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First American Cancer Patient to Receive Dicycloplatin (DCP) Chemotherapy Achieves Remission After Seven Weeks of DCP Capsules – A Case Report

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Abstract. *Background: The majority of bladder cancer patients experience recurrence. Cisplatin is the standard chemotherapy for muscle-invasive bladder cancer though adverse effects are often severe. Case Report: Intravenous (IV) dicycloplatin (DCP) sustained remission in an American bladder cancer patient for five years. A recurrent mass was observed in July 2021. The patient received DCP capsules for seven weeks with no significant side-effects. Complete blood count with differential and a basic metabolic panel showed no adverse effects of DCP capsules on the bone marrow, liver or renal parameters. Cystoscopy after oral DCP found no evident bladder tumors; cytology was negative for high-grade urothelial carcinoma. Conclusion: In this patient, DCP-capsules appeared to be as effective as DCP-IV for achieving bladder cancer remission. Both forms of DCP chemotherapy are convenient, active against several cancer types, with decreased adverse effects compared to cisplatin. Both have been available for treating cancer patients in China. A USA clinical trial of DCP in bladder and other cancers appears warranted.*

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Bladder cancer (BC) cases steadily declined by about 1% per year from 2008 to 2017. Still, 17,200 deaths are expected in 2021. An estimated 83,730 adults in the United States will be diagnosed with BC this year. Men are about 4 times more likely than women to develop this malignancy. Among men, BC is the fourth most common cancer and the eighth most common cause of cancer death (1).

The main type of BC is non-muscle invasive tumors (T1, Ta), treated with complete transurethral resection, followed by BCG (Bacillus Calmette–Guérin) intravesical immunotherapy. The vast majority of patients with high-risk BC endure recurrence, progression of disease, or die within ten years (2-7). In England, among those diagnosed with BC, 75% survive for 1 year or more, 55% for 5 years, and around 45% for 10 years after diagnosis (8-10).

Recurrence and survival depend on initial tumor stage and grade, with 5-year recurrence rates in about 65% of patients with non-invasive or in situ tumors, and 73% of patients with slightly more advanced disease. Blute et al noted that the high recurrence rate in the first two years after diagnosis warrants an intense surveillance schedule (11). According to Cambier and colleagues, patients at high risk of recurrence and progression do poorly on current BCG maintenance schedules. Alternative treatments are needed (12, 13).

Cisplatin chemotherapy is a standard protocol for muscle-invasive BC (13, 14). It improves survival, presumably by treating micrometastatic disease and pathologic down-staging. Cisplatin plus gemcitabine (CG) is frequently substituted for the classic MVAC combination (methotrexate, vinblastine, doxorubicin, cisplatin) to increase tolerability. In advanced or metastatic urothelial cancer, studies show non-inferiority of CG *versus* MVAC with fewer adverse effects (15). However, adverse effects of cisplatin are often constraints to full dosage and long-term use.

Dicycloplatin (DCP), a novel platinum analog, was developed in China. It possesses an excellent safety profile. An-Tuo-Ke-Jin, the capsule formulation of DCP, was developed in 1992 for oral administration. Subsequently, DCP intravenous injection was developed for a phase I human clinical trial (16, 17). A phase II clinical trial using DCP+paclitaxel in non-small-cell lung cancer patients was completed in 2009 (18). In March 2012, DCP injection was approved for solid tumor chemotherapy by the State Food and Drug Administration of China (SFDA; Certificate Nos. H20120020 and H20120021).

Of note, carcinoma shares many common risk-factors or major cause-mechanisms with other chronic diseases, including type 2 diabetes and heart disease. They may relate to one another in multiple pathways. Several meta-analyses suggest that type 2 diabetes and heart disease show an increased risk of bladder, endometrial and other cancers. Inflammation can be a major cause of cancers; it may also play significant role in age-related diseases including diabetes, cardiovascular and autoimmune diseases (19-21). Khanna *et al*. summarized that exposure to endogenous and exogenous free radicals can damage cell DNA through oxidation and strand breaks, interfering with DNA repair. The resulting genetic mutations can lead to cancer (22). Khansari and colleagues stated that inflammation induces oxidative stress and reduces cellular antioxidant capacity. Overproduced free radicals react with cell membrane fatty acids and proteins, impairing their function permanently. Free radicals can also lead to mutation and DNA damage predisposing to cancer (23). Knowing the role of free radicals in cancer and chronic diseases would encourage antioxidant and lifestyle strategies to prevent and manage these diseases.

Case Report

The history of this case: A Caucasian American male ex-smoker was diagnosed with a malignant bladder tumor (non-invasive high-grade papillary urothelial carcinoma on right lateral wall) at the age of 65 in 2016. He underwent complete transurethral resection (TURBT), declined BCG immunotherapy and then traveled to Beijing, where he received DCP chemotherapy (24). He received 300 mg by intravenous (IV) injection weekly for eight weeks. In addition, he received encapsulated DCP (An-Tuo-Ke-Jin); four capsules (12 mg DCP) were taken three times a day for six weeks. Adverse effects included moderate back and leg aches. There was no emesis or alopecia; weekly blood counts declined but remained within normal limits (24).

After completion of DCP treatment, the patient was seen quarterly, semiannually and yearly for surveillance at WVU Ruby Hospital, Morgantown, WV, USA. Cystoscopy through January 2020 revealed no recurrence of tumor (Figure 1A and B). Computed tomography - intravenous pyelogram evaluations indicated no upper urinary tract or metastatic lesions. Cytology collected during each cystoscopy found no malignant cells (24-27). Of note, during the 5 years of his remission, the patient received DCP chemotherapy once a year. That "booster" consisted of 300 mg of DCP by IV weekly for two weeks when he traveled to China in 2017, 2018 and 2019. The boosters were given to prevent tumor recurrence.

Due to the Covid-19 pandemic, annual surveillance was paused and travel to China blocked.

In early May of 2021, the patient developed acute symptoms of coronary artery disease - angina presence unspecified: ST elevation myocardial infarction (STEMI). Of note, he has a long-term history of Type 2 diabetes and essential hypertension. On May 7, 2021, the patient underwent off-pump quadruple coronary bypass grafting by Johns Hopkins Medicine Cardiothoracic Surgeons at Suburban Hospital in Bethesda, MD, USA. The patient developed postop pleural effusion on the right side, confirmed as chylothorax, with a triglyceride content of 190 mg/dl (Pleural fluid triglyceride concentration > or =110 mg/dl is highly suggestive of a chylous effusion), on July 23, 2021. Thoracentesis was performed three times. Conservative treatment was followed with a fat-restricted, Green Mediterranean Diet (28-30). A chest x-ray in mid-December showed only a small amount of pleural effusion. The patient exhibited no evidence of congestive heart failure before and after heart surgery.

In July of 2021, eighteen months after his last bladder surveillance, WVU urologists found a papillary mass on the right lateral bladder wall at the site of the original high grade (HG) transitional cell carcinoma (TCC) in 2016 that was considered recurrence based on its gross features. No other masses or lesions were noted within the bladder lumen (Figure 1C).

From July 4 to July 13, 2021, the patient received 3 DCP capsules 3 times daily (one capsule contains 3 mg DCP, thus he received 27 mg/day orally). From July 14 through August 20 of 2021, he received 4 DCP capsules 3 times daily (total 36 mg/day orally). During the first 5 weeks of oral DCP treatment, the patient experienced minimal side-effects. During the last 2 weeks, he reported low energy, anorexia, and decreased sensitivity to taste. Generally speaking, there were no significant side-effects. On August 13, 2021, complete blood count with differential and basic metabolic panel showed no adverse effects of DCP on bone marrow, liver or renal parameters (Table I and Table II).

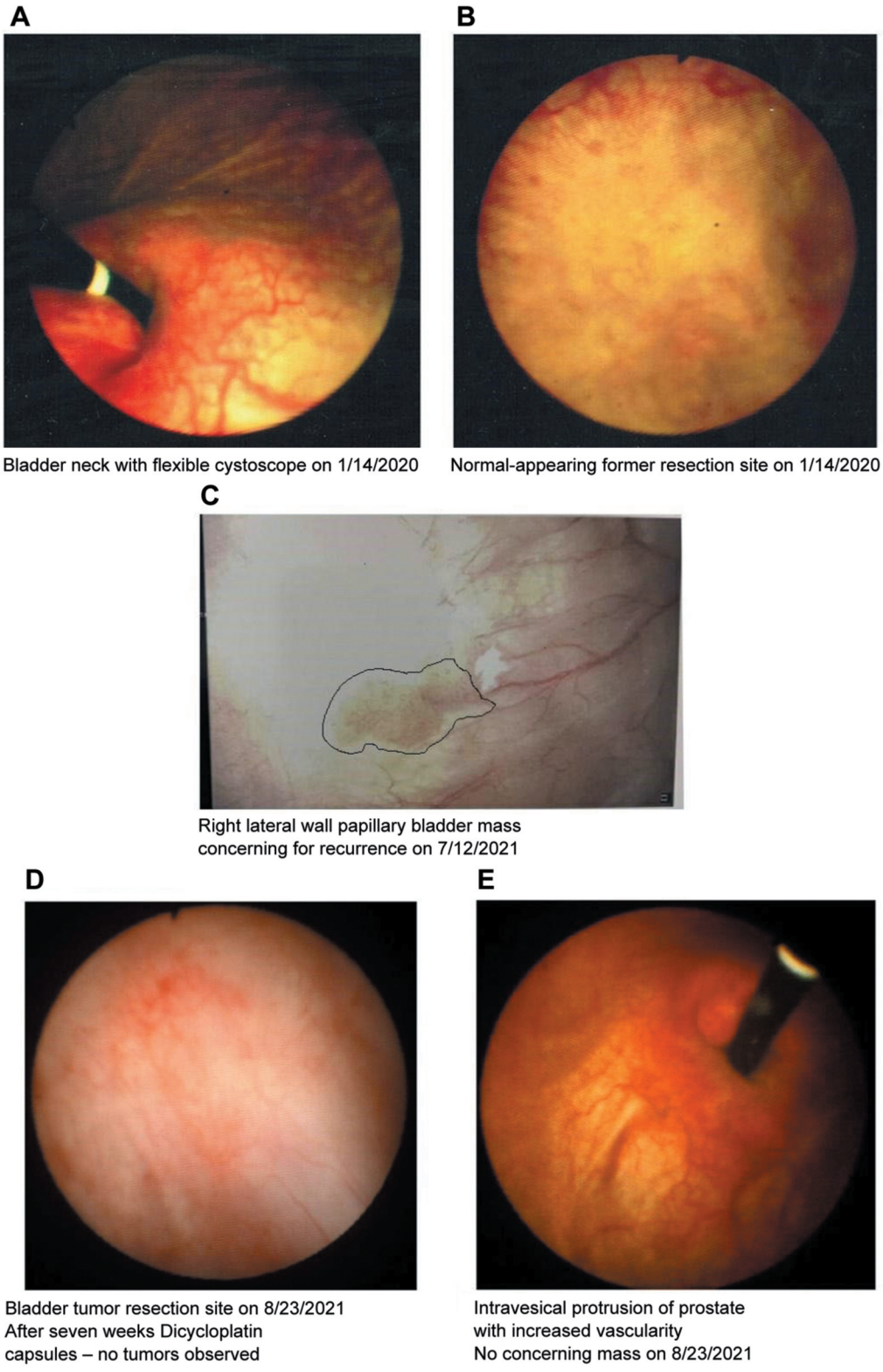

Figure 1. *Cystoscopy images of the bladder resection site and recurrent tumor. Images were acquired during the cystoscopies on January 14, 2020; July 12, 2021; and August 23, 2021. A and B: The resection site appears normal; no recurrent mass was seen on January 14, 2020. C: The recurrence of papillary bladder mass observed on July 12, 2021 is shown in the circled area. D and E: Old TURBT site after a seven-week course of oral dicycloplatin appears normal on August 23, 2021, no evidence of bladder tumor.*

Table I. *Complete blood count with differential on August 13, 2021.*

White blood cell	4.8×10^3/μl	$3.7\text{-}11.0\times10^3$/μl	
Red blood cell	4.64×10^6/μl	$4.50\text{-}6.10\times10^6$/μl	
Hemoglobin	12.6 g/dl	13.4-17.5 g/dl	L
Hematocrit	39.6%	38.9-52.0%	
Mean corpuscular volume	85.3 fl	78.0-100.0 fl	
Mean corpuscular hemoglobin	27.2 pg	26.0-32.0 pg	
Mean corpuscular hemoglobin concentration	31.8 g/dl	31.0-35.5 g/dl	
Red cell distribution width-coefficient of variation	16.6%	11.5-15.5%	H
Platelets	244×10^3/μl	$150\text{-}400\times10^3$/μl	
Mean platelet volume	11.8 fL	8.7-12.5 fl	
Neutrophil %	55%	%	
Lymphocyte %	27%	%	
Monocyte %	12%	%	
Eosinophil %	5%	%	
Basophil %	1%	%	
Neutrophil #	2.66×10^3/μl	$1.50\text{-}7.70\times10^3$/μl	
Lymphocyte #	1.31×10^3/μl	$1.00\text{-}4.80\times10^3$/μl	
Monocyte #	0.58×10^3/μl	$0.20\text{-}1.10\times10^3$/μl	
Eosinophil #	0.23×10^3/μl	$\leq0.50\times10^3$/μl	
Basophil #	$<0.10\times10^3$/μl	$\leq0.20\times10^3$/μl	

Table II. *Basic metabolic panel on August 13, 2021.*

Sodium	138 mmol/l	136-145 mmol/l	
Potassium	4.3 mmol/l	3.5-5.1 mmol/l	
Chloride	103 mmol/l	96-111 mmol/l	
CO_2 total	27 mmol/l	23-31 mmol/l	
Anion GAP	8 mmol/l	4-13 mmol/l	
Calcium	9.4 mg/dl	8.8-10.2 mg/dl	
Glucose	161 mg/dl	65-125 mg/dl	H
Blood urea nitrogen	14 mg/dl	8-25 mg/dl	
Creatinine	0.96 mg/dl	0.75-1.35 mg/dl	
Blood urea nitrogen/creatinine ratio	15	6-22	
Estimated glomerular filtration rate	80 ml/min/BSA	≥60 ml/min/BSA	

The patient was scheduled for a TURBT on August 23, 2021. He signed a consent form and was prepared for the TURBT procedure. However, due to chest pains the night before - in light of quadruple bypass earlier in the year, and requirement of general anesthesia for the TURBT - the procedure was changed to flexible cystourethroscopy with bladder barbotage under local anesthesia to evaluate the status of his bladder tumors after seven weeks of oral DCP chemotherapy. The cystoscopy on August 23, 2021 found no evidence of bladder tumors. Furthermore, cytology was negative for high-grade urothelial carcinoma (Figure 1D and E).

Conclusion

As reported in earlier articles, the adverse effects of DCP are tolerable compared to other platinum compounds, such as cisplatin and carboplatin (24-27). *In vitro* and *in vivo* studies demonstrated that DCP shares the same molecular mechanisms with cisplatin and carboplatin. Clinical studies of DCP-IV in cancer patients have shown similar efficacy and improved therapeutic ratio *versus* other standard IV platinum drugs (16, 27). In the patient reported here, oral DCP capsules appeared to be equally effective as DCP IV in suppressing his bladder cancer. If oral DCP is as efficacious as DCP IV, and both have a better therapeutic ratio than cisplatin or carboplatin, then clinical trials of DCP in bladder cancer patients in the USA appear warranted.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

Conception and design: Jing Jie Yu, Xuqing Yang, Thomas Hogan; Patient care: Mohamad W. Salkini, Fayyaz Haider Hashmi, Stanley J Kandzari, Chad Morley, David Zekan, Zachary Werner, Dorian J. Williams, Yi Guo, Thomas Lewis Matthew, Michael Spangler, Jing Jie Yu; Data collection and assembly: Jing Jie Yu, Yi Guo; Manuscript writing: All Authors. Final approval of manuscript: All Authors.

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