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COMMENTARY

Living with Advanced Kidney Cancer and Treatment with Cabozantinib: Through the Eyes of the Patient and the Physician

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ABSTRACT

This article is co-authored by a patient with advanced renal cell carcinoma and his treating oncologist. The patient relates his personal experiences in struggling with cancer, including physical limitations, but also details his psychological, existential and spiritual distress through the cancer journey. The patient shares a proactive approach to the most common side effects of therapy. The professional reflects on the rapid development of new therapy options; the implications for clinical practice by the management of long-tem therapy; how to deal with patient expectations; and the management of patient distress as an integrated part of the contemporary approach for treating kidney cancer.

Keywords: Cabozantinib; Distress; Renal cell carcinoma

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THE PATIENT'S EXPERIENCE

> "Nobody can go back in time to start a new beginning, but anyone can start today to make a new ending." [1]

Five years ago, I turned 55 years old and was diagnosed with kidney cancer. I had my left kidney removed due to the cancer. The tumor was the size of a fist. After the surgery, I received the good news that all cancer had been removed and that I had tested free from cancer. However, because the characteristics of the cancer were aggressive, I was told that there was more than a 50% risk of relapse. Therefore, I was offered the opportunity to participate in an adjuvant clinical trial that was designed to prevent relapses.

I accepted the offer to take part in the adjuvant clinical trial. The therapy provided in the trial resulted in the development of toxicity, and so I began a process of learning how to cope with the side effects of this toxicity. Unfortunately, after about 9 months on therapy, I had a relapse of the cancer. After the relapse, I started on a new medicine. However, after approximately 9 months on the new treatment, it was found that the cancerous nodules had begun to grow quickly in size. So I had surgery to remove the cancer in my abdomen. The surgery was successful, and this gave me hope. I therefore had one more operation to remove the cancer in my lung, which also proved successful in removing the cancer.

I was declared cancer free once again. It felt great. I was relieved and could breathe easily again. Throughout the whole process, I had hoped along with my spouse, family and friends that this joyful moment would finally come. Now it was here—HURRAY.

However, this feeling of joy and ease of life lasted only 6 weeks. After the first scan it appeared that the cancer was back. This time in my abdomen and a new lesion in the right kidney, which was the only one I had left. It was a hard blow to take! Just as quickly as there had been a promise of life, and the future looked bright, the hope of being cured from cancer was shattered. I had thought for a while that I had control over the future. However, this unfortunate news triggered a crisis and a deep fear of how the course of illness would now affect my future, as well as that of my wife and family. The crisis I now found myself in triggered a period in which I had to reassess my life, as I was not sure that I would live another year. I spent 2 days in my garage. I had a huge urge to clean up and throw out things I no longer needed. My wife and I went for a long walk along the beach on the Danish west coast to feel the wind blow in our hair and to feel the salty air on our faces. I thought it would be the last chance I had to say goodbye to nature. I also have a motorcycle and I was ready to sell it in the fall. I therefore went on a long farewell journey with it to say goodbye, as I did not expect to live beyond the next spring.

I realized that I was fragile, and I did not have any control over my life. I felt powerless. Dying was not something I had ever considered. Nevertheless, it was now a reality of my life. It is a frightening experience to feel that you have no power to affect change in the process that is destroying your life. The only thing that I could control was my faith. I found comfort for my suffering and powerlessness through my faith in God. From the biblical stories I read, I saw God could be closest to me in times of deep suffering. The knowledge made it possible for me to face the horrific reality I was personally facing in my life—without allowing that reality to destroy me. I also knew that this truth had made it possible for others before me to find comfort when feeling powerless—without becoming hopeless. When all hope seemed lost and all possibilities had been exhausted, the account of the crucified and risen Christ put me in a completely different frame of mind, one in which I could see life and its possibilities as being constantly renewed. The suffering was not removed from my life. The chaos did not disappear like dew from the morning sun. However, I was now able to find peace no matter whether the future was life or death. I was able to experience my challenges with suffering and the prospect of death through the lens of my faith in God.

At the time of writing I have been taking cabozantinib for the last 3 years. Below is a description of the side effects caused by this medication which I have been experiencing daily. For the purpose of simplicity, I describe only the main side effects that I have been dealing with on a daily basis, together with the lessons I have learnt during the course of the treatment.

Mucus: I have had problems with irritated mucous membranes in the nose, mouth, throat and eyes as well as in the anal region. Therefore, I have received appropriate medication to reduce these side effects, such as Vaseline to lubricate the nasal passage and viscous eye drops to lubricate the eyes, as needed.

Diarrhea: Throughout the treatment, I have received loperamide tablets, plant fibers (FiberHUSK) and lactic acid bacteria to alleviate diarrhea. At times, the diarrhea was so overwhelming that I went to a nutritionist to learn about alternative dietary options to prevent it. I received a diet plan that included cooked vegetables to be served with chicken or fish—and was told to avoid cabbage. In addition to the diet, the nutritionist recommended I take two capsules of slippery elm, which help to restore the mucous membranes in the stomach and intestines. The diet changes were effective; before these changes I could easily take up to eight loperamide tablets a day, and now I only need three, and have far better stool control.

Pain in my feet: I had never had to care for my feet before I received the cancer diagnosis. They could always accompany me, wherever

and whenever I wanted, without an issue. Now this has changed. I need to moisturize my feet with cream every morning and evening, using a special foam cream designed for people with diabetes. I drink Oil of Life to soften the skin lesions under my feet. I take a footbath once a week where I remove hard skin, and I have a regular appointment with a foot care specialist every 4 weeks so that the hard skin can be removed.

When taking 60 mg cabozantinib a day, I regularly need to take a break from the treatment for 1 or 2 days, as an overdose builds up, and the pain in my feet becomes worse. The break needs to be timed well; if I take the break too late, my feet are so painful that I feel the pain in every step I take. I then make myself a promise that the next time I will take a break a little earlier. However, it is very difficult to time the break, and the pain can suddenly reappear without warning. In the past 6 months, it has been necessary to intermittently take a total of 18 days off medication to reduce the pain in my feet.

Muscle pain and fatigue: I find it difficult to prevent the muscle pain and fatigue, and consequently experience many daily restrictions. For example, I can no longer go for long walks like I used to, due to the pain in my feet, and I can only ride my bicycle for a very limited distance, due to the muscle pain.

Over the last 5 years, I have had to make some difficult lifestyle choices. Just 1 year ago, I realized that I no longer had the physical capacity to work full time. I therefore reduced my working week to 32 h and now only work 4 days a week. Nine years ago, my wife and I built our dream house. Due to my reduced capacity, we also arrived at the very difficult decision to sell the house, as I could not manage to maintain such a large house and garden. Although at the time we felt it was too early to sell our beautiful house, now that it has been sold and we have moved into a townhouse, it has proven to be the right choice for us.

I still have my motorcycle. For many years, I have dreamed of going on a long motorbike ride around Norway. In August this year, I took an 11-day trip and drove 2700 km in Norway on my bike (Fig. 1). As I could not keep on my special diet while on my road trip, I proactively increased the loperamide intake to have regular bowel movements. I did not need to take painkillers; I believe that all the curves on the Norwegian roads released so many endorphins in my body while I was riding the motorcycle that I did not need pain medication. I feel that, despite the cancer diagnosis and treatment with cabozantinib, there has still been room for a good quality of life. The treatment course I have been on is not something I could have done alone; I am very grateful to the support and encouragement given by my wife throughout the treatment process, even though it has sometimes been difficult for her. I am grateful to family, friends, work colleagues and the health professionals who have also supported me. They have all, in their own ways, helped me to live a productive daily life, despite my limitations.

THE PHYSICIAN'S PERSPECTIVE

Until recently, the outcome for patients with kidney cancer was dismal. Fifty years ago, at the time Robson introduced the standard for radical nephrectomy in localized kidney cancer [2], the 5-year overall survival rate for kidney cancer was approximately 20% [3]. This poor figure was a reflection of the few early warning signs of localized cancer, with the classical triad of pain, hematuria and flank mass seen in only 10% of patients; consequently, the majority of patients presented with symptoms from distant metastases. With the development and widespread application of computer tomography (CT) technology [4], the current standard is the diagnosis of an asymptomatic localized kidney cancer as an incidental finding in approximately 70% of patients [5]. Improved surgical procedures, with laparoscopic nephrectomy, laparoscopic partial nephrectomy, robotic assisted (partial) nephrectomy and ablative techniques, have enhanced outcomes, with nephron-sparing techniques often used for small renal masses. Survival has increased as a consequence of stage migration and improved surgery, and the contemporary benchmark is a 5-year overall survival rate of 70% for patients with kidney cancer [5].

Fig. 1 A dream became reality. Open space in mountain-rich Norway, traveling 2700 km on a bike. The picture depicts a view of the Geiranger inlet, western Norway. The patient with metastatic renal cell carcinoma was taking cabozantinib 60 mg daily

The history of medical therapy for advanced or metastatic renal cell carcinoma (mRCC) includes many frustrating years for patients, families and physicians, as kidney cancer is resistant to chemotherapy and conventional radiotherapy, rendering no therapy options for patients with metastatic disease until 30 years ago when in the 1980s cytokine therapy with interferon and interleukin-2 were introduced. Interferon therapy resulted in a modest 3-month survival improvement, while treatment with interleukin-2 resulted in complete response and potential cure in 5–7% of patients, although toxicity hindered the widespread use of this drug [6]. In essence, therapy enabling the immune system to be released to fight cancer was established in mRCC. Within the last 10 years, immunotherapy has been taken to the next level with the introduction and approval of checkpoint inhibitors, i.e. antibodies targeting the CTLA-4, PD-1 and PD-L1 inhibitory receptors on T-cells or tumor cells [7, 8].

The genetic basis for the origin of clear cell renal cell cancer was identified in 1993 [9]. Mutation in the von Hippel–Lindau tumor suppressor gene, located on chromosome 3, leads to a pseudo-hypoxic state, with no feedback regulation. Consequently, the normal renal cell becomes a renal cancer cell in a process in which the accumulation of hypoxia-inducible factors (HIFs) in the cell leads to the production of vast amounts of vascular endothelial growth factors (VEGF), resulting in excess angiogenesis. Within the last 12 years, our understanding of this critical process has resulted in regulatory authorities approving VEGF-targeted antibodies or tyrosine kinase inhibitors (TKI) and mammalian target of rapamycin (mTOR) inhibitors, including sunitinib, sorafenib, pazopanib, axitinib, bevacizumab, everolimus, temsirolimus, lenvatinib and cabozantinib [10].

However, chronic inhibition of VEGF ultimately leads to resistance and treatment failure. Data have shown upregulation of the receptor tyrosine kinases MET and AXL after chronic treatment with VEGF inhibitors [11]. Cabozantinib is an oral inhibitor of VEGF, MET and AXL. Preliminary results in a phase 1 study suggest that cabozantinib is able to overcome the mechanisms of resistance to antiangiogenic therapy [12]. A confirmatory, randomized, open-label, phase III trial (METEOR) of cabozantinib versus everolimus in clear cell

mRCC with progressive disease after treatment with prior VEGF TKI has been completed [13]. The median progression-free survival in that study was almost doubled with cabozantinib versus everolimus (7.4 vs. 3.8 months, respectively), the objective response rate was 21 versus 5%, respectively, and overall survival was improved by almost 5 months (21.4 vs. 16.5 months, respectively) [14]. This is the first and only study to date in patients with mRCC showing significantly improvement in all three efficacy endpoints compared with the standard comparator. Other intriguing data have emerged from a phase II study on combined treatment with lenvatinib, a multiple TKI targeting VEGF and fibroblast TKIs, and everolimus [15]. In essence, the history of medical treatment options for mRCC has changed from not to hot: no other cancer has seen such large amount of new treatment options within a 10-year period that have received the approval of regulatory authorities, changed clinical practice and extended the outcome for patients [16].

The story of the patient who co-authored this article is a story of the advent of new treatment options in kidney cancer. The patient had a left-sided nephrectomy in 2012. Histopathology showed 8 cm clear cell RCC, Fuhrman grade 3, with areas of necrosis, clear margins and negative lymph nodes; thus, stage pT3apN0. Due to the high risk of recurrence, the patient was included in an adjuvant trial of pazopanib versus placebo (PROTECT) [17]. Unfortunately, after 9 months of treatment, the patient had biopsy-proven recurrence in the lung and retroperitoneal lymph nodes in 2013. Unblinding showed treatment with adjuvant pazopanib. According to the Memorial Sloan Kettering Cancer Center (MSKCC) [18] and International Metastatic renal cell carcinoma Database Consortium (IMDC) [19] criteria, the patient had favorable prognosis. However, after only 9 months of therapy with sunitinib 50 mg daily (4 weeks on, followed by 2 weeks off), the patient showed disease progression with a $>$ 20% enlargement of retroperitoneal lymph nodes. The patient then underwent metastasectomy of both retroperitoneal lymph nodes and the lung metastasis. Histopathology of all lesions showed clear cell RCC with clear margins. As all metastatic lesions were resected, the patient stopped systemic therapy and was subject to control alone. Unfortunately, after only 2 months off therapy, repeat CT showed recurrence in retroperitoneal lymph nodes and a new lesion in the right kidney. The patient was then enrolled in the METEOR study and received cabozantinib for 3 years. In November 2017, a new lesion appeared in the pancreas. A biopsy showed clear cell RCC, and therapy was changed to nivolumab.

The story of this patient provides insights of a qualitative nature for living with mRCC. Recent progress in our understanding of RCC biology and treatment options have all been applied in the case of this patient. The role of metastasectomy after commencement of systemic therapy is still unclear [20]. As clearly illustrated by the patient, chronic therapy leads to chronic toxicity. Therefore, patient education to handle toxicity and a proactive approach are key for successful therapy. Most side effects appear in a cyclic fashion, and thus it is imperative to take a treatment break for 1 or 2 days to avoid the build up of an overdose to unwanted toxicity; however, many patients have difficulty in recognizing the need for such treatment breaks and actually taking them. When cancer is approached as a chronic disease, the relationship between the medical oncologist team and the patient changes into collaboration that lasts over many years. Moreover, the implications for clinical practice by the management of long-tem therapy and its toxicities have been considerable. Clinical practice has adapted to accommodate these needs by increasingly incorporating clinical nurse specialists and a telephone hot-line into their management strategy and by improving the involvement of the general practitioner and community care in the multidisciplinary care of the patient. Thereby, few medical oncologists can oversee the treatment of large numbers of mRCC patients in the few high-volume centers. Notable, clinical practice also includes the integration of one or several clinical trials in a contemporary treatment course of a patient.

A special learning point is how to deal with patient expectations. With new drug releases

almost annually, patient expectations increase; but most patients only receive two or three different therapies before deterioration [21, 22]. The patient's expectations of cure, both at the time of nephrectomy and metastasectomy, is illustrative as despite what the patient was actually told, or has understood, the issue of how we manage patient expectations is raised. Hope is part of human nature, but hope can be adjusted according to new circumstances. For the patient undertaking a cancer journey, it is the medical oncologist's noble task to serve as a travel guide, to translate new disease status information, modified according to patient level, and thereby calibrate patient expectations.

It is essential that hospital staff understand and address patient distress with the aim of optimizing care and quality of life throughout the years. According to the National Comprehensive Cancer Network, distress is a multifactorial unpleasant experience of a psychological, social, spiritual and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment [23]. As effectively illustrated by the patient in his story, repeated episodes of distress can be expected in the cancer journey. The case reported here is the first documentation of a patient with mRCC that existential and spiritual beliefs affect how the patient lives and copes with the disease, enabling peace of mind and providing ways to handle the fear of death. With the extended lifespan of patients due to improved therapies, psycho-oncology and distress management to improve quality of life will become an integrated part of cancer care in mRCC.

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