

A translational study “case report” on the small molecule “energy blocker” 3-bromopyruvate (3BP) as a potent anticancer agent: from bench side to bedside

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Received: 9 January 2012 / Accepted: 14 January 2012 / Published online: 11 February 2012
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Abstract The small alkylating molecule, 3-bromopyruvate (3BP), is a potent and specific anticancer agent. 3BP is different in its action from most currently available chemo-drugs. Thus, 3BP targets cancer cells’ energy metabolism, both its high glycolysis (“Warburg Effect”) and mitochondrial oxidative phosphorylation. This inhibits/ blocks total energy production leading to a depletion of energy reserves. Moreover, 3BP as an “Energy Blocker”, is very rapid in killing such cells. This is in sharp contrast to most commonly used anticancer agents that usually take longer to show a noticeable effect. In addition, 3BP at its effective concentrations that kill cancer cells has little or no effect on normal cells. Therefore, 3BP can be considered a member, perhaps one of the first, of a new class of anticancer agents. Following 3BP’s discovery as a

novel anticancer agent in vitro in the Year 2000 (Published in Ko et al. *Can Lett* 173:83–91, 2001), and also as a highly effective and rapid anticancer agent in vivo shortly thereafter (Ko et al. *Biochem Biophys Res Commun* 324:269–275, 2004), its efficacy as a potent anticancer agent in humans was demonstrated. Here, based on translational research, we report results of a case study in a young adult cancer patient with fibrolamellar hepatocellular carcinoma. Thus, a bench side discovery in the Department of Biological Chemistry at Johns Hopkins University, School of Medicine was taken effectively to bedside treatment at Johann Wolfgang Goethe University Frankfurt/Main Hospital, Germany. The results obtained hold promise for 3BP as a future cancer therapeutic without apparent cyto-toxicity when formulated properly.

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Keywords 3-bromopyruvate · Cancer · Liver cancer · Fibrolamellar carcinoma · Mitochondria · Warburg Effect · Hexokinase 2 · Positron Emission Tomography (PET)

Introduction

As depicted in Fig. 1, the alkylating agent 3BP covalently pyruvylates certain proteins generally at cysteine residues. The pyruvylated proteins, e.g., isocitrate lyase (Ko and McFadden 1990) and an aldolase (Meloche and Monti 1967) often lose their biological activity. The “hands on” discovery by coauthor YHK in the year 2000 of 3BP as a potent and specific anticancer agent, published in 2001 (Ko et al. 2001), was based on results of much previous work on cancer metabolism in the laboratory of the corresponding author (PLP) (Reviewed in Pedersen 1978; Pedersen 2007a; Pedersen 2007b; Mathupala et al. 2009; Mathupala et al. 2010), and on YHK’s prior graduate (M.S., Ph.D.) work in enzymology at Washington State University (Ko and McFadden 1990; Abeysinghe et al. 1991).

Assigned by coauthor PLP the role of identifying (discovering) an anticancer agent specifically targeted at energy metabolism, YHK knew that the essential criteria for success (Pedersen 2007a) were to find an agent that 1) leaves normal cells intact while 2) inhibiting both the most common biochemical phenotype of cancer cells, i.e., the “Warburg Effect”, elevated glycolysis even in the presence of oxygen (Warburg 1956), and also mitochondrial ATP production. Then, both energy (ATP) production factories (mitochondria and

glycolysis) of the cancer cells would be destroyed and normal cells would remain intact. After an extensive study of the literature, YHK selected only a few candidate compounds (<20) for the initial screen, and of these showed that only one, i.e., 3-bromopyruvate (3BP), met the two criteria noted above (Ko et al. 2001). Later YHK would lead a team of investigators in an effort to test 3BP’s capacity to cure rats bearing large solid tumors. Significantly and surprisingly, all the treated animals were cured, i.e., all tumors were eradicated (Ko et al. 2004). Moreover, eradication occurred quickly (<1 month). Thereafter, the animals lived out a normal life without return of cancer (Ko et al. 2004).

Significantly, 3BP as an “Energy Blocker” specific for cancer cells that exhibit a “Warburg Effect” is quite different in its action from most currently available chemo-drugs that frequently target either some aspect of nucleic acid metabolism or signal transduction pathways. Rather, 3BP, as noted above, targets a cancer cell’s energy metabolism, i.e., both glycolysis and mitochondrial oxidative phosphorylation (Ko et al. 2001). This inhibits total energy (ATP) production and depletes all energy reserves. This happens quickly (within minutes) and with little or no effect on most normal cells or the animals. In contrast, most commonly used anticancer agents take a longer period of time (weeks/months) to show a noticeable effect. Therefore, 3BP as a small molecule and covalent drug, is a very potent, rapid and quite specific anticancer agent (Reviewed in Mathupala et al. 2009, 2010).

Interestingly, and only very recently it was reported that many pipeline cancer drugs under study by major pharmaceutical companies are minimally effective (Jarvis 2011). Therefore, these companies are urgently looking for novel candidates to combine with their pipeline drug(s). In contrast to 3BP that targets cancer cells’ energy production factories (Ko et al. 2001), many of these pipeline drugs are based on targeting mTOR/ PI3K in cell signaling pathways (Jarvis 2011). Thus, the focus on signal transduction pathways for anticancer drug discovery may be waning. In addition, it was also reported (Guterman 2011) that a growing group of researchers from both academe and companies have initiated searches for covalent drug candidates. Clearly, the small molecule 3BP meets this specification as a promising anticancer agent as it is in fact a small molecule and it does bind covalently with efficacy and specificity to the active sites of certain enzymes (Staub and Denes 1967; Meloche and Monti 1967; Ko and McFadden 1990; Ko et al. 2001).

Significantly, much earlier work from the corresponding author’s laboratory (Bustamante and Pedersen 1977) reported that the “Warburg Effect” common to most cancers is due in large part to their overexpression of hexokinase 2 (HK2) that binds to the outer mitochondrial membrane. This likely helped lead in part to the most common imaging technique used today to detect cancer throughout the world, i.e., positron emission tomography (PET). Significantly,

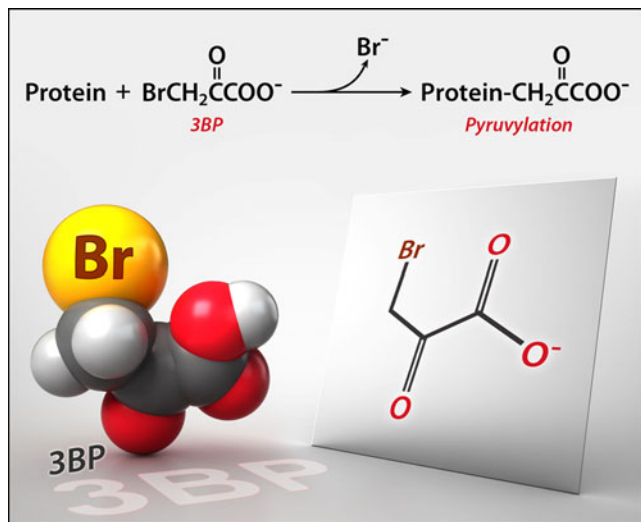
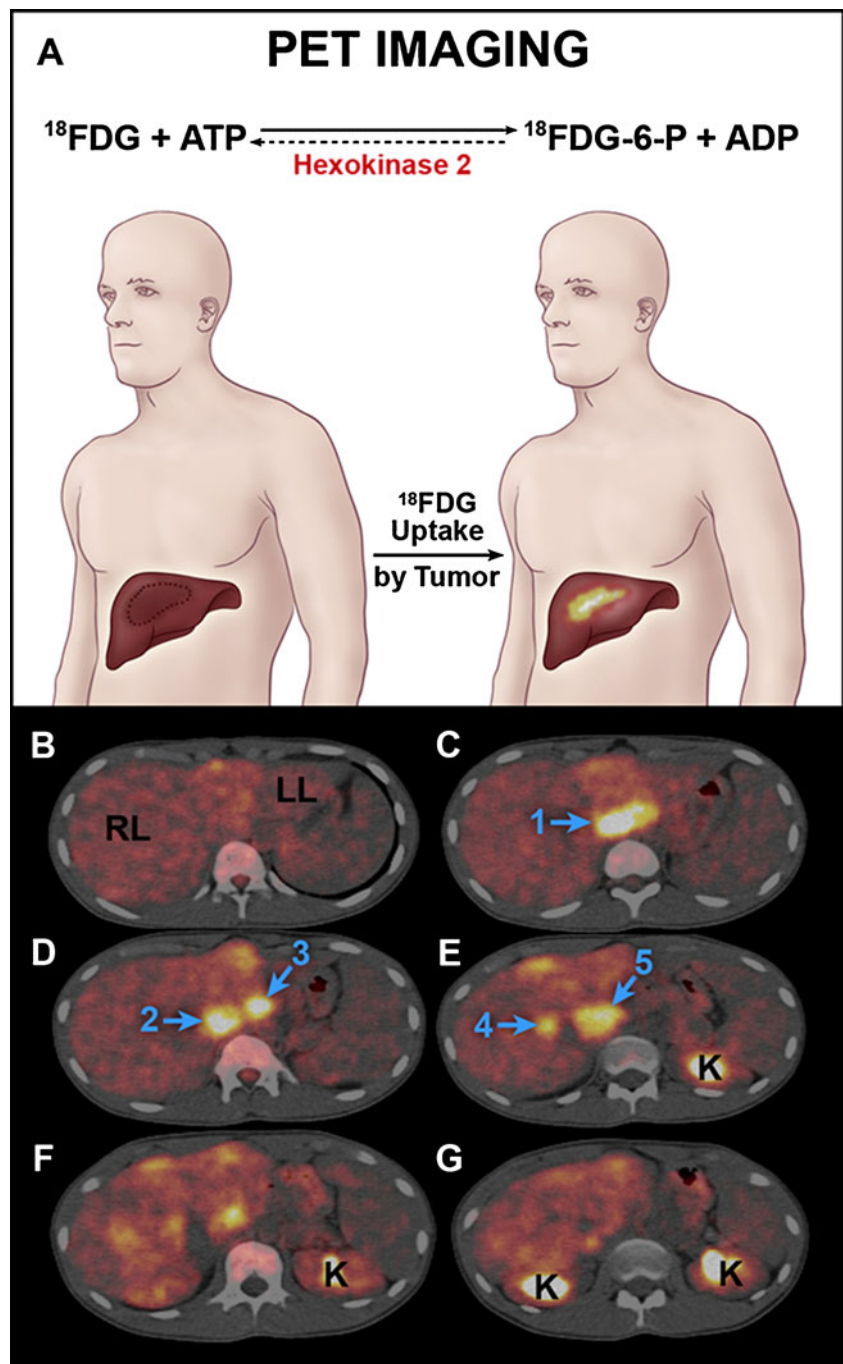


Fig. 1 Pyruvylation of Proteins with a Novel Small Anticancer Agent, 3-Bromopyruvate (3BP). 3BP, a small alkylating agent, pyruvylates proteins by releasing bromide ion (covalent modification). In general, the pyruvylation site on proteins is cysteine. Pyruvylated proteins often lose their biological functions resulting in cancer cell death. At the bottom of the reaction scheme, a space filling model of 3BP is reflected on the mirror as a skeletal formula structure ($\text{BrCH}_2\text{-CO-COO}^-$)

Fig. 2 Diagnosis of Cancer after Detection by PET Imaging. **a** Detection of cancer by Positron Emission Tomography (PET) imaging is based on highly overexpressed Hexokinase 2 (HK2) in cancers. PET imaging is used widely to detect cancers which consume glucose avidly. A glucose analogue, 2-fluoro-2-deoxy glucose (^{18}F FDG), is phosphorylated by hexokinase 2 at the 6th carbon with ATP to become 2-fluoro-2-deoxy glucose 6-phosphate (^{18}F FDG-6-P). Accumulation of the metabolically inactive ^{18}F FDG-6-P is detected by PET scanning imaging device and helps locate metabolically active cancers in the body. **b–g** Confirmation of presence of metabolically active cancers in the patient’s liver, bile duct, and lymph nodes based on PET scan imaging. Descending transverse axial plane views of the patient’s liver are shown after PET imaging (**b–g**). Abbreviations are: RL (right liver lobe), LL (left liver lobe), and K (kidneys). The highly metabolically active areas are indicated by blue arrows with numbers in **c, d, and e** 1 (bile duct area), 2–5 (lymph nodes). In addition, there are highly active focal regions in the right liver lobe as shown in **f**. The trace ^{18}F FDG is eliminated through the kidneys as evidenced by bright spots



detection of cancer by PET imaging is based on overexpression of mitochondrial bound HK2 (Fig. 2a). In this imaging method a labelled glucose analogue, 2- ^{18}F fluoro-2-deoxy glucose (^{18}F FDG), is phosphorylated by HK2 at the 6th carbon with ATP to become 2- ^{18}F fluoro-2-deoxy glucose 6-phosphate (^{18}F FDG-6-P). Such labelled FDG compounds were first developed by Ido and colleagues (Ido et al. 1978). Significantly, ^{18}F FDG-6-P is metabolically inactive and not further metabolized. Thus, its accumulation is detected by the PET scanning imaging and helps locate metabolically active (highly glycolytic) cancers.

Hence, it is suggested that PET scan positive cancer types may be benefited after treatment with a patented and proprietary formulation of 3BP. It is worth noting that unformulated 3BP may be harmful in some cases.

A case report

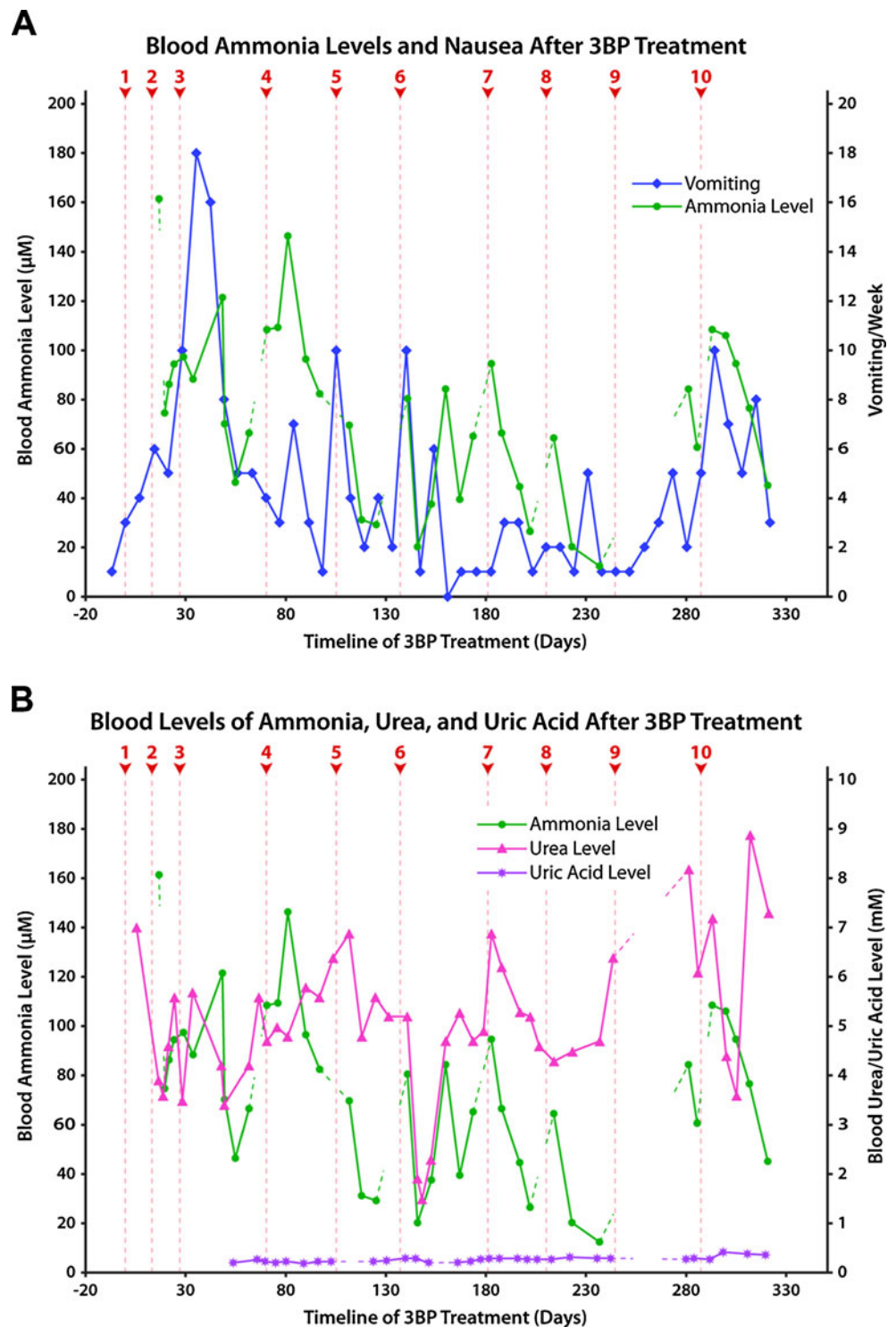
Herein, we present a 16-year-old Caucasian male with a palpable mass over the right upper quadrant of the abdomen. This patient was initially presented to the emergency

department of the Jeroen Bosch hospital in den Bosch, the Netherlands. His presenting symptom was abdominal pain localized to the spleen. His body temperature was 34.6°C at first presentation and his blood chemistry revealed high values of the liver enzymes alanine transaminase (ALT), aspartate transaminase (AST), and gamma glutamyl transpeptidase (GGT), indicating liver abnormality / damage. He was

hospitalized immediately and evaluated by Computed Tomography (CT), Magnetic Resonance Imaging (MRI), liver biopsy, echo imaging, and PET scanning. The PET scan suggested that the patient had very diffuse and metabolically active tumors in his liver (Fig. 2b and g). Indeed, all tests indicated primary liver cancer of the fibrolamellar carcinoma form (FLC). A second opinion was requested and provided by

Fig. 3 Monitoring Blood Ammonia, Nausea, Uric Acid, and Urea during 3BP

Treatments. **a** Blood Ammonia Levels (Left Axis) and Nausea (Right Axis) during 3BP Treatments. Each 3BP treatment is indicated at the top of the graph in red arrows and numbers. Nausea was determined as the number of vomiting episodes per week during the entire treatment period and is depicted in the blue graph. The greatest number of nauseous episodes was observed after the third treatment. This coincided with the patient's increased ill feeling. Similar spikes were noted directly following treatment 5 and 6, but with rapid recovery. These nauseous episodes gradually decreased, and the patient felt much better after about 20 weeks. Blood ammonia levels are indicated in the green graph. Interestingly, an increase of blood ammonia levels followed the second, third and fourth treatments and correlated with an increase in nauseous episodes. Then, blood ammonia levels and nauseous episodes began decreasing following subsequent 3BP treatments. **b** Comparison of Ammonia Levels with Urea and Uric acid Levels in Blood. Ammonia levels (green, left axis) were compared with both urea (pink, right axis) and uric acid (purple, right axis) levels in blood as a function of 3BP treatment time line. Note that during 3BP treatment ammonia levels fluctuated more than those of urea and uric acid



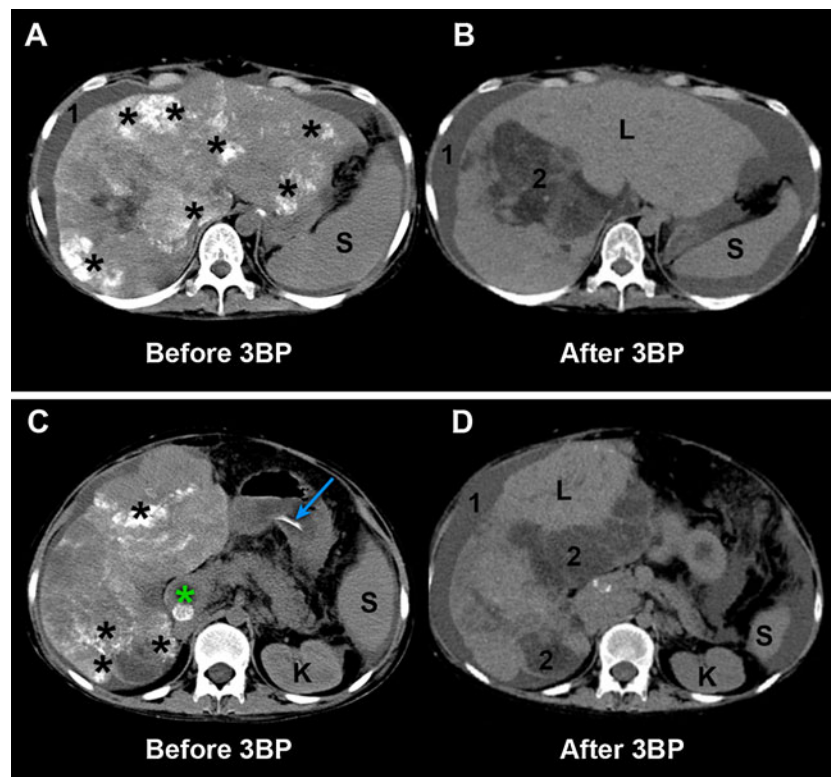


Fig. 4 Comparison of the CT images of the patient's abdominal area before and after 3BP Treatment. Selected pairs of transverse axial CT scans at identical positions in the abdomen immediately after treatment with two cytostatics (left images, considered as “before 3BP treatment”) and after the 9th treatment of 3BP (right images): In **a** Lipiodol® accumulations are indicated by black asterisks. They are dispersed throughout all sections of the liver (L), especially in the right lobe, indicating excellent localization and containment. Enlarged paramesenteric and coeliac lymph nodes are visualized in **c**, right under the green asterisk. The spleen (S) was enlarged due to complete blocking of the portal vein by a thrombus. This blocking was compensated by

formation of several arterial shunts (not presented in these images). After the 9th 3BP treatment, the images on the right were obtained. No Lipiodol® was used during 3BP treatment and subsequently no such signals are present in these images. Tumors had become necrotic (**b** and **d**) and encapsulated and showed fibrosis. Lymph nodes appeared stable in size and shape. The spleen size was drastically reduced. The ascites marked as “1” was evident before and after treatment. The blue arrow indicates the feeding tube present before 3BP treatment. After 3BP treatment, the patient was able to consume much more food and the feeding tube became unnecessary and removed

the Erasmus Medical Centre in Rotterdam, the Netherlands. It was confirmed that the abdominal pain was caused by a spleen infarct, induced by the pressure of the tumor on the blood vessels supplying the spleen. This resulted in splenic enlargement (Fig 4a and 4c) and some necrosis (Data not shown). The patient had no history of hepatitis and no positive tests for hepatitis.

There is no known treatment for FLC except transplantation, and the patient did not fulfill the requirements for this process due to the presence of tumor in the choleductus and spinal lymph nodes. Right after the diagnosis, Sorafenib had been approved for primary HCC patients as an orphan drug. Treatment with Sorafenib was started, varying the doses from 200, 400, to 800 mg/day. However, due to lack of experience with such young patients, the treatment outcome was carefully monitored and stopped according to the manufacturer's instruction when ALT and /or AST values exceeded the tolerable values. Initial results with Sorafenib were encouraging. Thus, tumor growth appeared to have halted during the first

2 months of Sorafenib application, even with some regression of tumor volume. However, after 6 months, CT scans indicated a renewed expansion of the tumor's mass, and Sorafenib treatment was halted. By now, the health condition of the patient had deteriorated, in fact, so far that he could not consume sufficient amounts of food to sustain life. On the basis of this condition, a duodenal feeding tube was installed and continuous (24 h) enteral feeding was started. The caloric intake was adjusted to 2000–3000 kCalories per day.

While the patient's health was deteriorating, a contact was established with research scientists (coauthors PLP and YHK) at the John's Hopkins University, School of Medicine (Year 2008) to learn about their promising experimental anticancer agent, 3BP. Other contacts were also made with TJV (coauthor) at the University of Frankfurt for the application of 3BP by a Transcatheter Arterial ChemoEmbolization (TACE) delivery method. Permission was obtained from the Ethics committee of the University of Frankfurt for the use of 3BP on this young male patient with FLC. The

patient's parents signed the necessary form of consent and the patient himself agreed to the treatment.

While waiting for the permission from the Ethics Commission and in view of his severe situation, it was decided that it would be essential to treat the patient as soon as possible with the currently approved cytostatics by TACE in order to halt the rapidly progressing tumor. Then, the first TACE was performed with Gemcitabine and Cisplatin on January 26, 2009. After delivery of these cytostatics, the blood vessels were blocked temporarily by EmboCept®. Then, the tumor locations were viewed immediately by infusion of Lipiodol® followed by a CT scan. Due to cyto-toxicity, this was the first and last use of these two chemo-drugs. Likewise, the use of Lipiodol® was not continued during 3BP treatment due to a possible interaction between Lipiodol® and 3BP. One month later, permission from the Ethics committee was obtained. The patient was treated immediately *via* TACE with specially formulated 3BP (patented and proprietary) twice on the first day of treatment (February 26, 2009), a total dose 250 mg. More clearly, the delivery was bolus, meaning a rapid push of the entire dose into the artery over just a few minutes. Therefore, the 3BP delivery can be called a 'Transcatheter Intra-Arterial Bolus Injection' followed by a brief embolization with EmboCept®. The patient did not experience any discomfort during the first treatment with 3BP. The only discomfort was caused by the fact that the second infusion took place one hour after the first, and the local anesthetic was becoming less effective. No other adverse effects were noted during the normal 4 h recovery period and the patient left the hospital at 6:00 pm. The patient felt very hungry and wished to go to dinner. It appeared that the treatment may have increased the patient's appetite. This was an initial sign and hope for relying less on the enteral feeding tube. Indeed, the 3BP treatment helped the patient consume sufficient calories.

Due to a large tumor burden at the presentation, it was determined to try to obtain a very high dosing with 3BP in the first treatment month. A second treatment was scheduled 2 weeks after the first, the third after 4 weeks. After the second application (128 mg), which went without any acute problems, the patient started to get disturbed. Four days later, the patient went into a hepatic coma and was hospitalized. Blood chemistry revealed an elevated level of AST and ALT, but not far beyond his usual levels. On the other hand, the blood ammonia level was about 120 μM (Fig. 3a and b, green graph), more than the maximum physiological levels for adults and children, 21–50 μM and 41–80 μM , respectively. The urea level was low (Fig. 3b, pink graph), an average of 5 mM, indicating a still functioning nitrogen detoxification of the liver and kidneys. Similarly, the blood uric acid remained constant at about 0.2 mM as depicted in Fig. 3b, purple graph. The normal ranges for blood urea nitrogen and uric acid are 2.1–7.1 mM and 0.2–0.5 mM, respectively.

The diagnosis was hepatic coma, which usually results in death. It was suspected that the patient was undergoing a potential tumor lysis syndrome (TLS) after three 3BP treatments. Without additional help from the hospital, the patient was allowed to leave the hospital by ambulance and transferred back home. After 4 h at home, he began to show signs of recovery, and by nightfall, he was completely back to baseline, with most of his mental capabilities functioning.

The recovery continued over the next day. The patient was able to consume food and have social interactions with his friends, without any memory of the comatic phase.

The treatment team, in close communication with the patient and his parents, and with their consent, decided to continue with the 3BP treatment as scheduled, with modifications in which the blood chemistry was carefully monitored. Especially, ammonia, urea, and potassium were added to the weekly schedule for monitoring. A medication for reducing blood ammonia in liver cancer patients, Hepamerz was prescribed (6000 mg/day) and used for the patient as needed, but always following application of 3BP.

Elevations of the patient's blood ammonia levels (left axis of Fig. 3a, green graph), were associated with nausea (right axis of Fig. 3a, blue graph). Urea (pink, right axis of Fig. 3b), and uric acid (purple, right axis of Fig. 3b) levels were followed during the entire 3BP treatments.

The ammonia levels following treatment rapidly rose and gradually went down during the following weeks. The nauseous episodes (defined here as "vomiting") preceded the rise in blood ammonia levels after each 3BP treatment. The greatest number of nauseous episodes was observed after the third treatment. This coincided with the patient's increased ill feeling. Similar spikes were noted directly following treatments 5 and 6, but with rapid recovery. These nauseous episodes gradually decreased, and the patient felt much better after about 140 days (Fig. 3a).

As indicated in Fig. 3b, ammonia levels fluctuated more than those of urea and uric acid during 3BP treatment. This is very interesting as FLC is eosinophilic which is indicative of a higher content of cellular protein than of nucleic acids. Therefore, it is suggested that the rise in blood ammonia following 3BP treatment was due to FLC cell death, releasing considerable amounts of cellular proteins. This elevation of blood ammonia may be characteristic of TLS of FLC as TLS is generally diagnosed by acute elevations of uric acid, potassium, and phosphorus in other cancers.

The effective killing of FLC by 3BP was more evident by comparing the CT images before (Fig. 4a and c) and after the 9th 3BP treatment (Fig. 4b and d). In Fig. 4a, Lipiodol® accumulation after TACE is indicated by black asterisks. They are dispersed throughout all sections of the liver (L), especially in the right lobe. The CT images depicted in Fig. 4b and d were obtained in the absence of Lipiodol®. Hence, these images do not show the bright signals. Pre 3BP

treatment enlarged paramesenteric and coeliac lymph nodes are visualized in Fig. 4c, right below the green asterisk. The pre 3BP treatment spleen (S) in Fig. 4a was enlarged due to complete blocking of the portal vein by a thrombus, when compared with the post 3BP treatment size of the spleen in Fig. 4b. Likewise, the spleen in Fig. 4c (pre-treatment) is much larger than that of Fig. 4d (post-treatment), documenting that the spleen size was drastically reduced after 3BP treatments. The portal vein thrombosis blockage was compensated by formation of several arterial shunts. Necrotic areas due to tumor death after 3BP treatment were evident as shown in Fig. 4b and d, and the tumor areas were encapsulated and showed fibrosis. Lymph nodes were stable in size and shape. Regeneration of liver tissue was also observed and the data are being analyzed for future publication.

The ascites as indicated as “1” in Fig. 4b and d were evident before and after treatment. The blue arrow indicates the feeding tube present before 3BP treatment. After 3BP treatment, the patient was able to consume much more food, so the feeding tube became unnecessary and was removed.



Fig. 5 Fighting against immortal cancer cells with immortal spirits of phoenix, Yvar Verhoeven, and 3-bromopyruvate (3BP). The photograph of the cancer patient (Yvar Verhoeven) in this Case Report was poised with a novel anticancer agent, 3-bromopyruvate (3BP) and his favorite legendary immortal bird, phoenix. The picture was taken on his 18th birthday, September 09, 2009 (09-09-09) at his home in the Netherlands, after his 7th treatment with 3BP. This was a very special day as he had been told that he would never make it to his 17th birthday. In the morning of this special day, the patient's parents were awakened with Yvar's "Happy Birthday" song hummed to himself. The silver necklace with a silver 3BP molecule as a space filling model on him was hand-made by his sister. The gold necklace with a copy of the cartouche of Tut Ankh Amen (rise of the 18th dynasty) was given to him by a relative of a deceased cancer patient. The immortal legendary bird, phoenix was very much favored by Yvar and the phoenix as depicted was tattooed on his upper arm at that time. It was his personal wish that immortal spirits of phoenix and himself will help win against the seemingly "immortal" cancer cells. Fight "immortality" of cancer cells with "immortal" spirits and 3BP

Pre existing ascites and edema continued to be a major problem for the patient, and despite daily exercise, his mobility continued to be limited. However, during the summer of 2009 he started to regain his physical strength and went out in his wheelchair regularly for a promenade. In addition, the patient celebrated his 18th birthday at his home surrounded by many friends and family members on September 9, 2009. The photo of the patient in Fig. 5 was taken on his birthday.

At the end of October 2009, a part of the discomforting ascites was removed by CT-guided puncture. About 1 l of ascites fluid was removed and sent to the pathology lab for cellular analysis. An outcome of an increased lymphocyte count with some mesothelial cells, but no malignant cells was obtained. This lack of tumor cells in the ascites suggested that the tumors in the liver were well encapsulated and dead. In December 2009 the edema and ascites were becoming more problematic. Liver functions were overloaded due to rapid destruction of the tumor cells resulting in the liver's inefficient detoxification. Despite regeneration of the healthy liver cells, this process apparently could not compensate adequately for the rapid destruction of tumor cells and could not detoxify the dead cancer cell debris fast enough. Consequently, the blood albumin levels were decreasing. The patient passed away 2 years after his first diagnosis due to an overload of liver function.

The patient (Fig. 5) was able to survive a much longer period than expected with an improved quality of life, which is clearly attributable to the treatment with 3BP.

Conclusions

- 1) 3BP is an inhibitor of cancers' two energy sources, glycolysis and oxidative phosphorylation *via* mitochondria. A patented and proprietary formulation of 3BP is safe at the concentrations (2–3.5 mg/kg body weight) employed for TACE delivery in humans. No major cyto-toxicities of this specially formulated 3BP have been observed. Please note that unformulated 3BP may be harmful in some cases.
- 2) Specially formulated 3BP is efficacious in killing fibro-lamellar hepatocellular carcinoma (FLC) tumor tissue.
- 3) Liver regeneration is not inhibited by 3BP treatment.
- 4) The rate of tumor necrosis due to 3BP treatment seems to exceed all known cytostatic drugs.
- 5) Careful monitoring of blood ammonia, uric acid, and urea levels is paramount during 3BP treatment.
- 6) The levels of albumin and bilirubins are also important parameters in assessing liver functions and in predicting a patient's survival during 3BP treatment.
- 7) In future clinical trials, earlier stage cancer patients with a lower tumor burden and positive PET scans may have

a much better outcome following treatment with specially formulated 3BP.

Acknowledgements Work reported here was supported in part by NIH grants CA 10951 and CA 08018 to PLP. YHK is very grateful to PLP's lab members, her Ph.D. thesis advisor, Dr. Bruce McFadden (Washington State University, Pullman, WA), Dr. André Goffeau (Université Catholique de Louvain, Louvain-la-Neuve, Belgium), Dr. Scott Mogel (Aalto Scientific, Ltd., Carlsbad, CA), Dr. Pam Meyer (Marbella, Spain), the honorable Judge Gregory Hopkins (Aurora, CO), Moshe Rogosnitzky (Adjuvant Medical Solutions, Telz Stone, Israel), Ilona McClintick (Baltimore, MD), and the Grow family (Murray, UT) who have been very supportive of her efforts to fight cancer. The authors are very grateful also to David Blum (JHU, Baltimore, MD) for his assistance with the artwork, Jos Kaldenhoven (Schijndel, the Netherlands) for photography and his expertise as a nurse, Dr. Dwight McKee (Life Plus International in Batesville, AR) and Dr. George Sack (JHU, Baltimore, MD) for carefully reading the Case Report and for helpful comments.

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