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Conservative Laparoscopic Surgery Plus Mifepristone for Treating Multifocal Renal Cell Carcinoma

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ABSTRACT

Cardiovascular complications of hemodialysis leading to shortened life spans, has led to the modern trend of recommending conservative laparoscopic surgery rather than bilateral nephrectomy for multifocal bilateral renal carcinoma. However, following repeated surgery for lesions reaching >3cm, eventually leads to renal failure, and hemodialysis will still be needed. By suppressing the immunomodulatory protein, called the progesterone induced blocking factor (PIBF), the progesterone receptor modulator mifepristone has been found to inhibit further metastatic spread of a variety of advanced cancers, leading to improved longevity and quality of life. To test a hypothesis that treatment with mifepristone can prevent growth of smaller multifocal renal cell carcinoma lesions to the point of requiring more surgery, after initial renal sparing surgery, a 58 year old man with multifocal renal cell carcinoma was prescribed 200mg daily oral mifepristone following laparoscopic removal of a large lesion in the right kidney, but not removing 3 smaller lesions in the left kidney. After 10 years of mifepristone treatment, the 3 left kidney lesions remained stable, and no new lesions appeared. Unfortunately, his diabetes caused renal failure, and bilateral nephrectomy was performed, followed by short term hemodialysis. Related to his lack of progression of his cancer, he was approved for kidney transplant. He is alive and well 17 years from original diagnosis, with no evidence of metastases from his renal cell carcinoma. Hopefully, this case will create an interest in a clinical trial of mifepristone, plus renal sparing surgery for multifocal kidney cancer to help determine if this man's apparent response to mifepristone was the exception or the rule.

Keywords

Bilateral renal cell carcinoma, Mifepristone, Nephron sparing surgery, Progesterone induced blocking factor, Progesterone receptor modulator.

Introduction

Renal cell carcinoma is the third most common genitourinary malignancy [1]. About 5% of patients with renal cell carcinoma will have bilateral renal tumors, with, or without, known hereditary renal cell cancer syndromes [2,3]. Most cases do not have a known genetic basis [3].

There are studies suggesting that there is a significantly higher rate of local recurrence in patients with the non-hereditary form of bilateral renal cell carcinoma compared to those patients with unilateral tumors [4]. Thus, patients with bilateral renal cell carcinoma are considered to have a shorter chance for long-term survival compared to patients with unilateral cancer [4].

The most recommended treatment for unilateral renal cell carcinoma is a radical nephrectomy of the affected kidney. Though bilateral radical nephrectomy has been, in prior years, the most commonly suggested treatment to prevent local recurrences and distant metastases for multifocal, bilateral renal cell carcinoma, consideration of surgical procedures that spare some renal function, i.e., partial nephrectomy, have been suggested as a possible alternative therapy [5,6].

This change in strategy, resulted from the realization that patients undergoing long-term dialysis are 10 to 30 times more likely to

die from cardiovascular disease than the general population [7,8]. Furthermore, hemodialysis is extremely expensive [9]. Though kidney transplantation may be a more reasonable option, there are still many drawbacks, e.g., availability, requirement of a 2-year cancer free interval, transplantation failure, and cost [10,11].

One alternative option for patients with bilateral renal cell carcinoma would be radio frequency ablation, if the tumors are small [12,13]. However, radio frequency ablation would not be suitable for larger tumors, tumors in close proximity to renal vessels or collecting system, or the ureter [14]. Furthermore, new lesions in a kidney previously treated with ablation, may not be safe to perform additional ablation related to the development of adhesions to surrounding viscera [14,15].

Renal sparing surgery (or sometimes called nephron sparing surgery) with partial nephrectomy seems to be the more preferable surgical technique in modern times amongst the experts in renal cancer [14]. However, these experts admit that this type of surgery is technically demanding and is associated with higher rates of peri-operative complications. Bratslavsky and Linehan also state that patients with bilateral renal cell carcinoma having nephron sparing surgery, related to its multifocal nature, are very likely to have locally recurrent disease [14].

Lowrance et al., also agree that repeat partial nephrectomies may be difficult related to adhesions and obliteration of normal anatomic places [15]. There is a high intra-operative complication rate of ~35% [16]. To prevent kidney damage, yet prevent spread of advancing cancer, one of the tenets of renal sparing surgery is to treat with careful vigilance and benign neglect by not performing surgery unless the kidney lesion reaches 3cm [17,18].

The ideal therapy would be to remove the larger lesions and treat with some type of medical therapy to prevent smaller lesions from reaching 3cm, thus preventing further surgical intervention. A case is presented, here, suggesting that post-operative treatment with a progesterone receptor modulator may be a medical treatment option to prevent smaller tumors from increasing in size, and thus sparing further surgery.

Case Report

A 58-year-old man presented with bilateral renal cell carcinoma not of the hereditary types. He had a tumor in the right kidney measuring 5.5cm and 3 lesions in the left kidney measuring 1.1cm, 1.7cm, and 2.1cm. There were metastases to the local lymph nodes on the right side.

The recommendation by the oncologic team was bilateral nephrectomy. The patient did not want to live his life on hemodialysis. Instead, he opted to have a laparoscopic right hemi-nephrectomy, and not perform surgery on the left kidney. As an alternative, he chose to be treated with single agent oral mifepristone tablets 200mg per day.

His 3 left kidney tumors remained stable for 10 years. Several years after his initial diagnosis, renal sparing surgery became more popular. Since no new lesions appeared, and the 3 lesions remained stable in the left kidney as evidenced by bi-annual computerized tomography, no further surgery was recommended. He had concomitant diabetes, which eventually caused him to go into kidney failure, and thus he had bilateral nephrectomy 10 years after initial diagnosis and was treated with hemo-dialysis. He continued mifepristone for one more year, and then stopped. He has had no side effects from taking the mifepristone.

After one year on dialysis, he was approved for, and had, a kidney transplant. He is now 17 years from his initial diagnosis. Despite immunosuppression for the kidney transplant, he has not developed any metastatic lesions or any new kidney lesions.

Though mifepristone was an approved drug already on the pharmaceutical market, it was required to obtain a compassionate use investigational new drug approval from the Food and Drug Administration for its use. The restricted use is based on the sensitivity to off-label use of a drug used to perform therapeutic abortions. It costs about $500 per month.

Discussion

Single agent mifepristone treatment has been used to provide an increased life span, and increased quality of life, in a large variety of different types of human cancers [19-27].

Because using mifepristone for cancer therapy is an off-label use, and at least the less expensive dosage of 200mg per day requires a compassionate use IND from the FDA, the drug has been mainly used for very advanced cancers that progressed despite standard therapy. The mechanism of action is likely related to inhibiting the cancer cells from producing a key intracytoplasmic protein, known as the progesterone induced blocking factor (PIBF), that seems critical for the cancer cells to escape cellular immune surveillance, similar to what is seen during pregnancy [28-30]. Thus, it is not surprising that a drug that can cause therapeutic abortions, has significant anti-cancer properties [31].

Though PIBF seems to be made by a variety of cancers, since its use was restricted to very advanced cancers, it is possible that PIBF could be made predominantly by stem cells, and thus, it may be beneficial only when the cancer cells reach a rapid proliferative state. The case described, here, is one of the unique opportunities to determine if mifepristone can be effective in less advanced slower growing cancers, to help prevent recurrence, or metastasis. Given the circumstances of avoiding the very serious condition of renal failure requiring hemo-dialysis, if bilateral radical nephrectomy had been performed, by resecting the largest lesion, but leaving 3 lesions behind, with no other chemotherapy or immunotherapy options at that time, the FDA granted a compassionate use IND for mifepristone for this case of bilateral multifocal renal cell carcinoma.

As frequently seen with mifepristone therapy, tumors do not necessarily disappear or shrink, but merely remain stable, as long

as the drug is continued [19-30]. Bilateral renal cell carcinoma is not considered advanced cancer with metastases to the contralateral kidney, but instead, a multi-focal disease that is more likely to lead to death by complications of eventual bilateral nephrectomy, or hemo-dialysis, or kidney transplant, rather than wide spread metastases [4,11,32-34].

Thus, based on the great outcome of the case described, one should consider as a possible treatment for bilateral or multifocal renal cell carcinomas, to perform renal sparing surgery on just the tumors >3cm, and to prescribe single agent oral mifepristone daily to maximize renal function by significantly delaying, or even preventing, second surgery, while at the same time inhibiting distant metastases and local tumor growth.

The response to mifepristone in this case could provide some food for thought to consider adding mifepristone immediately after surgery with no evidence of cancer spread to prevent recurrence or metastasis with other cancers.

The present case was described in a previous publication in 2016 [25]. Available donor kidneys for transplantation are in demand, and frequently patients with cancer are not considered candidates because they may develop metastatic disease, and thus not live as long as patients with other conditions leading to kidney failure. However, because the mifepristone allowed stable disease with no new kidney lesions or metastases, he was approved for kidney transplant.

To save about $500 per month for mifepristone, the patient chose (against our advice) to not continue on mifepristone shortly after his kidneys were removed. We were concerned that if there had been any metastatic lesions prior to the mifepristone, they may surface, especially since he would be taking drugs that may interfere with cancer immunosurveillance when taking immunosuppressives for kidney transplant. Thus, the importance of this further description of this case is to show that multi-focal renal cell carcinoma may remain local to the kidney, at least for a certain period of time, while taking this progesterone receptor antagonist, and thus kidney transplant may be successful. He has now completed 6 years cancer free following the kidney transplant while not taking mifepristone during this time.

This new manuscript, in contrast to the previous one in 2016, describes the benefits of renal sparing surgery and the risks of hemo-dialysis. This was not discussed at all in the previous case report. We would still recommend continuing mifepristone if eventual bilateral nephrectomy is performed, but for those patients who cannot afford $500 per month for mifepristone therapy, obtained by compassionate use, at least there is one case report precedent showing a disease-free state has occurred 6 years after cessation of this drug once bilateral nephrectomy was performed.

Mifepristone has also been found to provide palliation and increased longevity in other cancers including NSCLC positive for the epidermal growth factor receptor that progressed despite third generation tyrosine kinase inhibitors, pancreatic cancer, and fibrous osteogenic sarcoma [35-37].

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