Chlorine dioxide solution in metastatic uncurable cancer: case series

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Abstract

Immunotherapy has recently yielded tremendous progress in the fight against malignancies. Its precise mechanism of action remains controversial. Activated leukocytes release reactive oxygen species which kill cancer cells. In the body, chlorine dioxide, orally ingested degrades into free radicals such as found in neutrophils.

Chlorine dioxide is a potent oxidant with *in vitro* anticancer activity. Its precise mechanism of action has not been thoroughly explored, but it is proposed that it acts through the redox imbalance of cancer cells. Six patients were treated for metastatic cancer (breast, kidney, prostate, lymphoma, uterus and melanoma), on a compassionate basis. We report lasting tumor response with a combination of oral, enema and/or intravenous chlorine dioxide, without any side effects. This preliminary work suggest that chlorine dioxide and free radicals might be the mediators for immunotherapies. Chlorine dioxide is both a promising and unexpensive anticancer agent. Rigorous clinical trials are needed to confirm these preliminary results.

Keywords: Chlorine dioxide , cancer, immunotherapy, Warburg effect, reactive oxygen species, intermittent fasting, ketogenic diet.

Introduction

Immunotherapies targeted at cancer cells have yielded tremendous clinical results with both high and reproducible response rates. The immune system mediates the destruction of cancer cells by leukocytes, which release large amounts of reactive oxygen species (ROS), including hypochlorous acid (HOCl), and increase pro-oxidant levels in cancer cells (Freund et al., 2021; Galadari et al., 2017).Most cytotoxic drugs also increase intracellular ROS levels (Bajor et al., 2018; Petronek et al., 2021). It is widely accepted that the anticancer effect of these chemotherapeutics is due to the induction of oxidative stress (Perillo et al., 2020; van Loenhout et al., 2020; Yang et al., 2018; Yokoyama et al., 2017).The lethal concentrations of free radicals are generated by NADPH oxidase, from superoxide radical $O_{2\text{-}}$ which in turn will generate H_2O_2 that react with chloride and form the very toxic HOCl (Roos&Winterbourn, 2002). The HOCl has a cytotoxic effect, which is of great importance for the human immune system(Y. Huang et al., 2016).

Chlorine dioxide solution (CDS) is a potent oxidant and a prodrug of HOCl, widely used as a biocide (J. Huang et al., 1997; O Young, 2016; Ogata, 2012). CDS has cytotoxic effect on cancer cells(Ma et al., 2017). The cytotoxicity of CDS on cancer cells appears to be associated with the induction of oxidation that disrupts the delicate and controlled redox balance of cancer cells, which, induces apoptosis, pyknosis and necrosis. Thus, CDS has the potential to prevent tissue invasion and cell transformation (Y. Kim et al., 2016; Mytilineou et al., 2002; Ogata, 2007; Svenson et al., 2002; Yıldız et al., 2022).The cytotoxic effect of CDS was demonstrated by inhibiting the proliferation of human breast cancer, colorectal cancer, small cell lung cancer and human umbilical vein endothelial cell cancer cell lines (Y. Kim et al., 2016; Yıldız et al., 2022). Similarly, beneficial therapeutic effects of CDS have been reported as an adjunct to metabolic therapies for the treatment of pancreatic adenocarcinoma (Schwartz, 2017).

CDS does not appear to be toxic to normal cells, it was shown that CDS does not have an apoptotic effect on human gingival fibroblasts and does not decrease the viability of periodontal ligament stem cells (Nishikiori et al., 2008; Láng et al., 2021). Also, in the public health context, the oral use of CDS has been reported as a safe and effective therapy to treat COVID-19 (Aparicio-Alonso et al., 2021b, 2021a, 2021c; Insignares-Carrione et al., 2021; Mitchell, 2021).

Given the documentary evidence collected to date, we raised the possibility that a CDS may have an effective cancer treatment. We report cases of patients with metastatic cancers treated with maximum daily doses of 3 mg/kg (0.003 % chlorine dioxide) given orally, enema and/or via intravenous (Environmental Protection Agency, 2000; Insignares-Carrione et al., 2021). For the oral and absorption enema protocol used by all patients, it was produced by oxidation of 28% sodium chlorite ($NaClO_2$) with 4% hydrochloric acid (HCl) as the activator. The oral protocol doses were prepared with 20 ml to 30 ml of ClO_2 diluted in 1L of H_2O and the absorption enema protocol doses were prepared with 20 ml to 40 ml of ClO_2 diluted in 500 ml to 1000 ml of H_2O which was introduced with a nelaton rectal catheter to 30-50 cm (Aparicio-Alonso et al., 2021c; Ma et al., 2017). For the intravenous use, chlorine dioxide (ClO_2) was made and marketed by certificate chemical expert in Queretaro, México, and was produced by the membrane electrolysis method; the dose was prepared with 10-20 ml of ClO_2 diluted in 500 ml of NaCl 0.9 % and administered from 4 to 8 h according to the patient's tolerance (Aparicio-Alonso et al., 2021c; Kály-Kullai et al., 2020). The occurrence of adverse events and the manifestation of side effects that could be associated with the use of CDS were assessed.

Case presentation 1: Metastatic breast cancer.

In 2015, a 43-year-old Mexican female patient with no relevant medical history discovers a lump in the left breast with bloody discharge from the nipple and was diagnosed as breast cancer. The patient refused treatment. In 2020, the patient suffers a fracture of the hip and was diagnosed with metastasis, simultaneously, she started chemotherapy with abemaciclib 150 mg every 12 h and estrogenic antagonist fulvestrant 250 mg every 4 weeks, metastatic braking was reported. During chemotherapy, the patient had significant side effects such as gastritis, diarrheal episodes, atherosclerosis, hypertension, weight gain, skin dryness, limitation of movement, hair loss, abdominal distention, face rash and leukopenia, a medical reason for intermittent discontinuation of treatment.

In December 2020, concomitant with estrogenic antagonist, the patient started CDS therapy orally, via absorption enema and intravenously. In addition, the patient practices intermittent fasting for 23 hours. Currently the patient is in partial remission, with a thirty-month follow-up (Fig. 1).

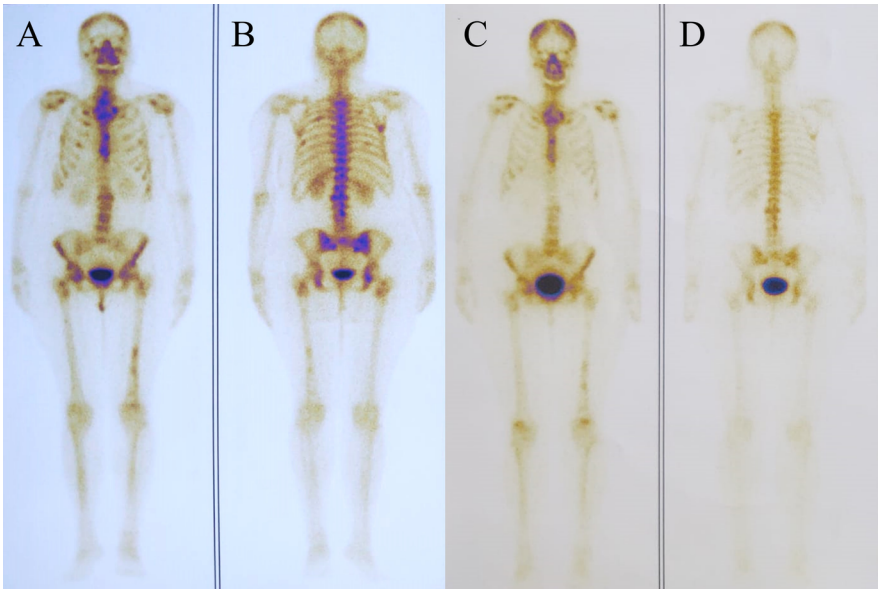

Figure 1: Scintigraphy of female patient (Case 1) with metastatic breast cancer. Images during chemotherapy, prior to CDS therapy, from 2019 ventral and dorsal view (A, B). Images during concomitant treatment with CDS, ventral and dorsal view of 2022 (C, D). A significante decrease in bone metastasis is present.

Case presentation 2: Metastatic prostate cancer.

In October 2019, a 64-year-old Mexican male patient with no relevant medical history attended a routine prostate examination and revealed abnormal prostate antigen values ($>$ 1700 ng/ml). Urinary and semen bleeding occurred promptly, and was diagnosed with metastatic prostate cancer. In February 2020, the patient refused chemotherapy and chose a metabolic therapy that consisted for 2.5 months of daily intravenous administration of the glucose analog 2-deoxy-D-glucose (2DG). Additionally, the patient followed a ketogenic diet and 20 h intermittent fasting. During therapy, the patient not had significant side effects.

In March 2020, the patient started the oral CDS protocol adding 1 ml of the vehicle DMSO 70% to solution and CDS absorption enema protocol. In 2021, the patient added 5 g of clinoptilolite zeolite to the diet, during fasting and before each meal. In 2022, the patient balanced oral and enema therapy with the intravenous CDS protocol, which he administered monthly according to previously described doses. Currently, the patient is without deficits or alterations in the daily routine. The patient has normal prostate antigen values and maintains a periodic control, with a forty-four-month follow-up (Fig. 2).

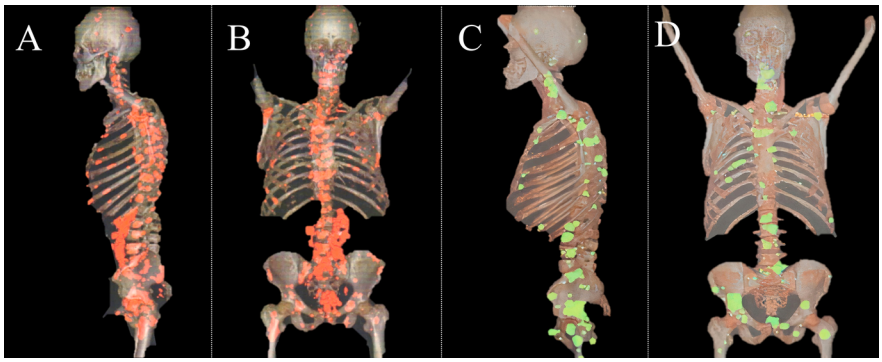

Figure 2: Positron emission tomography of a male patient (Case 2) with metastastic prostate cancer. Images confirmative the diadnosis of metastic cancer, 2019 (A,B). Images after CDS treatment, 2022 (C,D), important reduction in bone metastasis is observerd.

Case presentation 3: Metastatic kidney cancer.

In July 2018, a 65-year-old male Mexican patient with no previous medical history, but with type II diabetes, presented hematuria. A diagnosis of clear cell renal cell carcinoma was diagnosed and was tread with nephrectomy. In December 2018, at routine follow-up, two 4 mm and 5 mm (Fig. 3) lung nodules were detected, and the patient started targeted therapy with Axitinib 5 mg every 12 h and monthly immunotherapy with Pembrolizumab 100 mg/ 4 ml. The patient presented side effects such as constipation, indigestion, tinnitus, extreme fatigue, thrombocytopenia, cough, arthralgia, weight loss, rash and dysgeusia, a medical reason for intermittent discontinuation of treatment. In 2019, the size of one of the pulmonary nodules increased to 9 mm and 12 mm (Fig.4).

In December 2020, the patient decided to discontinue conventional therapy, and started the oral and absorption enema CDS protocol. Additionally, the patient practices a reduced protein diet. The patient manifested no side effects with CDS intake, currently continues the treatment and leads a normal life. As of 2023 the patient is in complete remission, with a fifty-eight-month follow-up.

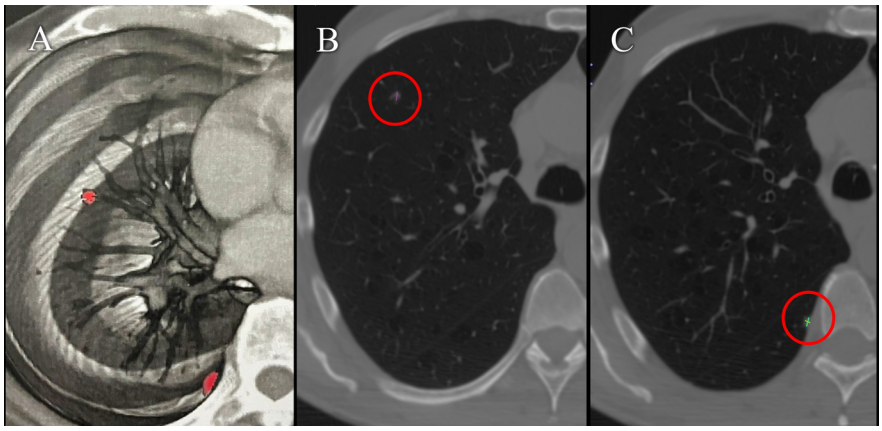

Figure 3: Positron emission tomography of a male patient (Case 3) with metastatic kidney cancer. In 2018, cancer cell activity was diagnosed in two nodules of the left lung (A) and the confirmative dimensions of 4 mm (B) and 5 mm (C).

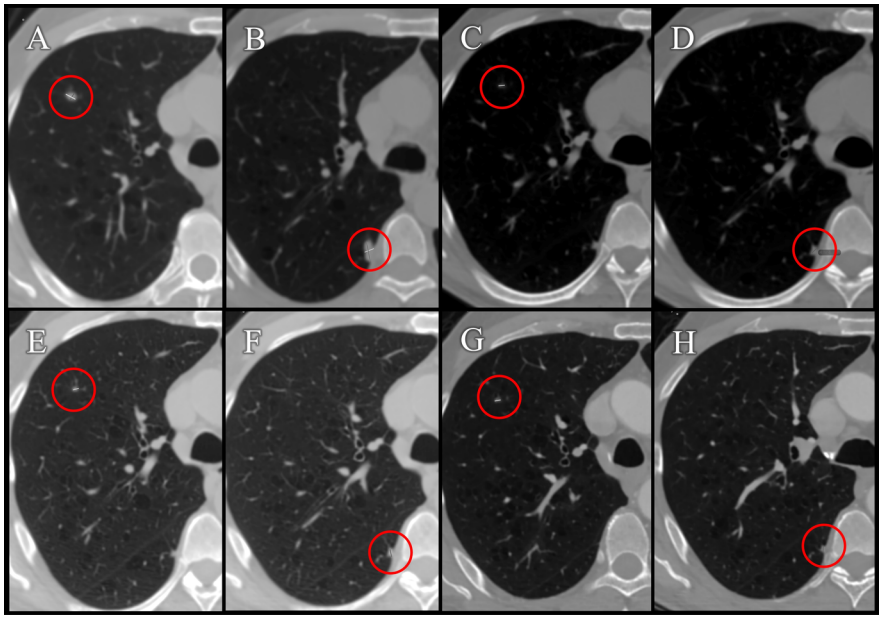

Figure 4: PET control studies (Case 3). Monitoring pulmonary nodules in axial views of the left lung. In 2019, during chemotherapy, an increase in nodules to 9 mm (A) and 12 mm (B) was observed. In the year 2020, during compassionate treatment with CDS, the nodules reduced in size to 3.5 mm (C) and 4.7 mm (D). In the year 2021, in the routine follow-up, a maintenance in the size of the nodules of 3.4 mm (E) and a decrease to 4.2 mm (F) is observed. In the year 2023, the patient continued compassionate treatment and the nodules kept a size of 3.4 mm (G) and reduced to 3.7 mm (H).

Case presentation 4: Metastatic non-Hodgkin's lymphoma.

In September 2019, a 73-year-old Mexican female patient, with no relevant medical history and a family history of cancer, presented incapacitating low back pain and the presence of an inflamed lymph node in the groin was found. The presence of grade 2 follicular lymphoma was confirmed by biopsy and it was diagnosticated as non-Hodgkin's lymphoma stage IV accorded to Lugano classification. In November 2019, the patient received eight chemotherapy sessions consisted Doxorubicin 2mg/ml every 21 days, additional with ketogenic diet. The patient reported nausea, vomiting, hair loss, weakness, weight loss and dry skin as side effects. After the chemotherapy sessions, the patient had bone metastasis and refused future sessions of chemotherapy and subsequent radiation therapy.

In December 2020, the patient decided to start the CDS oral protocol and 1 ml of the vehicle DMSO 70% to solution. In 2021, when the tumor did not respond, the patient had important lower back pain, due to pathological L3 fracture, a lumbar brace was prescribed for 3 months and CDS absorption enema protocol was added. Additionally, the patient practices intermittent fasting for 18-20 hours and consumes daily supplements at night of 5,000 IU vitamin D3, 1 g vitamin C, 1.1 g potassium and 250 mg magnesium. The patient continues a thirty-eight-month follow-up, in which a significant reduction of the tumors in the invaded tissues was observed (Fig. 5), currently, without metastatic activity (Fig. 6). The patient is in partial remission.

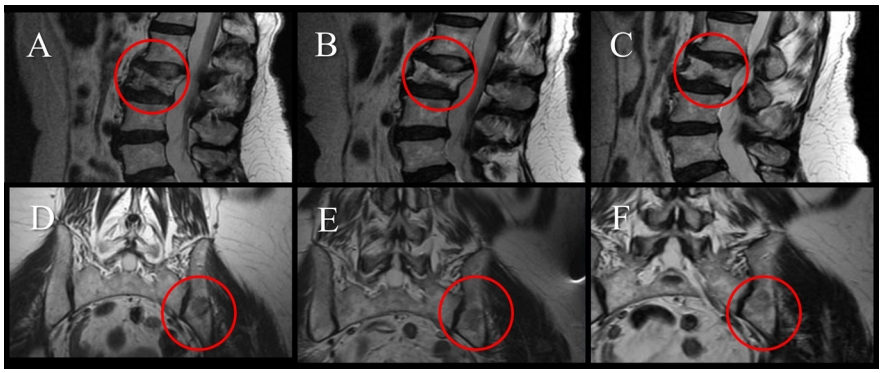

Figure 5: Magnetic Resonance Imaging (MRI) of female patient with metastatic non-Hodgkin's lymphoma (Case 4). Images in sagittal view showed pathological fracture in the L3 vertebra, 2020 (A), and the resolution from 2021 (B) and 2022 (C). Images showed decreased metastatic activity in both L3 and iliac bone from 2020 (D), 2021 (E) and 2022 (F).

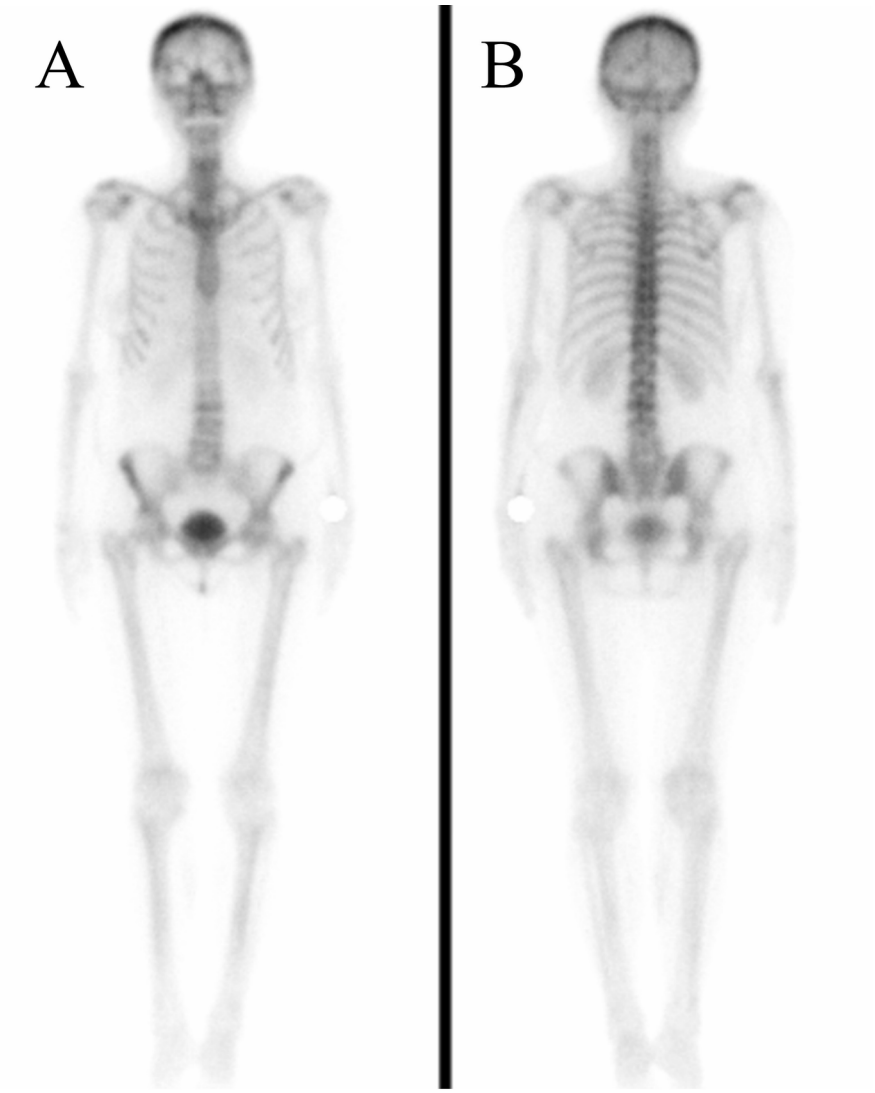

Figure 6: Scintigraphy of female patient with metastatic non-Hodgkin's lymphoma (Case 4). Images of ventral (A) and dorsal (B) view showed metastatic inactivity in bone from 2023. No scans from previous years.

Case presentation 5- Metastatic sarcoma of the uterus

In February 2015, a 58-year-old French female patient with no medical history was diagnosed with undifferentiated sarcoma of the uterus metastatic to the lung. The response to chemotherapy Ifosfamide, Adriamycin and Cisplatin was complete but transitory. Further treatment with Tabectedin and subsequent radiotherapy to the lung resulted in a complete response. In September 2016, the patient presented with cerebral hypertension and unrelenting pain. MRI demonstrated widespread carcinomatous meningitis. Tumor cells were present in the cerebrospinal fluid.

The patient was offered palliative chemotherapy which she refused but treated herself as follows: ketogenic diet; lipoic acid: 800 mg, twice a day; hydroxycitrate: 500 mg, three times a day; the CDS oral protocol. At night: 36 ppm of ClO_2 diluted in twenty-four drops of DMSO rubbed on the skin. The pain disappeared within days. Six years later, she is disease free and lives a normal life as a financial adviser.

Case presentation 6- Metastatic melanoma

In 2016, a 69-year-old female patient presented with high-grade melanoma on the right thigh. The tumor was excised, but it relapsed locally six months later. She was offered the following treatments: Interferon, Nivolumab, radiation therapy, Dacarbazine and more recently Pembrolizumab. None of these treatments resulted in any demonstrable antitumor response. In June 2021, a PET-scan revealed a metastatic inguinal lymph node.

Palliative care was offered to patient and was refused. She started the same treatment as Case presentation 5 and additionally consumes orally 75 mg methylene blue twice a day. The tumor disappeared within weeks. PET-scan with 2DG demonstrated a major metabolic response. Unfortunately, the tumor relapsed one year later with multiple skin metastases and after a last chance immunotherapy, she stopped feeding herself and died in October 2022.

Discussion

Chlorine dioxide therapies require controlled animal studies to evaluate posology and via of administration. The question of long-term efficacy and toxicity in patients on anticancer therapy is open. These cases suggest a broad spectrum of activity and lack of toxicity. In this article we report the use of a compassionate therapy based on chlorine dioxide solution (CDS) as part of the treatment of six clinical cases with metastatic cancer.

The first patient presented metastatic breast cancer, the initial treatment consisted of chemotherapy and estrogenic antagonist with significant side effects. By the patient's initiative, estrogenic antagonist was supplemented with CDS. The alternative rectal administration had a local as well as a systemic effect. Rectal administration has been described as a stable route, due to gastric pH elution and hepatic first pass (Davis et al., 2002; Hua, 2019). Also, possible systemic absorption via lymph nodes has been reported (Purohit et al., 2018). Likewise, the therapy was supplemented with intravenous chlorine dioxide therapy, an agent obtained by electrolysis method, due to full availability in the bloodstream (Ma et al., 2017). We suggest that, multiple administration routes increased the range of action of chlorine dioxide throughout the system. Additionally, intermittent fasting, a type of caloric restriction without malnutrition, was carried, which promotes anticancer adaptations, such as decreased production of growth factors, inflammatory cytokines, anabolic hormones and oxidative stress markers (Clifton et al., 2021; Longo & Fontana, 2010). According to the patient's evolution, she did not show clinical improvement until she started treatment with CDS, therefore, it is possible to suppose that CDS was the substance that made the difference in outcome. This suggests that the combination of chlorine dioxide with other therapeutic agents exhibits a synergistic anticancer effect.

The second patient with metastatic prostate cancer started his therapy with the temporary administration of 2DG. The 2DG is a non-metabolizable glucose analog in transformed cells, which interferes with glycolysis and leads to the expression of stress-related genes, which subsequently trigger apoptosis (Aft et al., 2002; Zhang et al., 2014). Treatment continued with the oral CDS in combination of DMSO. DMSO has a broad spectrum of pharmacological actions including anti-inflammatory, analgesic and membrane penetrating effects, its primary use is as a vehicle for other co-administered agents (Aronson, 2016; Gad & Sullivan, 2014). Oral therapy was supplemented with enemas and intravenous administration of CDS. CDS therapy, was supplemented with the clinoptilolite zeolite, for which has been reported to have an anticancer effect by modulating EGF-R, protein kinase B (PKB)/Akt and nuclear factor kB (NfkB) signaling, by the inhibition of transcription factor Nrf2 and the adsorption and deactivation ROS (DeNicola et al., 2011; Katic, 2006; Pavelić et al., 2001; Ryoo et al., 2016). This suggests that, possibly the induction of multiple redox changes has a relevant role in destabilizing the intracellular environment of cancer cells, thus, interfering with the Warburg effect phenotype.

The third patient had metastatic kidney cancer, he decided to stop initial treatment and started a second-line oral and enema CDS therapy. As chemotherapy and immunotherapy were discontinued, the reduction in lung nodule size appears to be a direct consequence of CDS administration.

The fourth patient presented a metastatic non-Hodking lymphoma that was treated initially with chemother-

apy sessions and continued thesecond-line therapy with CDS, administered systemically in combination with DMSO. In this case, the treatment was complemented with dietary supplements of vitamin D3, vitamin C, potassium and magnesium, correlated with *in vitro* and *in vivo* anticancer effects. First, low serum levels of vitamin D3 have been associated with carcinogenic tumor incidence and mortality (Grant et al., 2011; Grant & Mohr, 2009; Park et al., 2019; Vuolo et al., 2012). Also, vitamin C has been reported in preclinical studies to induce a redox imbalance and in combination with potassium to exhibit a synergistic effect on apoptosis in breast cancer cell lines (Frajese et al., 2016; Ngo et al., 2019). Similarly, magnesium supplementation has been explored to exert antitumor effects, such as inhibition of tumor growth in the primary site (Barbagallo et al., 2021). However, controlled clinical studies are required to clarify the role of supplementation in metastatic cancer and the facilitation of tumor implantation at its metastatic sites.

The fifth patient presented sarcoma of the uterus metastatic to the lung, meninges, and cerebrospinal fluid. Compassionate therapy was supplemented with lipoic acid and hydroxycitrate. Lipoic acid is a cofactor and has been reported in cancer cells to restrict proliferation, promote apoptosis, inhibit invasion, suppress cancer stem cell phenotypes, and have a potential role in improving the cytotoxicity of chemotherapy (Dozio et al., 2010; Farhat & Lincet, 2020; K.-H. Kim et al., 2018; Phiboonchaiyanan & Chanvorachote, 2017; Tripathy et al., 2018). Hydroxycitrate acts as a competitive inhibitor of ATP citrate lyase, has been shown to enhance immunity antitumor in an autophagy-dependent manner(Pietrocola et al., 2016).

The treatment with ClO_2 of the sixth patient was supplemented with methylene blue. A recognized electron carrier and, depending on the range of concentrations, can donate or accept electrons that could mediate electron flow from damaged mitochondrial respiratory complexes(Atamna et al., 2008; Poteet et al., 2012; Wen et al., 2011). Methylene blue has been shown to reverse the Warburg effect, attenuate anabolism, and inhibit glioblastoma cell proliferation (Pelgrims et al., 2000; Poteet et al., 2013). This suggests that in cancer cells, methylene blue restores normal oxidative phosphorylation, thus inhibiting cell cancer growth and proliferation, affecting the metastatic capacity of malignant cells (Pelgrims et al., 2000; Poteet et al., 2013).

Conclusion

For each case, after treatment with CDS in six different types of cancer, a significant antitumor response was observed in all metastatic tumors., with no associated side effects. The treatment based on chlorine dioxide is safe and cost-effective. Controlled clinical studies in patients with incurable advanced cancer are proposed to determine the efficacy and safety of CDS protocols.

Conflict of interest: None

M. Aparicio-Alonso treated four first patients. L. Schwartz reported the case five and six. L. Schwartz helped write the article. V. Torres-Solórzano wrote the draft of the article. All authors contributed to the discussion of the results.

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