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# Reflections on a Case of Cholangiocarcinoma; View from the Patient's Side

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**Abstract**

A year of dealing with cholangiocarcinoma cancer and outcome of various medical treatments as well as the influence of medical culture in handling patients is described. In addition, a few recommendations are provided that may help alleviate some of the difficulties in the way of helping patients.

## Introduction

Cancer has become the dominant disease of our time not necessarily because the rate of cancers have increased but most likely because humanity has managed to fight back and drastically reduce all the other diseases like Ebola, measles, chicken pox, whooping cough, etc., that killed humans before cancer strikes them. In other words, if we don't die of any other diseases, our chance of being hit by a cancer is very high. In fact, in some regions of the world where these other diseases predominate, cancer is not the number one killer but the non-cancer diseases are. There is higher chance for genetic errors as we age.

Bile duct cancer or cholangiocarcinoma is one of the rare forms of cancer that hits 2,000 to 3,000 people in the US each year but very few survive from it. This is mainly because bile duct cancer is a quiet disease that is often accompanied with no pain, and when diagnosed, it has already metastasized. According to National Cancer Institute, bile duct cancer occurs mainly in people between the ages of 58 and 72 but its rate in people at younger ages is much lower [1]. The chance of survival from bile duct cancer depends on how advanced the cancer is at the time of its discovery. My wife who was a healthy and active individual, was diagnosed with Cholangiocarcinoma on August 2014 at the age of 61. Even though it appeared at the time of diagnosis that her cancer was only in the liver, she died less than one year later on July 29, 2015. Below, I describe the life changing stages that we as a family went through starting from her diagnosis until her death. At the end of the article, I share a few lessons that we have learned from this sad experience hoping that they can help save or extend other lives.

## The Diagnosis

Tests conducted two years before her cancer showed that my wife had stones in her gull bladder. In 2013, in a business trip to Canada, after a meal with her colleagues, she felt severe pain in her abdomen which upon examination by x-ray turned out to be due to gull stones. The incident though painful did not repeat and no treatments was performed. A year later, in a visit to her primary doctor at the advice of her brother who had experienced rupture of the gull bladder, my wife asked that her gull stones be removed. The doctor ordered an x-ray that showed the stones but also, a shadow which was visible in her liver. The doctor who did not take the shadowy object seriously referred my wife to surgeon to remove the stones. At the same time, our neighbor, a radiologist when saw the x-ray, expressed concern and emphasized that we examine the liver further by CT-SCAN and MRI. The scans confirmed the presence of a diffuse tumor like tissue in the liver which prompted a biopsy examination. The diffuse tissue in question was not well defined which posed challenge in taking the biopsy sample. The result of the biopsy showed aggressive bile duct cancer. Our lives from the moment of this diagnosis was turned upside down. Next step was to remove the tumor as soon as possible before it invades the other organs. I assured my wife that" We'll do whatever can be done and we'll take you wherever there is the best treatment. I promised her that I believed a new tool "immunotherapy" was going to cure her."

## Tumor Removal

Hearing the word "aggressive tumor" from the pathologist placed our minds into overdrive. With the help of our great family doctor, we proceeded to schedule the surgery as soon as possible. Our family doctor first referred us to Dr. M at Duke Cancer Center, but as soon as we walked in his office, Dr M started talking about "prognosis". As we were not prepared to hear the word, we walked out of his office and headed home. Our family doctor also contacted a surgeon, Dr. P at Hopkins who specialized in removing bile duct cancer. To prepare for the surgery, he also arranged for us to complete all the necessary tests including blood test, MRI, CT-SCAN, and PET- Scan before we left for Hopkins. Soon, we drove to Baltimore and stayed at the apartments inside the Hopkins campus. The next morning, my wife was examined and scheduled for liver resection in 10 days. The surgery (on September 19) removed about 70% of her liver along with 5 lymph nodes which tested positive though not enlarged. My wife started her rapid recovery by walking the next morning. She spent 5 days at the hospital and another 5 days in a relative's house near Baltimore before we headed back home. During the whole time, she was very upbeat and positive.

## Chemo-and Radiation Therapy

Following the surgery, my wife underwent chemotherapy followed by radiation therapy at Greensboro's Cone hospital. For chemotherapy, gemcitabine (Gemzar) and Cisplatin, the two old standards for bile duct cancer were used in conjunction with steroids. The steroid which was given to help her tolerate the dose caused weight gain mostly in her abdomen area. She also tolerated the radiation therapy which followed the chemo. During the chemo- and radiation therapy, my wife

continued her work at home. Every Tuesday, her coworkers brought their lunch to our house to share with her.

## Relapse of the Cancer

Following the surgery, we made two follow up visits to Hopkins within 5 months. During each visit, CT-SCAN and examination by Dr. P showed no sign of cancer. However, on the third visit, in June, 2015, cancer was detected, not in the liver where originally was, but in the peritoneum. The surgeon told us that he could no longer help us, thus we were left on our own to figure out what to do next. Given that the news meant death sentence for my wife, we were devastated but still felt that we had to do something. Among the options, immunotherapy through clinical trials sounded plausible. But in reality, we would consider any technique no matter how drastic. Thus, we even considered a procedure known as Sugar-Baker, named after its inventor in which patient's abdomen is packed with warm chemo for 90 minutes and then closed off. At the end, we decided to pursue immunotherapy trials.

## The Leg Pain

One month after we heard the news of the cancer's return, my wife's leg started hurting. In fact, she had been ignoring the pain for about a week, when I informed Dr. S, the oncologist. Dr. S immediately sent us to the local hospital emergency. There, after waiting about 7 hours in the waiting room and another three hours on the bed parked in the hallway, X-ray was taken which showed that the pain in her leg was due to a blood clot. She was given prescription Xarelto which she continued to take from then on.

## Immunotherapy

We left Hopkins after the news of the cancer's return and drove towards North Carolina. On the way, while still in DC area, I consulted with my wife about going to see Dr. Rosenberg at NCI. Using Tumor Infiltrating Lymphocytes, or TIL, Dr. Rosenberg's team had treated another Cholangiocarcinoma patient (Melinda Bachini) who had recovered.1,2 My wife agreed and we immediately turned towards NIH. Security at the gate was very tight, after searching the car and luggage, they allowed us in and we headed towards Building 10. With no prior appointment, no one in Building 10 would talk to us. Fortunately, my previous e-mail contacts with the Clinical Trial Coordinator came in handy and after about two hours of negotiations, the coordinator and Dr. Groh, a researcher in Dr. Rosenberg's lab took us in. A quick look at our CT-SCAN showed that the procedure used for Ms. Bachini' cholangiocarcinoma would not work for my wife because my wife's tumor was diffused and they needed a well-defined tumor. Fortunately, they had another clinical trial at NCI that suited my wife's tumor but to enroll, we had to come back in 10 days. When we went back, many tests (Leukopheresis, Pulmonary Function Tests, Arteriogram, HIV and others) were performed and we were sent back home again. As we waited for the NCI trial to begin, we (me, our three kids, and several friends) started looking for clinical trials. Contacted many clinics. One trial that looked promising was at MD Anderson Cancer Center which was testing the Novartis compound BJG398. Other options we explored included Ketruda from Merck, Nivolumab from BMS which is a PD1 inhibitor, Dabrafenib and trametinib and many other compounds but none had a clinical trial that we could enroll immediately. One immunotherapy technique that I had read about was chimeric antigen [2] receptor-engineered T cells [CART], which had been tested at University of Pennsylvania. However, they did not have any clinical trial that we could enroll. Many molecules have been designed to target specific proteins that are related to the patients 'neoplastic conditions. Because of their specificity, the treatments involving these molecules were personalized and the drugs tailored to each person's cancer. One doctor that we visited was Dr. Azad at Hopkins who focused on IDH1 mutation in her clinical trials. Others were Dr. M. at Duke and Dr. S. at UNC. Dr. Azad's trial required gene profiling. Dr. S of UNC did not offer any trial and her visit was counterproductive. She showed up 2.5 hours late for her appointment and when she did come, she appeared very inconsiderate and only shouted at my wife and lectured her that "you are going to die, and should not do anything". When I intervened and told her that we are planning to do immunotherapy, she replied "no, I would not do it." The conversation at the Chapel Hill clinic in fact brought my wife into a deep heart break. On the way back, hoping to change her mental state, we turned toward Duke hoping to enroll in Dr. M's clinical trial. It was late in the afternoon when we got there and everyone had already left. The best they could do was to schedule a visit with triage nurse for next Monday. However, after we returned home, we learned that the appointment with triage nurse had been changed to appointment with Dr. M, who had agreed to see us that Monday. Dr. M. also agreed to order the gene profiling. In addition to the above visits, we also made an appointment with Dr. Borad at Mayo Clinic for simultaneous targeting of all of my wife's mutations with drugs.

## Gene Profiling

One month had passed since we enrolled in the NCI clinical trial, we still had hopes that the NCI will call us and that their trial will come to fruition but we received a notice that my wife's tumor did not contain any of the three proteins that NCI was planning to target, so it was back to the drawing board again. We had known from the very beginning that we needed to profile her tumor genes. About 7 months earlier, at the time of surgery, I had asked Dr. P if we could use the liver sample taken from my wife for immunotherapy. He did not respond. Now, I asked Dr. M at Duke to order the gene profiling, he agreed and thus his friend Dr. S in Greensboro ordered the gene profiling. But, the pathologist in Greensboro had sent the leftover sample from the biopsy for profiling which produced unreliable results. After a month of waiting and making additional requests, the pathologist at Hopkins sent the resected liver which had been sitting in paraffin at Hopkins since surgery. The results showed 4 types of mutations all of which were targetable (actionable genomic variants) according to Dr. Borad of Mayo Clinic. This result created some hope. But before the official results came out, my son and daughter who could no longer wait took my wife to MD Anderson in Houston, Texas to enroll in a phase II clinical trial that tested the Novartis compound, BJG398. Dr. Borad at Mayo Clinic who was eager to target all of my wife's mutations in Arizona was to wait until MD Anderson trial was completed.

## Last Stop

At MD Anderson, doctors first removed about one gallon of fluid that had filled the peritoneum cavity of my wife and had gone unnoticed in Greensboro. Following initial tests, my wife was given a few doses of the BJG398 drug (Phase II trial). However, her internal bleeding went uncontrolled and a blood clot had entered her lung. At the end, the complications resulting from this combination took my wife into a serious condition and she passed away on July 29, 2015 at about 7:30 PM from the complications of pulmonary embolism [3].

She did not benefit from the immunotherapy that was sure to save her life.

## Lessons of this Experience

If gene profiling had been ordered immediately after the tissue removal at Hopkins, then, the results of the gene profiling would be available for immunotherapy as soon as it was needed. As immunotherapy becomes a viable option, order the gene profiling as soon as tissue is removed from the patient.

If the surgeon and the immunotherapist (both in the same campus) were in contact and had communications with each other and referred patients to each other, then, valuable time would not be lost in finding and connecting the expertise. Communicate all available options to the patient. Refer the patient to other experts, especially if such options are readily available locally.

If it is known that the old chemo- and radiation therapies are not effective against cholangiocarcinoma or other cancers, patient should not be subjected to their severe side effects. Do not waste valuable time, money, and patient's hope on old technologies that are known to fail.

If all clinical trials are coordinated and paid for by a government agency, so much efforts and time is not wasted searching for relevant clinical trials, especially at a time when patient and her close relatives are already stressed out and exhausted. Create a central location for coordinating all clinical trials so that the information about them is readily available and their enrollment is easy, straightforward, and automatic.

This concern may be addressed through the creation of TAPUR, Targeted Agent and Profiling Utilization Registry Study.

Starting March 2016, there will be a comprehensive clinical trial that will test cancer immunotherapy [4] drugs at no cost to patients. This study which is called Targeted Agent and Profiling Utilization Registry Study (TAPUR) is a non-randomized clinical study, is for patients who have advanced cancer that does not respond to conventional therapy but have genomic variant that can be targeted. Patient are followed for the effects, and safety and efficacy.

Since it is known that Xarelto causes internal bleeding, more stringent monitoring is needed to assure patient safety. Monitor patients closely if they are suspected of having internal bleeding.

Even though medicine is a technical profession, doctors are dealing with people. An ounce of compassion can go a long way in helping the patients who have already lost hope and are struggling. Shouting at and telling a patient that he or she is going to die will not have any benefit but to depress the whole family and the patient at a time when they need uplifting. In other cultures, if a doctor detects that a patient appears ready to die, only close relatives are gently informed and not the patient! If you cannot help the patient, please do not hurt him/her by repeatedly telling them that they are going to die and thus destroy any residual hope that they may have gathered between visiting the previous doctor and you.

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