally designed for those indications[1–4]. In cancer research, many old drugs have been identified as possible useful by the Repurposing Drugs in Oncology project (ReDO)[5], an international collaboration focusing on the potential use of approved non-cancer drugs as a source of new cancer therapeutics.

Particularly, the metabolism-oriented approach is a promising field for cancer therapy. Typically, tumor cells increased glucose uptake to generate lactate even in the presence of oxygen, a phenomenon known as the Warburg effect or aerobic glycolysis[6] (Fig. 1). The high generation of energy with high ATP: glucose ratio occurring in normal cells, through the mitochondrial oxidative phosphorylation (OXPHOS), makes a switch in cancer cells to the less efficient process of aerobic glycolysis, characterized by low ATP: glucose ratio, inhibition of pyruvate dehydrogenase (PDH), the enzyme that catalyzes the oxidative conversion of pyruvate into acetyl coenzyme A in mitochondria, lactic acid fermentation and low energy production[7]. The excessive glycolysis and consequent overproduction of lactate leads to a state of metabolic acidosis in the tumor microenvironment. Lactate, derived from glycolysis, is absorbed by surrounding cells to support tumor growth and to inhibit mechanisms of cell death, such as apoptosis. This process promotes tumor progression and is considered a hallmark of cancer.

Sodium dichloroacetate (DCA), used to treat congenital lactic acidosis, can shift the tumor metabolism by reactivating the oxidative phosphorylation in the mitochondria. DCA works by inhibiting PDK, an enzyme that normally inhibits PDH[8]. By blocking PDK, DCA activates PDH and stimulates the mitochondrial oxidation of pyruvate. This disrupts the metabolic advantage of cancer cells and can potentially slow down

their growth. Additionally, DCA not only inhibits the growth and spread of tumors by reducing lactate production and counteracting the acidic microenvironment, but it also induces organelle remodeling by supplying pyruvate to the mitochondria. This leads to increased release of cytochrome c and other factors that promote apoptosis, as well as positive regulation of ROS levels, ultimately reducing cancer cell viability[9] (Fig. 2). Based on the metabolic modulation caused by DCA, the antitumor capacity of this compound has been studied, aiming to be used in the treatment of cancer[10–13].

Numerous studies have been performed in cell lines and animal models to unveil its efficacy as an antitumor drug[14–19]. Even so, the lack of controlled clinical studies makes the safety profile a concern. Making allowance for the aim of this work, we decided to set out what is known about the use of DCA for the treatment of cancer.

Therefore, this scoping review aimed to explore the existing scientific literature to provide an overview of the use of DCA (any dose, frequency, or route of administration) in adults with cancer.

Methods

This review was carried out following the methodological guidance from The Joanna Briggs Institute (JBI) manual for Evidence Synthesis and was reported using the PRISMA for Scoping Reviews extension. Our protocol was registered at the medRxiv database[20].

This review was conducted in 5 stages: identifying the research question, identifying relevant studies, study

Figure 1 | Warburg effect. Glucose metabolism in a normal cell (A) and a cancer cell (B). Figure created in Bio Render

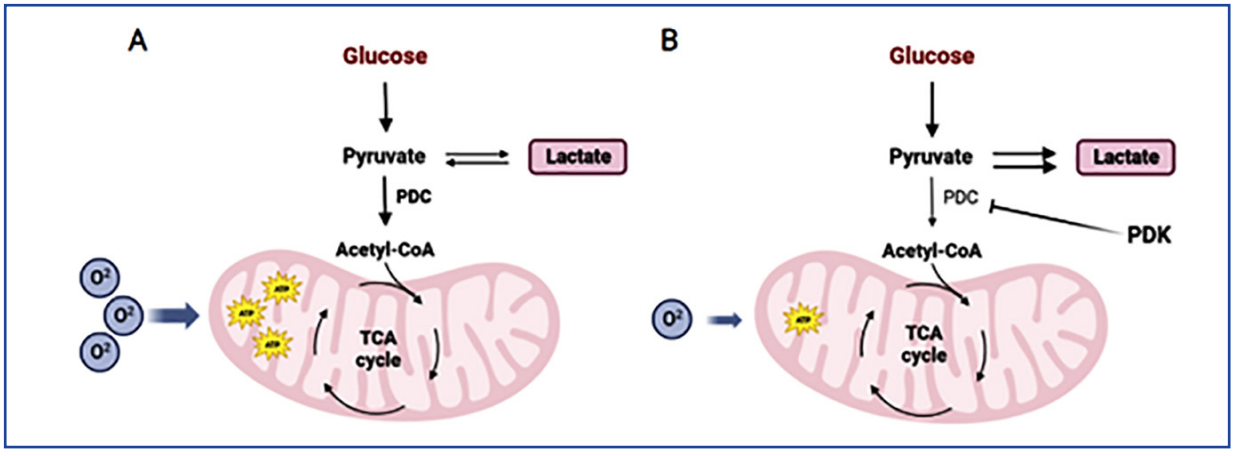
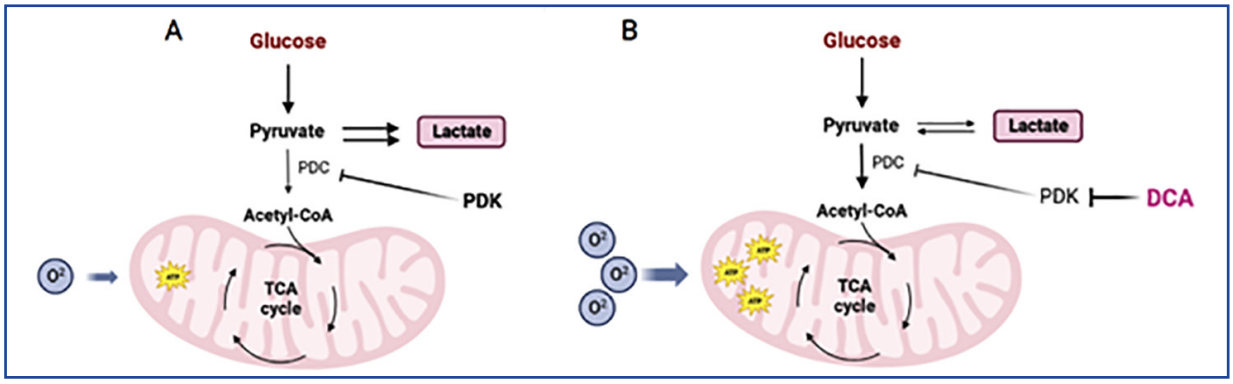


Figure 2 | DCA mechanism of action. The altered cellular metabolism found in cancer cells (A) is normalized by DCA through the inhibition of PDK (B). Figure created in Bio Render



selection, charting the data, and collating, summarizing and reporting the results.

For the first stage, we set the question: What is known in the existing literature about the use of DCA for the treatment of cancer in adult patients? To identify relevant studies, we searched in MEDLINE/PubMed and LILACS databases for potentially relevant records on 1 March 2023. The search strategy included Medical Subject Headings (MeSH) terms, and their relevant synonyms joined with Boolean operators, and was the following: (Dichloroacetic Acid OR "dichloroacetate sodium" OR dichloroacetate OR "sodium dichloroacetate") AND adult AND (cancer OR neoplasms). Searches were not restricted by publication date, place, or type of study. EPISTEMONIKOS, and Cochrane Library databases were explored on 1 March 2023 to identify systematic reviews and meta-analyses. Additional studies were added by scanning references of relevant articles.

The studies were identified based on the eligibility criteria: All types of study design were included, publications reporting on adult patients diagnosed with any type of cancer, publications reporting dichloroacetate sodium treatment in combination or not with other drugs, publications written in English, Spanish, Portuguese, Italian, and French. We excluded publications reporting on children or pregnant women, and studies on cell lines or animal models.

After removing duplicates, two researchers (CB and RPM) screened the results at the title/abstract level and second at the full-text level independently. Discrepancies were resolved by consensus between the two reviewers.

Data were extracted by two researchers (CB and RPM), and disagreements were resolved by consensus. Extracted data included study characteristics, study design, participant population, condition, DCA composition, DCA doses, DCA route of administration, treatment duration, concomitant treatment, follow up; adverse events reported, and outcome measures.

Finally, the PRISMA flowchart was used to present the study selection process[21]. The data from each article was presented in descriptive form and quantitative results were presented as appropriate in a table form.

Results

Study selection

A total of 52 scientific articles were identified through searches of MEDLINE/PubMed and LILACS, and 3 articles were found through searches of Epistemonikos and The Cochrane Library. Additionally, 22 registers were identified from the ClinicalTrial database. All searches were conducted on 01/03/2023. Four additional records were identified by searching references (Khan et al. 2016[22] and Khan et al. 2017[23]) or by connecting with authors (Khan et al. 2013 and Khan et al. 2014). The titles and abstracts were assessed for their relevance to the review based on the eligibility criteria, where 63 citations were excluded, resulting in 12 citations for full text review. One citation was excluded because full text was not available (Figure 3).

Characteristics of included studies

The 12 included studies were published between 2010 and 2019; seven studies were from Canada, three were from United States of America, one from Australia, and one from Japan. Study designs were clinical trials (n = 4), case report (n=6), and case series (n = 2) (Table 1).

Case reports

We reviewed six case reports that reported varying levels of efficacy. The most relevant characteristics are summarized in Table 2.

The first report we came across detailed the use of DCA therapy for pain reduction in a patient with carcinoma metastasis in their leg (Khan et al. 2011). The authors noted a significant decrease in tumor pain without any adverse events over a period of 20 months of treatment[32].

In a subsequent study, Saito et al.[29] described the case of a patient diagnosed with advanced gastric cancer who received a combination treatment of 5-aminolevulinic acid (ALA), hyperthermotherapy, immunotherapy, chemotherapy and DCA. The patient survived for one year and seven months, and no adverse events related to DCA treatment were reported. In that same year, Strum et al[30] published a case report of a patient with non-Hodgkin's lymphoma who began a DCA regimen, along with high caffeine supplements and vitamins, on their own. The authors observed full remission of the patient's condition, with no reported adverse events except for mild peripheral neuropathy after 4 years of treatment.

In 2013, Khan et al.[31] reported on a 72-year-old woman with renal cancer who was treated with DCA for 3 months before experiencing symptoms of peripheral neuropathy. A follow-up examination showed no evidence of recurrence 5 years after the start of DCA treatment.

Figure 3 | Prisma Flowchart. Flow diagram showing the study selection

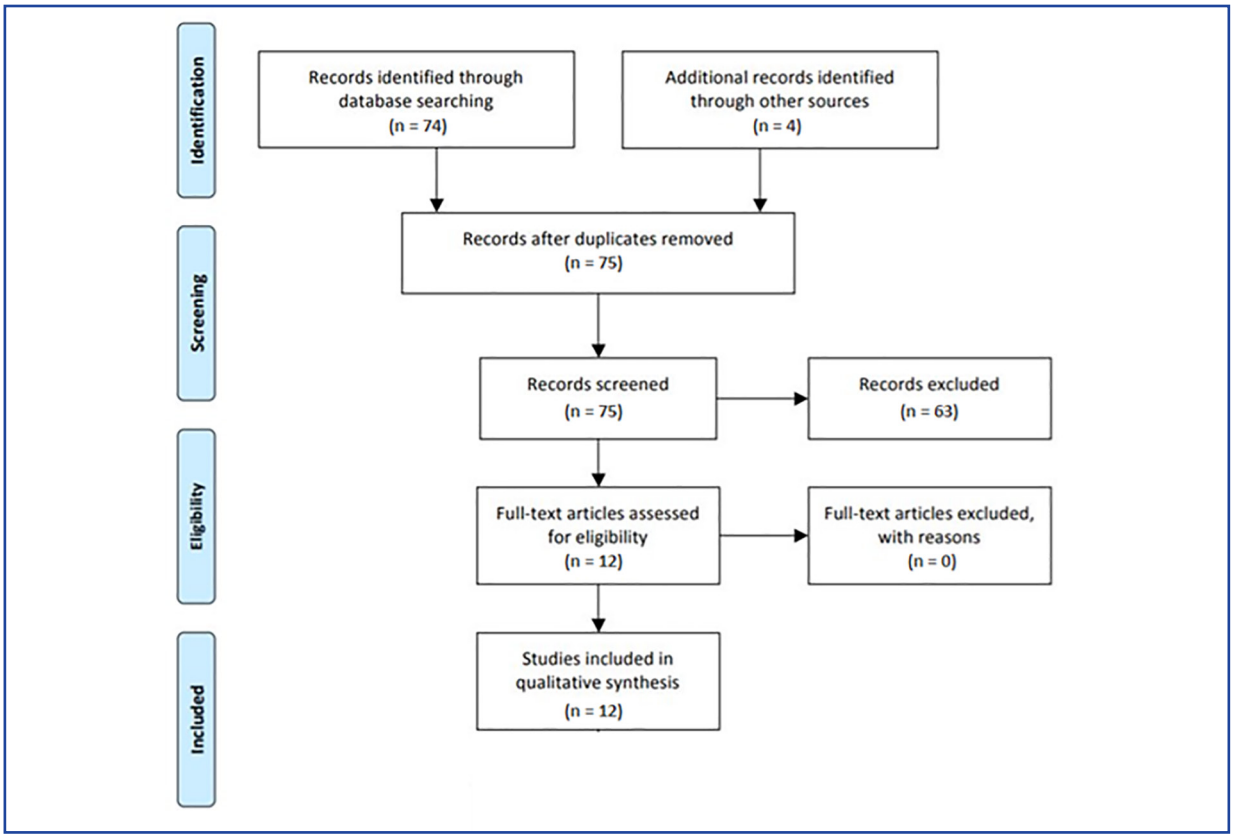


Table 1 | Characteristics of included studies

Author, year, citation	Study design	Sample size	Condition
Tian et al. 2019[24]	Trial (phase 2)	6	plateau phase myeloma
Khan et al. 2017[23]	Case Report	1	metastatic melanoma
Khan et al. 2016[22]	Case Report	1	colon cancer
Chu et al. 2015[25]	Trial (phase 1)	23	treatment-refractory advanced solid tumors
Garon et al. 2014[26]	Trial (phase 2)	8	non-small cell lung cancer / breast cancer
Dunbar et al. 2014[27]	Trial (phase 1)	15	gliomas or metastases CNS
Khan et al. 2014[28]	Case Series	2	colon cancer/ angiosarcoma
Saito et al. 2013[29]	Case Report	1	scirrhous stomach cancer
Strum et al. 2013[30]	Case Report	1	non-Hodgkin's lymphoma
Khan et al. 2013[31]	Case Report	1	renal squamous cell carcinoma
Khan et al. 2011[32]	Case Report	1	poorly differentiated carcinoma
Michelakis et al. 2011[33]	Case Series	5	glioblastoma multiforme

In a case study reported by Khan et al. in 2016[22], a woman with stage IV colorectal cancer received intravenous DCA therapy along with chemotherapy, vitamin D and C, and natural supplements to mitigate the risk of DCA side effects. Mild post-infusion sedation was the only side effect noted at the higher DCA dose (4000 mg i.v. (66 mg/kg)). After about 6 months of

Table 2 | Case reports

Author, year, citation	Sex	Age	DCA doses	Route	DCA dosing	DCA composition	Time DCA treatment
Khan et al. 2011[32]	M	71	1500 mg/day 2 week on/1 week off cycle	oral	500 mg T.I.D	Not reported	8 months
Khan et al. 2013[34]	F	72	1500 mg/day 2 week on/1 week off cycle	oral	500 mg T.I.D	Not reported	3 months
Saito et al. 2013[29]	F	35	150 mg/day	oral	50 mg T.I.D.	Hospital preparation	20 months
Strum et al. 2013[30]	M	52	1,000 mg/day	oral	1,000 O.D.	Not reported	4 years
Khan et al. 2016[22]	F	57	3000 mg to 4000 mg/week 1000 mg/day	IV oral	IV 500 mg B.I.D	Tokyo Chemical Industry	4 years
Khan et al. 2017[23]	M	32	1500 mg/day 2 week on/1 week off cycle	oral	500 mg T.I.D	Tokyo Chemical Industry	4 years

B.I.D.: twice a day; T.I.D.: three times a day; O.D.: once a day; IV: intravenous

treatment, the patient discontinued chemotherapy (Folfiti - Bevacizumab) but continued DCA therapy at a higher dose of 4500 mg i.v. weekly, which did not result in any significant changes in the disease but caused mild numbness of the fingers and toes and asymptomatic liver enzyme elevations - both of which were diagnosed as DCA side effects. The DCA therapy was interrupted for 3 months to allow the resolution of the side effects. During this period, only natural therapies were given, and the patient's mild DCA neuropathy resolved while liver enzymes began to improve. Oral DCA therapy (500 mg (8.2 mg/kg) twice a day) was later initiated along with neuroprotective supplements. The attempt to increase the dose to 500 mg three times a day was not possible due to adverse events (significant asymptomatic liver enzyme elevation and increase in neuropathy) that resolved after a brief interruption, with the patient returning to the original treatment schedule. After almost 4 years of therapy, CT scans revealed stable disease.

In a study by Khan et al. in 2017[23], a male patient with metastatic melanoma was treated with oral DCA in a 2-week on, 1-week off cycle of 500 mg taken 3 times per day (17 mg/kg per day) for 4 years. To minimize the risk of DCA side effects, the patient was also prescribed three natural medications: oral acetyl L-carnitine, benfotiamine, and R-alpha lipoic acid. During the periods when the patient was taking DCA, he experienced a slight reduction in sensation in his fingertips and toes and had slightly reduced ability to concentrate. These mild symptoms were attributed to DCA-related neuropathy, and they resolved during the weeks when the patient was not taking DCA. Despite these mild side effects, the patient remained stable and was able to work full-time.

Case Series

Michelakis et al. (2010)[33] conducted a case series involving five patients diagnosed with glioblastoma multiforme who were treated with DCA. The treatment regimen involved an initial oral dose of 12.5 mg/kg twice a day for a month, which was then increased to 25 mg/kg twice a day. In cases where dose-limiting toxicity occurred, a dose de-escalation protocol was followed, whereby the dose was reduced by 50%. The patients were monitored for up to 15

months, during which the only apparent adverse event was peripheral neuropathy. The degree of peripheral neuropathy varied among patients and was dose-dependent but reversible. When the dose was decreased to 6.25 mg/kg twice a day, none of the patients had clinically significant peripheral neuropathy. At month 15 of DCA therapy, all patients except one were clinically stable, and at month 18, they were alive and without adverse events (Table 3).

Later, Khan et al.[28] reported a case series of 3 patients with advanced cancer of which we analyzed only the two adult patients included. Both were treated with naturopathic treatment, vitamins and, intravenous DCA, and favorable responses were observed. The first patient, with a metastatic colon cancer, received 3 doses of DCA (3000 mg, 3500 mg, and 3700 mg). After the second infusion, the patient noted chills, sweats, and fatigue, and after the third one, he experienced fatigue and malaise whereby he decided to stop the treatment. A month later it seemed to show tumor stability. The second patient had a metastatic angiosarcoma and underwent treatment with intravenous DCA, starting at a dose of 3000 mg per week and gradually increasing to 5000 mg twice per week over a period of two weeks. In addition, the patient received concurrent radiotherapy for a spine metastasis. After eight months of treatment, the patient remained clinically stable and did not experience any adverse events. However, the patient decided to discontinue the treatment and seek other alternative therapies.

Trials

The review consisted of four trials, two of which were Phase 1 trials that assessed the safety and tolerability of DCA (Chu et al. 2015[25] and Dunbar et al. 2014[27]), and two Phase 2 trials principally assessing response to treatment (Tian et al. 2019[24] and Garon et al. 2014[26]). All the trials utilized a commercial formulation of DCA, provided by TCI America. Except for Tian et al. 2019, the others used DCA as the only treatment (Table 4).

Chu et al. conducted a phase 1 study involving 23 patients, of whom only 3 were able to complete the third cycle of DCA with stable disease. Ten patients did not finish the first cycle, with 7 experiencing disease progression and 3 withdrawing consent due to adverse events. Fatigue (34.8%), neuropathy (34.8%), and nausea (17.4%) were the most reported adverse events. Grade 3 toxicities were predominantly fatigue (17.4%) and neuropathy (13.0%). Importantly, neuropathy was reversible in most cases. However, one patient developed grade 3 neuropathy after receiving 17 doses of DCA, which did not resolve after 14 days of stopping DCA. This patient also had clinically progressive disease at the time of stopping therapy. While 8 of 23 patients had stable disease, most of the cohort was unable to continue treatment for this duration.

The other Phase 1 study was carried out by Dunbar et al. They included 15 individuals, but due to patient withdrawals, only eight patients were included in the final analysis. Of these eight subjects, the median duration of DCA treatment was 34 days (range 26-312 days), and all were clinically and radiographically stable at the end of the fourth week. At the time of result submission, three patients were still alive, while five had died. Two patients in the study reported grade 1 neuropathy, leading to a dose adjustment in one of them who was taking 6.25

Table 3 | Characteristic of patients included in Michelakis et al. (2010)[33]

Patient	Sex	Age	Time	Evolution	Peripheral neuropathy		
					25 mg/kg. B.I.D	12.5 mg/kg B.I.D.	6.25 mg/kg B.I.D.
1	M	58	7 months	Stable	grade III	grade II	none
2	F	47	11 months	Stable	grade III	grade II	none
3	M	52	3 months	IH/death	grade I	grade I	–
4	M	45	15 months	Stable	grade III	grade I	none
5	F	30	15 months	Stable	grade III	grade I	none

Table 4 | Clinical trials

Author, year, citation, ID	Phase	Sample size	Sex (M/F)	Age	DCA doses	Treatment duration
Tian et al. 2019	2	6	5/1	Mean 65.6 years Range 52-77 years	Start: 25 mg/kg B.I.D. Day 4 and onward: 6.25 mg/kg B.I.D. Day 8: a single dose of 25 mg/kg	3 months (Follow up 9 months)
Chu et al. 2015 NCT00566410	1	23	11/12	Range 36-75 years	28 days cycle Starting dose: 6.25 mg/kg B.I.D. VO Cohort 1: 6.25 mg/kg B.I.D. Cohort 2: 12.5 mg/kg B.I.D. Cohort 3: 12.5 mg/kg B.I.D. Expansion: 12.5 mg/kg B.I.D.	Range 1-8 months
Garon et al. 2014 NCT01029925	2	8	3/4	Range 38-77 years Mean 57 years	6.25 mg/kg B.I.D. VO	Median 12 days (range 4 to 72)
Dunbar et al. 2014 NCT01111097	1	15	8/7		Starting dose: 8.0 mg/kg B.I.D. 12.5 mg/kg B.I.D or 5.0 mg/kg B.I.D. Post GSTZ1/MAAI genotype: EGT carriers 3+3 design non-EGT carriers 4.0 mg/kg B.I.D.	Median 34 days (mean=75.5 days; range: 26–312 days) One patient remains on study at 330+ days (twelfth cycle).

mg/kg B.I.D. Another patient withdrew from the study due to the worsening of pre-existing gait abnormalities, which improved after the patient stopped taking the drug. Additional grade 1 and 2 adverse events were also reported. It is important to note that all the patients were genotyped based on haplotype variation in the glutathione transferase zeta 1/maleylacetoacetate isomerase (GSTZ1/MAAI) gene to determine dosing.

In addition, two Phase 2 trials were included. Tian et al. reported in a group with patients with plateau phase myeloma, that peripheral neuropathy was the only significant side effect observed during DCA treatment, which was only seen after chronic use and it was reversible. Furthermore, five out of six patients who participated in the trial had preexisting neuropathy, and the treatment did not greatly exacerbate their condition. The researchers concluded that the serum DCA concentrations achieved were possibly not sufficient to affect tumor development.

In another Phase 2 trial, Garon et al. studied eight patients with non-small cell lung cancer. All of them experienced mainly low-grade adverse events. None of the patients required a dose reduction, but three of them had their doses delayed. Two patients died 4 and 7 days after the treatment began. Due to the lack of observed clinical benefits and the two deaths, it was decided to close the study.

Finally, from the records identified from Clinical Trial database, NCT05120284 is currently recruiting patients with Glioblastoma Multiforme, with an estimated completion date of 2025. NCT00540176, have not been published although it was completed in 2014, and NCT00703859, was discontinued before enrolling its first participant.

Discussion

Drug repurposing offers a cost-effective approach to the battle against diseases such as

cancer. One of the key advantages of this strategy is that it often takes advantage of drugs whose safety profiles are already well established. In this sense, many drugs are being evaluated to be repositioned.

Dichloroacetate, also known as DCA, is a drug that inhibits a crucial enzyme in the glucose metabolic pathway and has been tested in clinical trials for metabolic disorders. Recently, there has been a growing proposal to utilize this mechanism to counteract the "Warburg effect" observed in cancer cells. As a result, scientists have started using it in animal models and in vitro assays, followed by its application in human studies. DCA has also emerged as a potential therapeutic option to treat endometriosis, representing its latest application in the repurposing field. However, despite being a relatively old drug, there is a need to understand its safety profile. In this work, we reviewed the existing scientific literature on the use of DCA in adult patients with cancer to evaluate mainly the safety profile and efficacy. To our knowledge, this is the first review on the use of DCA in cancer treatment.

We included 12 studies with 65 patients. Six studies were case reports, two were case series, and four were early-stage clinical trials. It is important to highlight that most of them do not have a controlled methodology. Besides, there is a high degree of heterogeneity between them. The most common tumor was glioblastoma (15 patients), followed by lung cancer (7 patients) and myeloma (6 patients). Other cancers reported were gastrointestinal tumors, melanoma, angiosarcoma, breast cancer, non-Hodgkin's lymphoma, and renal carcinoma. Finally, 24 patients from 2 studies had treatment-refractory or poorly differentiated solid tumors. In addition, the length of the treatment was diverse. Also, DCA was used alone or in combination with other drugs, and some of the studies reported a very short time of use, which makes it difficult to assess the efficacy of the treatment. However, Phase 2 clinical trials did not demonstrate effectiveness, and they were not followed by Phase 3 studies. In fact, one of the Phase 2 studies included was terminated early due to lack of efficacy.

DCA doses were similar in most of the studies (6,25 mg/kg and 12,5 mg/kg BID, when administered per os) but not all of them came from commercial formulations.

The doses used were variable, not only the initial doses, but also the treatment cycle schemes, loading and maintenance. Moreover, commercial formulations were not used in all the cases. The most widely used average dose is 6.5 mg/kg BID.

Finally, regarding adverse effects, it is well known that chronic use of DCA causes reversible peripheral neuropathy, among other unwanted events. This happens because of the accumulation of DCA due to the inactivation of GSTZ1-1. The most frequent adverse events in the evaluated studies were asthenia, reversible neurologic events like peripheral neuropathy, gait disturbances, ataxia, hypersomnolence, increase in liver enzymes, abdominal pain, edema, nausea, and vomiting. In general, toxicity was described as dose dependent. In several cases, the loss of follow-up made it impossible to determine the reversibility of the neurologic events, and many patients withdrew their consent to participate in the study. Furthermore, the Phase 2 trial developed by Garon et al., was prematurely closed due to patient´s safety criteria, considering that the use of DCA caused two early patients' death. The clearance of DCA mainly depends on the GSTZ1-1 enzyme, which function can alter the drug metabolism. The GSTZ1-1 gene exhibits polymorphisms that result in slow or rapid metabolizer phenotypes[34]. This is an important finding that may explain, at least in part, the variability in the response to DCA treatment in different patients and diseases.

This study has limitations. Assessing the effectiveness has been challenging due to the patients and studies characteristics, and the absence of a comparator. Also, there are questions about the general quality and reliability of the findings because most of the studies included in the analysis were case reports or case series.

To summarize, even though numerous studies have been published in animal models on the use of DCA to treat cancer, there are not enough publications on its controlled use in humans. We conclude that there is insufficient evidence to state neither the effectiveness nor the safety of DCA treatment in cancer patients.

Conflicts of interest: None to declare

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