A potent anticancer agent, 3-bromopyruvic acid (3-BrPA), for the treatment of bladder cancer: a case report

Abstract

Background: 3-Bromopyruvic acid (3-BrPA), a halogenated analog of pyruvate which exploits alkylating properties, is a new and potent anticancer agent targeting various cancel cell types. 3-BrPA targets cancer cells' energy metabolism, both its high glycolysis ("Warburg Effect") and mitochondrial oxidative phosphorylation. 3-BrPA is more selective for cancer cells resulting in minimal cytotoxicity to normal cells. We report the case of a patient with urothelial cancer, who underwent 3-BrPA treatment.

Case presentation: A 100-year-old man presented to the clinic with a complaint of gross hematuria. ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography demonstrated a mass located in anterior wall of the bladder and right hilum of the lung. Pathological diagnosis of transurethral biopsy was high-grade, non-invasive papillary urothelial carcinoma. He was treated with intravesical and intravenous administrations of a patented and proprietary of 3-BrPA. Treatment was well tolerated, with no systemic adverse effects. No evidence of recurrence and metastasis was observed during the treatment and few months of follow-up period without further treatment.

Conclusions: This case illustrates the safety and efficacy of intravesical and intravenous administration of 3-BrPA on the urothelial tumor, which would assist in optimizing therapeutic regimen of 3-BrPA in future clinical oncology.

Keywords: Bladder cancer, Urothelial tumor, 3-Bromopyruvic acid, Warburg effect

Introduction

Bladder cancer (BC) is one of the most common cancers that causes approximately 430,000 incident cases and 165,000 deaths per year worldwide [1]. Urothelial carcinoma, also known as transitional cell carcinoma (TCC), is the most common histologic type of the BC, constituting approximately 95% of all cases [2]. The current accepted pathway for bladder cancer patients is to have a flexible cystoscopy, then a transurethral resection of bladder tumor (TURBT) as the initial intervention to remove all visible tumors and to provide specimens for pathological examination to determine stage and grade [3,4]. TURBT is commonly followed by local treatment with either intravesical chemotherapy or immunotherapy [5]. The type and number of intravesical instillations given depend on numerous factors, including grade, stage, multifocality of the tumor, and tolerability [6]. The most commonly employed intravesical agents are immunomodulatory agents such as Bacillus Calmette-Guérin (BCG) and chemotherapeutic agent, usually Mitomycin C. Although intravesical therapy has been extensively investigated to be effective for many years, its use is still problematic due to a diverse array of genitourinary and/or systemic complications such as cystitis, penile lesions, symptomatic prostatitis and fever[7].

Tumor cells have a unique energy metabolism, consuming more glucose than normal cells and even in the presence of oxygen convert the majority of pyruvate into lactate ("Warburg Effect" or "aerobic glycolysis") [8]. There has been a steadily growing research interest in 3-BrPA, a halogenated analog of pyruvate, as a promising glycolytic inhibitor and specific anticancer agent with little or no effect on most normal cells. 3-BrPA inhibits the activity of a number of glycolytic enzymes including hexokinase 2, glyceraldehyde 3-phosphate dehydrogenase, phosphoglycerate kinase, and pyruvate kinase, all of which are often overexpressed in tumor cells. Moreover, 3-BrPA also inhibits the activity of mitochondrial proteins/enzymes including isocitrate dehydrogenase, and the phosphate carrier. Furthermore, 3-BrPA is known to block Complex I and II of the respiratory chain causing and additional decline in ATP Production. As a result, 3-BrPA serves as a potent energy blocker followed by ATP depletion and apoptosis [9]. 3-BrPA may specifically enter tumor cells via lactate transporter MCT1(monocarboxylic acidic transporter 1) that is overexpressed in most tumor cell. This specificity allows 3-BrPA to be more selective for malignant cells leaving normal cells unharmed. 3-BrPA anticancer therapy would be beneficial due to a minimal systemic toxicity and side effects assuring a normal quality lifestyle [8,9]. Delivery

method of 3-BrPA can be versatile depending on the cancer type and location. When 3-BrPA is closely delivered to a tumor (i.e., via bladder wash, vaginal wash, and mouthwash) or into a tumor, it can be very effective as a stand-alone cancer treatment [9]. We herein report the case of a 100-year-old man who received intravesical and intravenous infusions of a patented and proprietary of 3-BrPA for a high grade, papillary urothelial carcinoma.

Case presentation

In February 2018, a 100-year-old male patient with a medical history of coronary artery disease and hypertension presented to the Anne Arundel Urology, Annapolis Office, USA with the complaint of a month-old gross hematuria. He has never smoked and did not consume alcohol. His family medical history revealed that his father had a malignant neoplasm of brain and his sister had a malignant tumor of breast. A Cystoscopy was performed revealing a 1cm tumor at the bladder dome but a urine cytology test was normal and demonstrated no evidence of cancer. A computed tomography (CT) scan was further performed and showed a 1 x 1 x 1.8 cm soft tissue mass at the anterior bladder wall. A whole-body PET/CT scan revealed focal abnormal uptake in the anterior bladder with SUV maximum of approximately 18.0 **(Figure 1-A1 and A2)** and focal abnormal uptake right hilum suspicious for pathologic lymph node or primary lung carcinoma or active granulomatous disease (**Figure 3A)**. Following diagnosis, medical clearance bladder tumor biopsy was planned in March. However, biopsy was delayed due to high blood pressure. He continued to have gross hematuria and started a ketogenic diet with some supplements while waiting for the biopsy. In April 2018, prior to the bladder biopsy, laboratory investigations and CT of chest, abdomen and pelvis were performed. Laboratory examinations showed normal values with the exception of a decreased hematocrit level of 35.6 % (reference range, 37.5 to 51.0) and an elevated Hemoglobin A1c level of 6.3 (reference range, 4.8 to 5.6). CT showed prominent 1.5 x 1 cm right hilar lymph node in lung and polypoid mass in the anterior wall mid bladder, which was unchanged in size in comparison to previous February examination. At the end of April, bladder biopsy was successfully taken and showed a high grade, aggressive urothelial cancer **(Figure 2).** Prophylactic antibiotics were administered at the time of biopsy. The pathologic report indicated a diagnosis of cT1N0M1 or cT1N0M0. After discussing 3-BrPA treatment plan **(figure 5)**, including the education about its anticancer effects and possible side effects with the patient and his family, written informed consent was obtained for the treatment. In late April 2018, few days after the biopsy, he started a specially formulated 3-BrPA treatment of cancer located inside the bladder with washes introduce through via a catheter (1.2mM of 3-BrPA in 500mL normal saline). Hematuria resolved but was observed occasionally only after the catheter usage. At the end of June, a week after the 1st cycle of 3-BrPA intravesical treatment, a whole-body PET/CT was performed and demonstrated no bladder mass but the right hilar node showed peak activity 7.8 SUV, compared to 6.1 on the prior CT **(figure 3B)**. Additionally, there was a new finding, a focus of activity in the infra hilar vasculature corresponding to a small less than 100 mm node, 3.7 SUV**.** In late July, he started 1st cycle of intravenous (IV) 3-BrPA treatment at a dose of 3.7 mg/kg, added to 0.9% 500mL normal saline, by slow IV infusion for 4 weeks. 12 days after the IV treatment, 2nd cycle of intravesical 3-BrPA treatment was restarted. The Patient was closely monitored for adverse effects during the whole treatment period. Treatment was well tolerated, with no systemic or unexpected adverse effects. The only adverse effects were an explosive diarrhea, which was started after the increase of wash concentration and worsen upon starting of IV 3-BrPA treatment and fatigue. Watery diarrhea was continued for about 2 months during the treatment. One of his diet supplements, Magnesium was hold. Clostridium difficile test was done for the possibility of C. difficile infection but the result was negative. The patient could not receive the intravesical and IV treatment of 3-BrPA simultaneously and Days off of treatment were needed due to symptoms of fatigue such as dizziness and headache. In September 2018, after the 2 cycles of wash and 1 cycle of IV treatment, a whole-body PET/CT scan showed no residual or recurrent tumor in bladder **(figure 1B)** but still one noticeable spot in right hilar lymph node of lung, SUV 5.7 and granuloma in the right lower lobe **(figure 3C)**. In March 2019, follow up PET scan revealed no cancer showing in the bladder or other area **(figure 1D**) but 15 mm right hilar nodule or mass, unchanged from previous September, 2018 scan **(figure 3D).** In late April 2019, 2nd cycle of 3-BrPA IV treatment was restarted for the lung lesions for 6 weeks. In September 2019, he underwent CT scan on the chest, abdomen and pelvis which demonstrated no evidence of metastatic lung disease, revealing that spot in right hilar lymph node is unlikely to be malignant **(figure 4)** and also no cancer showing in bladder or other area. No further 3-BrPA treatment and imaging were performed due to the positive clinical outcome.

Discussion

3-BrPA, a small molecule acting as an alkylating agent, is considered as a potent anticancer agent, due to its ability to inhibit pivotal glycolytic enzymes and mitochondrial proteins. Its anti-cancer action leads to the induction of massive cell death in rapidly growing cancer cells. 3-BrPA has been studied and proved as a promising anticancer agent in various in vitro and in vivo studies [10, 11, 12, 13]. However, there is lack of human studies on 3-BrPA in clinical settings. To the best of our knowledge, there are no available clinical trials regarding 3-BrPA approved from drug regulatory authority. To date, there are only two case studies of clinical application of 3-BrPA. This case is the first reported of a patient with bladder cancer receiving intravesical and intravenous 3-BrPA treatment. Specially formulated 3-BrPA was delivered inside the bladder via a catheter to treat cancer located inside the bladder. The delivered 3-BrPA is retained inside the cavity for a period of time sufficient to attack cancer cells. Additionally, intravenous delivery of 3-BrPA was administered to minimize and prevent additional metastatic spreads. ^{18}F-FDG PET/CT was periodically performed prior to, during and after the 3-BrPA treatment since imaging plays a mainstay role in the evaluation of BC, especially for diagnosis, local and distant staging and treatment follow up [14]. A follow up PET/CT scan obtained at the completion of intravesical and IV treatment showed that he was in clinical remission without residual or recurrent tumor in bladder and lung metastasis.

Since elderly person is at a greater risk for adverse drug reactions, he was closely monitored for the adverse effects for the duration of treatment. He only experienced a severe diarrhea when the 3-BrPA concentration was increased and it was getting worse with 3-BrPA IV treatment. During several months' treatment, no systemic adverse effect was observed for the patient.

The patient remained well after the 3-BrPA treatment, with no evidence of recurrence. This case potentially indicates the ability of 3-BrPA to eradicate cancer without apparent toxicity or recurrence. Moreover, intravesical administration of 3-BrPA has proved to be an effective and safe form of treatment for bladder cancer.

Finally, it should be emphasized that special formulation, proper administration and strict medical supervision are needed to maximize safety and efficacy and minimize cytotoxicity when using 3-BrPA in clinical settings.

Conclusions

The patient completed the scheduled treatment and improved clinically without major complications. This case reminds us that intravesical and intravenous administration of 3-BrPA has proved to be a generally safe treatment and potential cancer treatment. Whereas many in vitro and in vivo studies have confirmed its anticancer properties, the application in humans has not been tested by clinical trials. Further investigations, specially, controlled trials are therefore needed to demonstrate the safety and anticancer efficacy of 3-BrPA in clinical oncology under strict medical supervision.

Abbreviations

^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose Positron emission tomography/computed tomography; TURBT, Transurethral resection of the bladder tumor

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

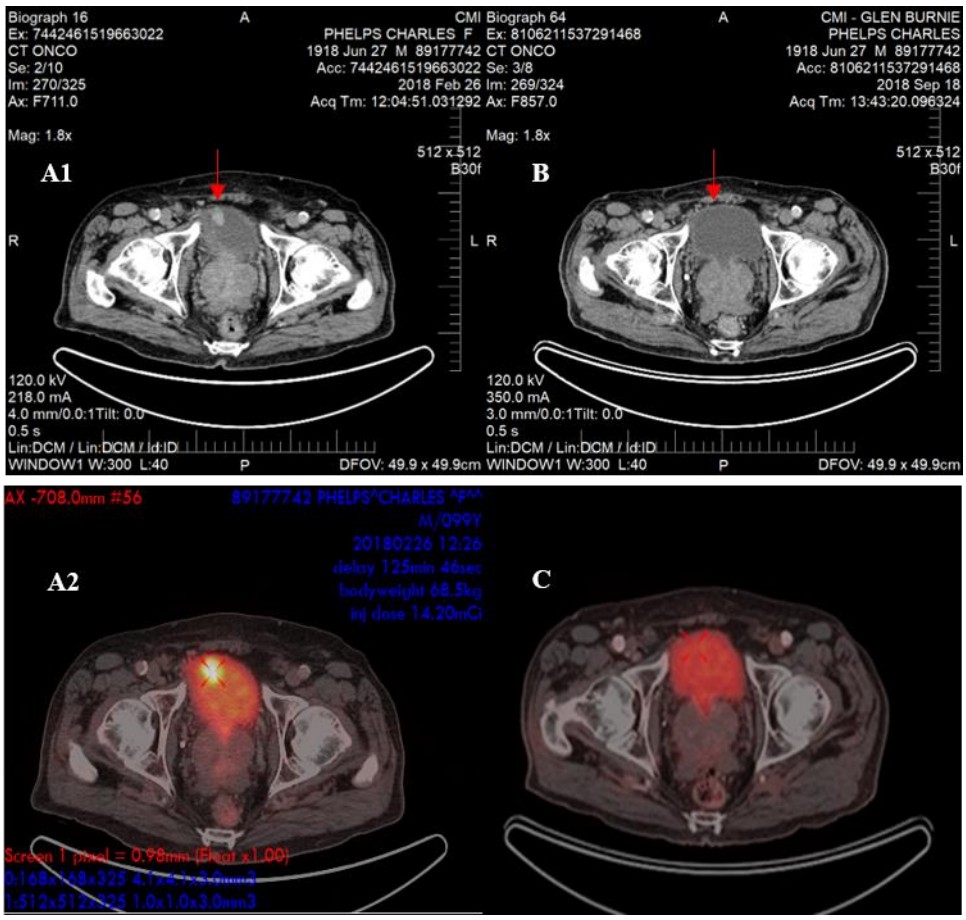

Figure 1. Comparison of the whole-body ^{18} F-fluorodeoxyglucose PET/CT images of the patient's bladder area before and after 3-BrPA intravesical treatment. (A1) 2018.02.26. CT. Baseline prior to treatment. (A2) 2018.02.26. **Baseline prior to treatment. PET.** Focal abnormal uptake identified in the anterior bladder with SUV maximum of approximately 18.0 and central decreased uptake likely reflecting relative necrosis. **(B)** 2018.09.18. At completion of second cycle of intravesical 3-BrPA treatments. No residual or recurrent tumor showing. **(C)** 2019.03.08. No abnormal FDG PET uptake noted in the bladder.

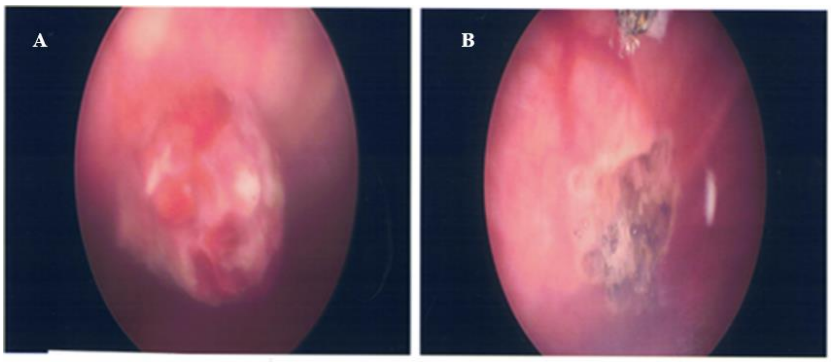

Figure 2. Bipolar transurethral resection of dome of baldder tumor.. **(A) Prior to Biopsy. 2018.04.25.** Pathological diagnosis of transurethral biopsy was high grade papillary urothelial carcinoma. No invasion is identified. No muscularis propria is identified in the tissue received **(B) After the Biopsy.** The specimen consists of several fragments of red to dark gray soft tissue which from 0.1 to 0.4 cm.

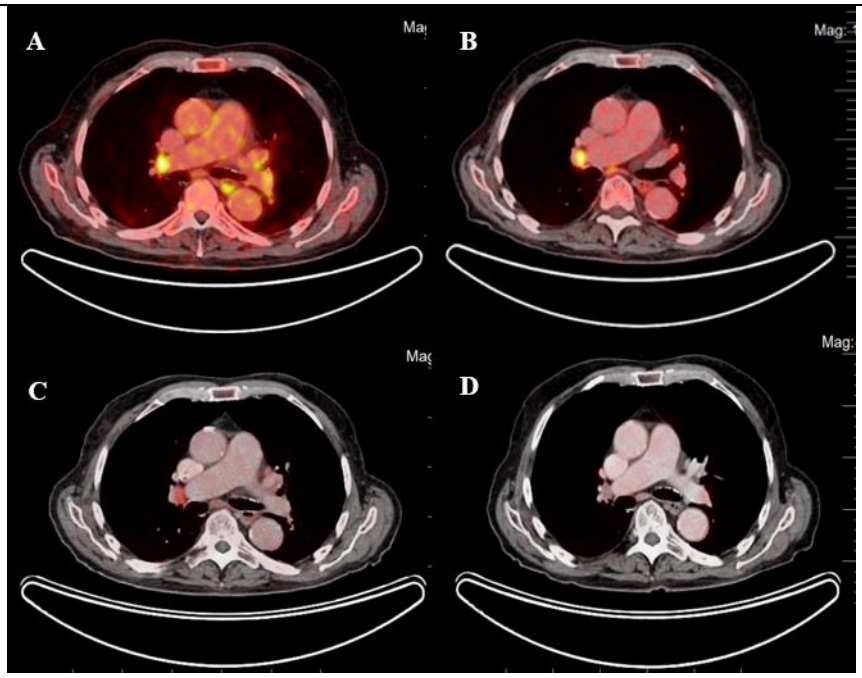

Figure 3. Comparison of the whole-body ^{18} F-fluorodeoxyglucose PET/CT images of the patient's lung area (right hilum lymph node) before and after 3-BrPA intravenous treatment. (A) 2018.02.26. Baseline prior to treatment. A hypodense lesion in the right superior hilum which is strongly FDG avid with a FDG maximum of approximately 6.1 (1.3 cm anteroposterior x 1.0 cm transverse). **(B)** 2018.06.22. The right hilar node shows peak activity 7.8. **(C)** 2018.09.18. At completion of first cycle of IV 3-BrPA treatments. One noticeable spot in right hilar lymph node of lung, which may represent a hilar metastasis or primary lung cancer or granulomatous process (SUV Max : 5.7) **(D)** 2019.03.08. No pulmonary infiltrate, mass or effusion. Right hilar lymph node measuring 15 mm in greatest dimension with a peak uptake of 6 SUV.

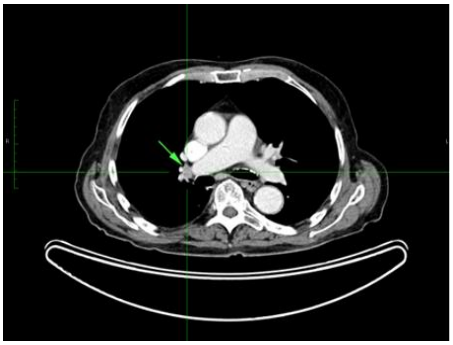

Figure 4. CT of chest with contrast. 2019.09.25. At completion of second cycle of IV 3-BrPA treatments. No metastases or pleural fluid in lung. Spot in right hilar lymph node was unlikely to be malignant.

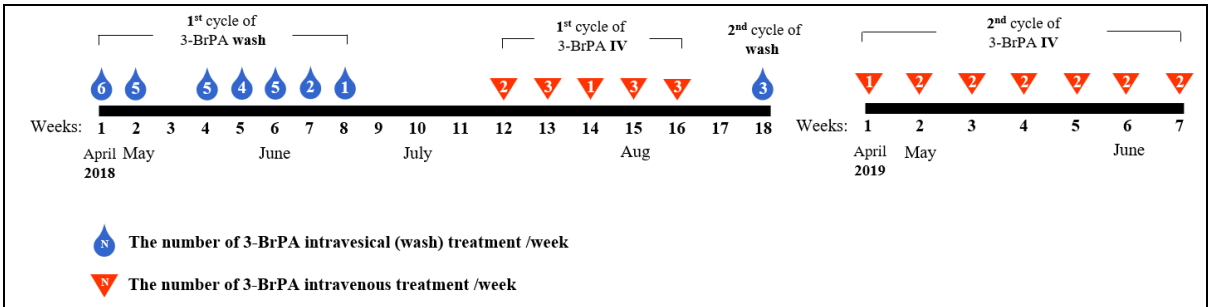

Figure 5. 3-BrPA Treatment Schedule.

References

1. Marcus G. K. C, Aidan P. N. Epidemiology, aetiology and screening of bladder cancer. Transl Androl Urol 2019; 8(1):5-11.
2. Steve G, Charles J. R, Virginia U. Bladder Cancer Detection and Monitoring: Assessment of Urine-and Blood-Based Marker Tests. Mol Diagn Ther (2013) 17:71-84.
3. Simon R, Ailsa B, David M, et al. The influence of TURBT on staging of bladder cancer. Uro Nephrol Open Access J. 2019;7(1):15-18.
4. Anastasios A, Theo M. Best practice in the treatment of nonmuscle invasive bladder cancer. Ther Adv Urol. 2012 4(1) 13-32.
5. Thiru P, Paul C, Gayathri B, et al. Intravesical Gemcitabine versus Intravesical Bacillus Calmette-Guerin for the Treatment of Non-Muscle Invasive Bladder Cancer: An evaluation of Efficacy and Toxicity. Front. Oncol. 2017. 7:260
6. Grace C, Arun S, Michele B, et al. Recent advances in the diagnosis and treatment of bladder cancer. Cheung et al. BMC Medicine 2013, 11:13.
7.Yuqing Liu, Jian Lu, Yi Huang, et al. Clinical Spectrum of Complications Induced by Intravesical Immunotherapy of Bacillus Calmette-Guerin for Bladder Cancer. Hindawi Journal of Oncology. Volume 2019.
8. Tengjiao F, Guohui S, Xiaodong S, et al. Tumor energy metabolism and potential of 3-Bromopyruvate as an inhibitor of aerobic glycolysis: Implications in tumor treatment. Cancers 2019, 11, 317.
9. Young H. Ko, Katarzyna N, Margarida C, et al. 3-Bromopyruvate as a potent anticancer therapy in honor and memory of the late Professor Andre Goffeau. Wiley Yeast, 2018;1-11.
10. J.-Z. Q., H. Xin, B.J. N. 3-Bromopyruvate induces necrotic cell death in sensitive melanoma cell lines. Biochemical and Biophysical Research Communications 396 (2010) 495-500.
11. Jean-F. H. G., Young H. Ko, Michael S. T. et al. Novel therapy for Liver Cancer: Direct Intraarterial Injection of a Potent Inhibitor of ATP Production. Cancer Research 62, 3909-3913, July 15, 2002.
12. Young H. Ko, Barbara L. S., Yuchuan W. et al. Advanced cancers: eradication in all cases using 3-bromopyruvate therapy to deplete ATP. Biochemical and Biophysical Research Communications 324 (2004) 269-275.
13. Young H. Ko., Peter L. P., J.F. G. Glucose catabolism in the rabbit VX2 tumor model for liver cancer: characterization and targeting hexokinase. Cancer Letters 173 (2001) 83-91.
14. Kirsten B, Baris T, Peter L C. PET/CT and MRI in Bladder Cancer. J Cancer Sci Ther. 2012 July 30; Suppl 14(1).