Dichloroacetate (DCA) prevents cisplatin-induced acute kidney injury (AKI) by regenerating renal tubular cells

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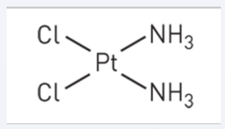
Background and Aims

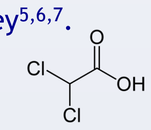


Cisplatin is a simple inorganic molecule, and it is one of the most widely used and one of the most potent chemotherapy drugs.

Cisplatin and related platinum based therapeutics, are used for the treatment of testicular, head and neck, ovarian, cervical, non small cell lung carcinoma and many other types of cancers[1,2]

The use of Cisplatin in cancer therapy is limited by two main factors : acquired resistance and severe side effects in normal tissues, of which the **main dose limiting side effect is nephrotoxicity[3,4].**

Cisplatin Nephrotoxicity (leading to AKI) is a result of apoptosis and shedding of both the proximal and distal tubular cells – more so in the proximal tubule in the kidney[5,6,7].



Dichloroacetic acid (DCA) is a simple chemical compound and it is currently used clinically for the treatment of lactic acidosis[8], since it inhibits pyruvate dehydrogenase kinase and increases pyruvate consumption through oxidative phosphorylation in mitochondria.

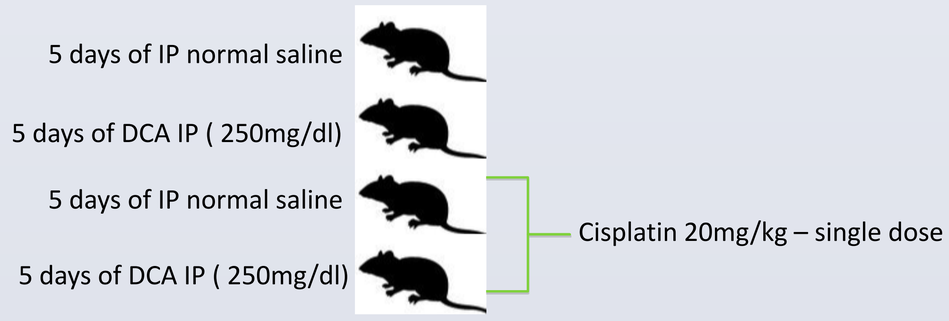
Reprogramming of tumor cell metabolism to a glycolytic phenotype (Warburg effect) has been recognized as a hallmark of tumor progression in a variety of cancers and reversing this phenotype is now regarded as an important new target for cancer therapy[9,10]

DCA is being trialed as an anti cancer drug because of its capacity to reverse the Warburg effect in tumors by decreasing glycolysis and increasing oxidative phosphorylation[11,12,13]

In our preliminary studies we found that DCA, protects the kidney form Cisplatin induced AKI (unpublished)

In this study our aim was to investigate the mechanism of AKI prevention

Methodology and Results



4 groups of male-8 week old, balb/c mice (n>6) were either pretreated with saline or DCA by Intra peritoneal (IP) injections, daily for 5 days, and then Cisplatin was injected to two groups as above. Saline and DCA only groups were included as controls

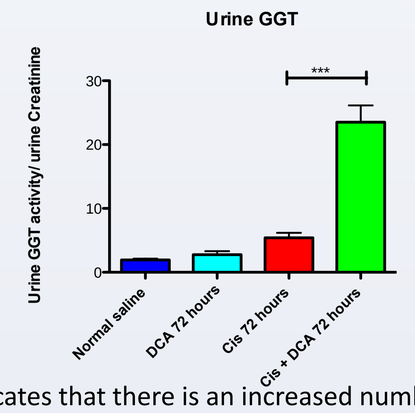
BrdU – a cell proliferation marker, was injected (20mg/kg) to all the mice 2 hours before sacrificing them.

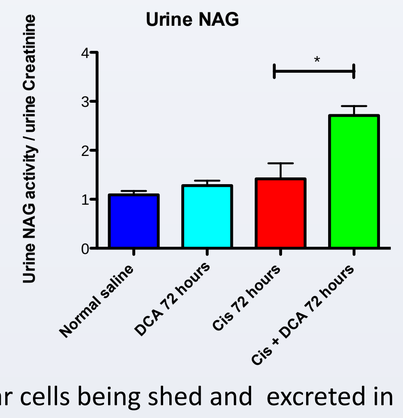
Mice were sacrificed 72 hours after the cisplatin injection and kidney injury markers in serum were measured - which showed elevated serum creatinine (Cis vs Cis+DCA 1.9±0.2 vs 0.6 ±0.1 mg/dl, p <0.0001) and BUN (Cis vs Cis+DCA 46.4±3.2 vs 27.1±1.8 mg/dl, p<0.0001) in the cisplatin only treated group

The histology suggested protection of the kidney when cisplatin is combined with DCA where as the Group which received cisplatin only, showed extensive tubular injury.

The arrow heads indicate apoptotic bodies - note more apoptosis in Cisplatin only group

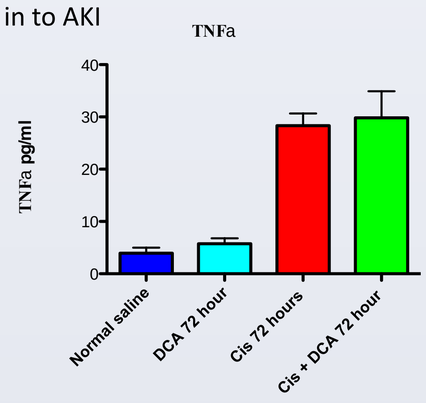
The urinary markers of kidney injury, γ-glutamyltranferase (GGT) (Cis+DCA vs Cis 23.50 ± 2.6 pg/ml vs 5.4 ± 0.7, p<0.0001) and N-acetyl-β-(D)-glucosaminidase (NAG) (Cis+DCA vs Cis 2.7±0.19 vs 1.4±0.3 pg/ml, p<0.01)- showed a significant increase in the Cisplatin/DCA co-treatment group compared to the Cisplatin only groups.



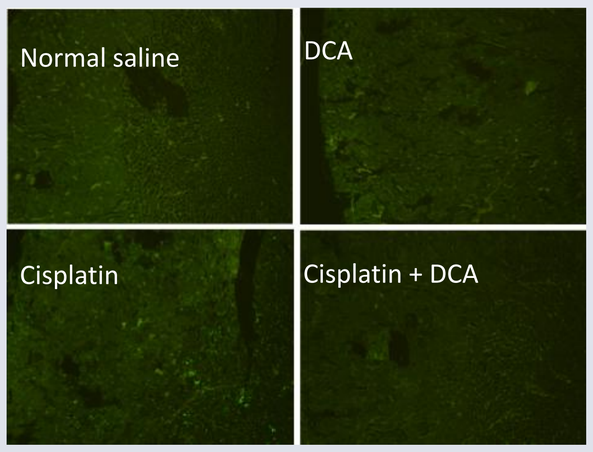


This indicates that there is an increased number of tubular cells being shed and excreted in urine in the co-treatment group though it does not progress in to AKI

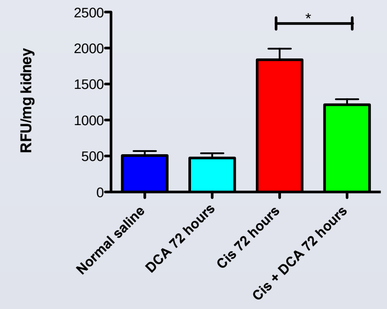
Measurement of TNF alpha, which is a marker of inflammation indicated that there is no difference in the level of inflammation in either of the Cisplatin treated groups
(Cis vs Cis+DCA 28.3±2.3 pg/ml vs 29.8±5.1 pg/ml)

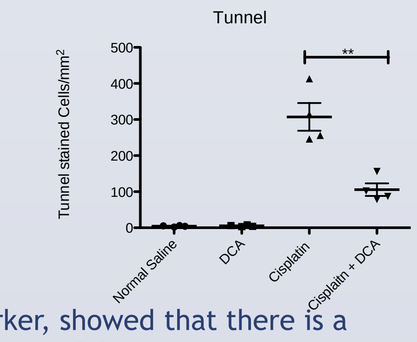


Kidney caspase 3 activity and the TUNEL assay, which are markers of apoptosis, showed that there was significantly less apoptosis in the cisplatin/DCA co-treatment group compared with the cisplatin only group

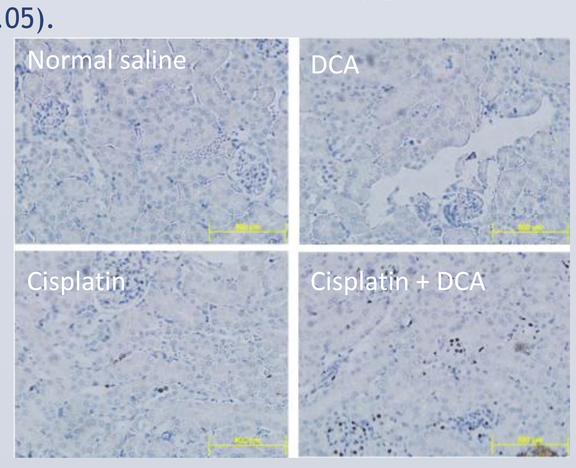


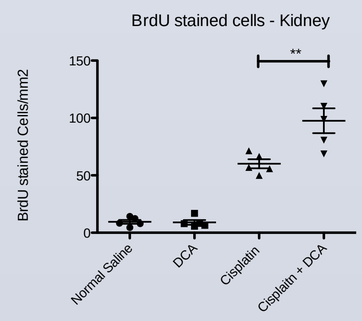
A significantly fewer TUNEL+ cells were noted in cisplatin/DCA cotreatment group compared to Cisplatin only group





BrdU incorporation – which is a cell proliferation marker, showed that there is a significantly a higher number of new cells in the cisplatin/DCA co-treatment group compared with the Cisplatin only group (Cis+DCA vs Cis 98±11vs 60±4 cells/mm^2, p<0.05).





Conclusions

DCA protected mice from cisplatin-induced nephrotoxicity. Renal tubular damage and apoptosis were significantly ameliorated by DCA administration and this response appears to be due to apoptosis inhibition and enhanced regeneration of proximal tubule cells.
Increased regeneration of proximal tubular cells while the cisplatin toxicity persisted resulted in more renal tubular cell markers being be shed in urine
DCA is a promising anti-cancer agent and this work supports its translation for clinical use in conjunction with cisplatin.

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