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Combination Therapy With Sodium Dichloroacetate and Potassium-Sodium Citrate in Patients With Stage IV Pancreatic Cancer

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Abstract

Sodium dichloroacetate (DCA), which reverses the Warburg effect of cancer cells, contributes to the alkalinization of the tumor along with a mixture of potassium-sodium (K/Na) citrate hydrate. We retrospectively evaluated the effect of the combination therapy of these in patients with stage IV pancreatic cancer. A total of 135 patients from February 2019 to August 2026 were included in this study. Eligible patients were divided into four groups: group D (DCA alone every other day), group DC (both DCA and K/Na citrate every other day), group D/C (either DCA or K/Na citrate on alternating days), and group DX (DCA every other day with ivermectin and tamoxifen every third DCA treatment). Simple pairwise comparisons of the Kaplan-Meier survival curves using the log-rank test showed significant differences between the D and DC groups and between the DC and DX groups, whereas no significant differences were observed in the other pairwise comparisons. On the other hand, the multivariable time-dependent Cox regression analysis, which accounts for the time from diagnosis to the initiation of treatment, showed a significantly higher hazard in the D, D/C, and DX groups than in the DC group. These findings suggest a potential survival benefit associated with the combination of DCA and K/Na citrate.

Categories: Therapeutics, Oncology, Gastroenterology
Keywords: alkalinization, cancer metabolism, open survival time, sodium dichloroacetate, sodium potassium citrate, stage 4 pancreatic cancer, tumor microenvironment (tme), warburg effect

Introduction

Despite recent advances in treatment strategies, pancreatic cancer remains one of the most lethal malignancies. At diagnosis, most patients already have locally advanced disease or distant metastases. Although fewer than 20% of patients are candidates for surgical resection, surgery alone is rarely curative. Moreover, the number of available anticancer agents for pancreatic cancer is limited compared with that for other malignancies. While molecularly targeted therapies such as RAS (Renin-Angiotensin System) inhibitors and immune checkpoint inhibitors are expected to improve clinical outcomes, conventional cytotoxic agents with substantial toxicity remain the first-line treatment [1].

Warburg reported that cancer cells metabolize glucose and produce lactic acid even under normoxic conditions [2-4]. Excess lactate production acidifies the tumor microenvironment (TME) through the sodium-hydrogen (Na+/H+) exchanger NHE1 [5,6]. This acidic TME promotes cancer cell proliferation, invasion, and metastasis. In addition, it attenuates the efficacy of chemoradiotherapy and inhibits apoptosis [7,8]. Actually, elevated lactate levels and the resultant acidic TME cause poor patient prognosis [9,10].

A growing number of clinically approved non-oncologic drugs have demonstrated antitumor potential. Among these, a mixture of potassium-sodium (K/Na) citrate and sodium dichloroacetate (DCA) may ameliorate this acidic TME and suppress cancer progression. K/Na citrate has long been used safely to treat metabolic acidosis. Previous studies have shown that K/Na citrate suppresses tumor growth through the inhibition of the IGF-1R/AKT/PTEN/eIF2A pathway and phosphofructokinase 1 [11,12]. K/Na citrate reduces the viability and migratory ability of human pancreatic cancer cells, partly through reduction of intracellular Ca2+ levels. Furthermore, the combination of gemcitabine and sodium citrate was reported to exert synergistic antitumor effects on pancreatic cancer cells, possibly due to a slight increase in pH that influences gemcitabine efficacy [13]. In a pancreatic cancer xenograft mouse model, daily oral administration of K/Na citrate neutralized the TME and enhanced the efficacy of anticancer agents [14].

On the other hand, DCA has been used to treat congenital lactic acidosis for a long time [15]. It reverses the Warburg effect by inhibiting pyruvate dehydrogenase kinase, thereby increasing mitochondrial pyruvate flux and promoting glucose oxidation instead of glycolysis. Consequently, DCA reduces lactic acid production

and increases superoxide generation, which induces mitochondria-dependent apoptosis [16]. In addition, DCA influences stemness-associated properties in pancreatic cancer cell lines and restores drug sensitivity in paclitaxel-resistant cells by promoting citric acid accumulation [17,18]. We previously reported that the combination of DCA and omeprazole exerted an antiproliferative effect on human colon cancer cells and on human fibrosarcoma cells inoculated into nude mice, and the addition of tamoxifen to this regimen showed a synergistic effect in a patient with bile duct cancer [19,20]. We also described several cases in which the combination of DCA, omeprazole, tamoxifen, and ivermectin markedly alleviated tumor-associated symptoms [21]. We included this combination therapy of DCA, tamoxifen, and ivermectin as one of the comparator groups in this study.

While investigating the potential of the DCA-citrate combination to modulate the acidic tumor microenvironment, we noted a possible association between concomitant citrate administration and prolonged survival. We therefore conducted a retrospective study of patients with stage IV pancreatic cancer to further evaluate this association.

Materials And Methods

This was a retrospective observational study that evaluated the association between combination therapy with DCA and K/Na citrate and clinical outcomes in patients with stage IV pancreatic cancer who visited Hibiya Uchisaiwaicho Clinic in Tokyo, Japan. This combination therapy was performed in addition to the standard chemotherapy. The study was approved by the Hibiya Uchisaiwaicho Clinic Ethics Committee (approval number: PC-CT-0012017, dated December 31, 2018) and was conducted in accordance with the Declaration of Helsinki. The study period was from February 2019 to August 2026. Written informed consent for treatment and publication of anonymized data was obtained from all patients.

Study population

A total of 135 patients were identified through a retrospective review of their medical records. The inclusion criterion was patients with stage IV pancreatic cancer, and the exclusion criterion was incomplete clinical data on prior treatment at another institution.

Patients were classified into four groups (D, DC, D/C, DX) according to the treatment received. Patients in group D received DCA alone at 333 mg (2.21 mmol) twice daily every other day. Patients in group DC received DCA at 333 mg twice daily, and K/Na citrate at 1 g (1.43 mmol K citrate and 1.33 mmol Na citrate) three times daily, both every other day. Patients in group D/C received DCA at 333 mg twice daily, and K/Na citrate at 1 g three times daily on alternating days. Patients in group DX received DCA at 333 mg twice daily every other day, with ivermectin at 12 mg (0.0137 mmol) twice daily and tamoxifen citrate at 10 mg (0.0177 mmol) twice daily administered with every third DCA treatment.

Data collection, monitoring, and assessment

Potential confounding factors were the performance status of the patients, number of metastases, variations in concurrent chemotherapy and radiotherapy regimens, and the number of treatment cycles. Patients' clinical status was monitored through regular blood tests, tumor marker assessments, and imaging examinations, including computed tomography and ultrasonography. The starting point was the day of a definitive Stage 4 diagnosis.

Survival was estimated using the Kaplan-Meier method, and differences among the groups were calculated using the log-rank test and time-dependent Cox regression analysis. All statistical analyses were performed using EZR version 4.5.2 (Jichi Medical University, Shimotsuke, Tochigi, Japan), and statistical significance was defined as a two-sided alpha level of 0.05.

Results

Table *1* summarizes the overall patient characteristics, treatment regimens, and treatment duration. A total of 135 patients were included, comprising 74 men and 61 women. The mean age at the first visit was 67.4±10.2 years, ranging from 41 to 91 years. All patients were treated as outpatients, and the mean overall survival was 10.8±7.37 months. Radiotherapy was administered to 36.3% (n=49) of patients, and chemotherapy was administered to 94.1% (n=127). Some patients did not receive chemotherapy because of advanced age and/or patient preference. Patients received one or more anticancer agents, most commonly gemcitabine and nanoparticle albumin-bound paclitaxel, followed by S-1. The numbers of patients in groups D, D/C, DC, and DX were 45, 16, 42, and 32, respectively.

Parameters		Values
Time from diagnosis to treatment initiation	Mean±SD	3.46±4.16
Age (years)	Mean±SD	67.4±10.2
	Range	41~91
Sex, n (%)	Male	74 (54.8%)
	Female	61 (45.2%)
Survival time (months	Range	1~37
	Mean±SD	10.8±7.37
Chemotherapy and radiotherapy		
Radiation, n (%)		49 (36.3%)
Chemotherapy, n (%)	Total	127 (94.1%)
	Gemcitabine and nanoparticle albumin-bound paclitaxel	80 (59.3%)
	S-1	45 (33.3%)
	Oxaloplatin, irinotecan, leucovorin and 5-fluorouracil	34 (25.2%)
	Nanoliposomal irinotecan, 5fluorouracil and leucovorin	17 (12.6%)
	Gemcitabine	17 (12.6%)
	Gemcitabine and S-1	11 (8.15%)
	Irinotecan and S-1	2 (1.48%)
	Irinotecan	1 (0.74%)
	Irinotecan and oxaloplatin	1 (0.74%)
	Irinotecan, S-1 and gemcitabine	1 (0.74%)
	Olaparib	1 (0.74%)
Treatment patterns, n (%)	DCA alone (D)	45 (33.3%)
	DCA and K/Na citrate on alternating days (D/C)	16 (11.9%)
	DCA and K/Na citrate every other day (DC)	42 (31.3%)
	DCA, tamoxifen, and ivermectin (DX)	32 (23.7%)
Duration of treatment (months), mean±SD	Total	7.31±6.64
	DCA alone (D)	5.09±3.64
	DCA and K/Na citrate on alternating days (D/C)	9.63±5.91
	DCA and K/Na citrate every other day (DC)	10.3±9.17
	DCA, tamoxifen, and ivermectin (DX)	5.41±4.29

TABLE 1: Patient characteristics, treatment regimens, and treatment duration

DCA: sodium dichloroacetate; K/Na: potassium-sodium

Peripheral neuropathy manifesting as numbness was observed in 31.1% of patients based on outpatient interviews and neurological examinations. All cases were classified as Grade 2 according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 [22], and no Grade 3 or higher adverse events were observed.

The mean treatment duration was longer in group D/C (9.63±5.91 months) and group DC (10.3±9.17 months)

than in group D (5.09±3.64 months) and group DX (5.41±4.29 months). The clinical characteristics and treatment-related factors of the four treatment groups are shown in Table 2.

Parameters		Group D	Group D/C	Group DC	Group DX
Sex, n (%)	Male	24 (53.3%)	9 (56.3%)	25 (59.5%)	17 (53.1%)
	Female	21 (46.7%)	7 (43.7%)	17 (40.5%)	15 (46.9%)
Age (years), mean±SD		69.6±8.72	61.1±12.9	67.0±10.3	67.9±9.59
Survival time (months), mean±SD		8.4±5.19	11.8±6.69	13.71±9.33	9.72±6.19
Time from diagnosis to treatment initiation (months), mean±SD		3.31±3.70	2.19±3.31	3.45±4.37	4.31±4.80
Radiotherapy, n (%)		14 (31.3%)	10 (62.5%)	10 (23.8%)	15 (46.9%)
Chemotherapy, n (%)		36 (80.0%)	16 (100%)	42 (100%)	28 (87.5%)

TABLE 2: Comparison of clinical characteristics among treatment groups

The four groups were: Group D (DCA alone every other day), group DC (both DCA and K/Na citrate every other day), group D/C (either DCA or K/Na citrate on alternating days), and group DX (DCA every other day with ivermectin and tamoxifen every third DCA treatment)

The mean survival time was longest in the DC group (13.71 ± 9.33 months), followed by the D/C group (11.8 ± 6.69 months) and DX group (9.72 ± 6.19 months), and was shortest in the D group (8.40 ± 5.19 months). The mean time from diagnosis to treatment initiation was 4.31 ± 4.80 months in the DX group, 3.45 ± 4.37 months in the DC group, 3.31 ± 3.70 months in the D group, and 2.19 ± 3.31 months in the D/C group. Radiotherapy was administered to 31.3%, 62.5%, 23.8%, and 46.9% of patients in the D, D/C, DC, and DX groups, respectively. Chemotherapy was administered to 80.0%, 100%, 100%, and 87.5% of patients, respectively.

Kaplan-Meier survival curves according to treatment regimen, together with median survival times and pairwise comparisons using the log-rank test with Bonferroni adjustment, are shown in Figure 1. Kaplan-Meier analysis demonstrated differences in survival among the four treatment groups. The median survival times were 14 months in the D group, 16 months in the D/C group, 26 months in the DC group, and 12 months in the DX group. In pairwise comparisons, survival was significantly longer in the DC group than in the D group (Bonferroni-adjusted P = 0.0049) and the DX group (Bonferroni-adjusted P = 0.000186). No significant differences were observed between the D and D/C groups (Bonferroni-adjusted P = 0.804), the D and DX groups (Bonferroni-adjusted P = 1.00), the D/C and DC groups (Bonferroni-adjusted P = 0.164), and the D/C and DX groups (Bonferroni-adjusted P = 0.978).

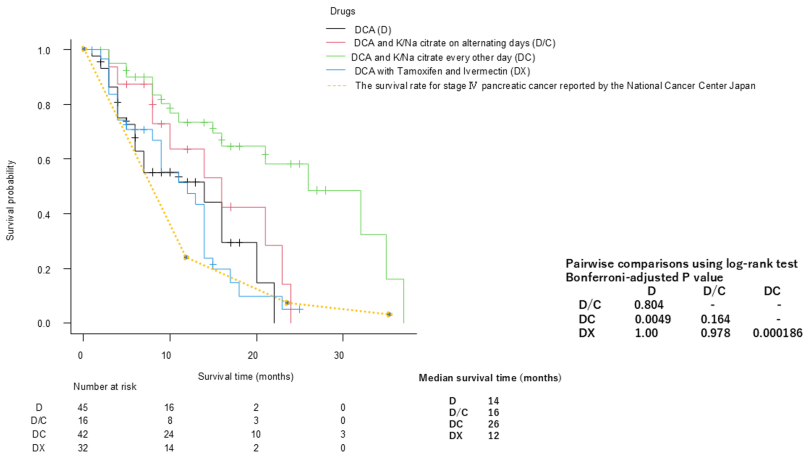


FIGURE 1: Kaplan-Meier survival curves according to treatment regimen, together with median survival times and pairwise comparisons using the log-rank test with Bonferroni adjustment

The survival rate for stage **IV** pancreatic cancer (yellow dotted line) was reported by the National Cancer Center Japan [23].

Group D: DCA alone every other day; Group DC: both DCA and K/Na citrate every other day; Group D/C: either DCA or K/Na citrate on alternating days; Group DX: DCA every other day with ivermectin and tamoxifen every third DCA treatment.

DCA: sodium dichloroacetate; K/Na: potassium-sodium

The results of the multivariable time-dependent Cox proportional hazards analysis, including Bonferroni-adjusted P values, are presented in Table *3*. In the multivariable time-dependent Cox proportional hazards analysis, age was significantly associated with overall survival (HR, 1.03; 95% CI, 1.01-1.05; Bonferroni-adjusted P = 0.032). Chemotherapy was also significantly associated with overall survival (HR, 0.342; Bonferroni-adjusted P = 0.00026). In contrast, sex (male: HR, 0.982; Bonferroni-adjusted P = 1.00), time from diagnosis to treatment initiation (HR, 1.59; 95% CI, 1.12-2.25; Bonferroni-adjusted P = 0.073), and radiotherapy (HR, 0.702; Bonferroni-adjusted P = 0.413) were not statistically significant. Compared with the DC group, the D, D/C, and DX groups showed significantly higher hazards of death, with HRs of 3.02, 3.53, and 3.41, respectively (Bonferroni-adjusted P = 0.00028, 0.00078, and 0.00002, respectively).

Parameters	HR	95% CI	Bonferroni-adjusted P value
Sex, male vs female	0.982	0.703-1.37	1
Age, per 1 year increase	1.03	1.01-1.05	0.032
Time from diagnosis to treatment initiation (months)	1.59	1.12-2.25	0.073
Radiotherapy, yes vs no	0.702	0.491-1.00	0.413
Chemotherapy, yes vs no	0.342	0.206-0.567	0.00026
Group D vs DC	3.02	1.79-5.09	0.00028
Group D/C vs DC	3.53	1.87-6.66	0.00078
Group DX vs DC	3.41	2.05-5.69	0.00002

TABLE 3: Multivariable time-dependent Cox proportional hazards analysis of overall survival

Group D: DCA alone every other day; Group DC: both DCA and K/Na citrate every other day; Group D/C: either DCA or K/Na citrate on alternating days; Group DX: DCA every other day with ivermectin and tamoxifen every third DCA treatment.

DCA: sodium dichloroacetate; K/Na: potassium-sodium

The comparison between the DC and D/C groups yielded different results in the unadjusted Kaplan-Meier analysis and the multivariable time-dependent Cox regression analysis. In the pairwise log-rank comparison shown in Figure *1*, no statistically significant difference was observed between the DC and D/C groups after Bonferroni adjustment (Bonferroni-adjusted P = 0.164). In contrast, the multivariable time-dependent Cox regression analysis showed a significantly higher hazard in the D/C group than in the DC group (hazard ratio, 3.53; 95% confidence interval, 1.87-6.66; Bonferroni-adjusted P = 0.00078). Figure *1* shows the crude survival distributions between treatment groups, whereas Table *3* estimates the association between treatment group and overall survival after adjustment for covariates and treatment timing. Therefore, the results of Table *3* may be more appropriate for evaluating the treatment-group association after accounting for potential confounding and time-dependent treatment exposure.

Discussion

The findings of this study suggest that the administration of DCA and citrate might be associated with prolonged overall survival. Many case reports, including ours, have suggested the potential efficacy of DCA; however, only a few clinical studies have evaluated it in a systematic manner [24]. Dunbar et al's phase I study in patients with recurrent malignant brain tumors reported some instances of disease stabilization [25]. On the other hand, the phase II study by Garon et al. in patients with metastatic breast cancer or lung cancer was terminated because of serious adverse events [26]. Powell et al. evaluated DCA in combination with cisplatin and radiotherapy for head and neck cancer [27]. Taken together, DCA has a long clinical history, but none of these studies advanced to phase III.

Several case reports have described the effects of oral K/Na citrate administration in patients with cancer [28,29]. A Japanese group reported the effects of alkalization therapy in patients with stage IV pancreatic cancer in retrospective studies [30-32]. This therapy consists of an alkaline diet and the administration of citric acid with bicarbonate. Patients with a mean urine pH of 7.5 or higher had a median overall survival of 29.9 months, which was close to the median overall survival of 26 months in our DC group.

A recent trend in cancer therapy has been to identify gene mutations in individual patients and select appropriate molecularly targeted agents. The recent widespread use of the RAS inhibitor daraxonrasib may substantially alter the prognosis of patients with pancreatic cancer. In contrast, the combination of DCA and K/Na citrate can be applied to many types of cancers that undergo anaerobic metabolism. Patients with stage IV pancreatic cancer frequently present to our institutions, and many describe the diagnosis as a death sentence. Despite ongoing therapeutic advances, achieving a cure remains extremely difficult. Nevertheless, we believe that continued efforts may lead to meaningful clinical progress.

Limitations

This study has several limitations. First, the sample size was small. Second, because this was a retrospective study, selection bias and unmeasured confounding could not be excluded. Third, the high loss to follow-up may have introduced bias and affected the interpretation of the results. In addition, there are no objective indicators to confirm whether alkalinization was actually achieved in cancer tissue. A prospective,

randomized controlled trial is needed to establish the efficacy of this combination therapy.

Conclusions

DCA, which reverses the Warburg effect in cancer cells, contributes to the alkalinization of the tumor along with a mixture of K/Na citrate. We evaluated the effect of the combination therapy in patients with stage IV pancreatic cancer. In a single-center retrospective analysis, better overall survival was observed in the group that received both DCA and K/Na citrate. However, given the potential for bias and confounding factors inherent in observational studies, a prospective randomized controlled trial is essential to establish the true efficacy of this combined therapy.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Supervision: Tatsuaki Ishiguro

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Hibiya Uchisaiwaicho Clinic Ethics Committee issued approval PC-CT-0012017. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Ryumei Hugh Ishiguro and Miyu Ishiguro contributed equally to this study.

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