Case Report

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Palliative Benefits of Treatment of Advanced Urothelial Cancer with A Progesterone Receptor Antagonist

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ABSTRACT

Background/Objective: Treatment with daily oral mifepristone, a progesterone receptor (PR) antagonist which blocks immunomodulatory proteins e.g., the progesterone induced blocking factor (PIBF) that require activation of membrane (m) PRs for its production has provided marked palliative benefits and extension of life in patients with a large variety of different types of very advanced cancer. This is the first case demonstrating palliation for urothelial cancer.

Case Presentation: Oral single agent mifepristone was prescribed to a 73-year-old male with advanced urothelial cancer who had no more treatment options who was suffering from severe back pain and marked weakness. Within four weeks of taking the mifepristone his back pain had markedly improved and he was gaining strength in his legs. His weakness had been exacerbated by a neuropathy side effect from bevacizumab. At six months, he remains markedly free of back pain and is no longer wheelchair confined but walking with a cane.

Discussion: Urothelial cancer can now be added to the long list of various types of end stage cancer that responds even when there are no more treatment options available other than hospice in patients with end stage cancer.

Conclusion: Since oncologists do not seem interested in treating end-stage patients with off-label treatment options that have been anecdotally proven to be highly effective, hopefully this case will encourage clinical endocrinologists to consider treatment of patients with advanced cancer with immunoendocrine therapy (endocrine drugs to stimulate endogenous anti-cancer cellular immune reactions) and to encourage scientists to help develop even more effective immunoendocrine drugs.

Keywords: Bladder Cancer; Mifepristone; Nuclear Progesterone Receptor; Membrane Progesterone Receptor; Progesterone Induced Blocking Factor; Progesterone Receptor Membrane Component 1 Protein

Introduction

Based on similarity between the fetal semi-allograft and malignant tumors, i.e., rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance, it was hypothesized that cancer may utilize the same mechanisms established for survival of the fetus to proliferate and metastasize [1] Since the presence of nuclear progesterone receptors (nPRs) in tumors e.g., breast, ovarian, endometrium, and prostate, are generally associated with a better prognosis, cancer cell line studies to determine if immunomodulatory proteins utilized by the fetal-placental unit are also made by various cancer cell lines to possibly escape immune surveillance was performed, but these cancer cell lines were chosen that were devoid of the nPR [2-6]. One of these immunomodulatory proteins called the progesterone induced blocking factor (PIBF) was found to be produced by various cancer cell lines devoid of the classical nPR [2,7]. Another P associated immunomodulatory protein that seems to play a role in cancer progression is the progesterone receptor membrane component-1 (PGRMC-1) protein [8-12].

The PR antagonist mifepristone was found to suppress both messenger RNA and the PIBF protein in several cancer lines and was found to improve both longevity and quality of life in controlled studies of murine spontaneous leukemia, and lung, prostate and testicular cancers [6,13-15]. This manuscript will review the experience with treating patients with end stage cancers of various types devoid of the nPR with oral mifepristone. There have been several anecdotal case reports demonstrating considerable palliative benefit and increase in longevity in patients considered to be within 6 months of death from metastatic cancer with mifepristone treatment. They all (with the exception of one) had been treated with various anti-cancer drugs, and they were either off of all of these anti-cancer medications, or they were still on one drug, but progressing despite this drug, when started on single daily oral mifepristone 200mg/day (majority) or 300mg/day (minority). The benefit was found in various different types of cancer including thymic epithelial cell cancer, transitional cell carcinoma of the renal pelvis, malignant fibrous histiocytoma, leiomyosarcoma, colon cancer, pancreatic cancer, glioblastoma multiforme grade IV, fibroblastic osteosarcoma, non-small cell lung cancer (NSCLC), small cell lung cancer, and breast cancer devoid of the classical nPR [16-27]. The present case report describes a man with advanced metastatic urothelial cancer who similarly responded to mifepristone when other treatments were no longer effective.

Case Presentation

A 73-year-old male with severe hip pain was diagnosed with advanced urothelial cancer (probably of bladder origin) by biopsy. His primary lesion was 11 cm and was considered inoperable. Chemotherapy decreased tumor size to 5 cm, but the pain, mainly in his back, never abated and got worse. In addition, he developed a bilateral painful neuropathy which caused marked weakness in his legs. The chemotherapy was stopped. Neither gabapentin nor pregabalin reduced the pain or improved muscle strength. At this point, he was only able to ambulate with a walker. The oncologist now treated him with bevacizumab. Not only did this therapy not improve his pain, but the muscle weakness in both legs intensified so he was now confined to a wheelchair. The oncologist claimed that there were no other treatment options other than high dosage narcotics for the pain. He was at this point writhing in so much pain that they recommended hospice to provide relief of suffering until death which they estimated should be about one month. He instead chose to try 200mg/day oral mifepristone. After five weeks of exclusive mifepristone therapy 200mg per day, he reported hardly any back pain at all during the 4th-5th week of treatment and was gaining more strength in his legs. He had one day of absolutely no pain at all, which was the first time in three years.

He is still alive and doing well after six months of single agent mifepristone. He has little or no pain. A CT scan after two months of treatment showed no further metastases and no increase in tumor size. In fact, there was evidence of tumor necrosis.

Discussion

Similar to the long list of different types of advanced cancers with no more treatment options in patients with advanced cancers within 6 months of probable death, advancing urothelial cancer is another cancer that can be added to the list of advanced cancers in which treatment with mifepristone provides marked palliative benefit and extension of a decent quality of life. As frequently seen in other patients described, the palliative benefits manifested as considerable reduction in pain, marked improvement in energy, and improved clarity of mind that seems to occur shortly after starting the drug without evidence of marked tumor regression as seen in this patient with urothelial cancer. One could hypothesize these immunomodulatory proteins, which seem to be important in cancer invasion of normal tissue and evasion of immune surveillance, may contribute to the severe symptoms of advanced cancer. Hopefully this case will demonstrate very significant longevity as seen in some of the cases described where instead of dying within 6 months, they lived or are still living 5 years later or more with good quality of life [20-22,25]. Some patients stopped the mifepristone or reduced the dosage because of financial issues [17,18].

Sometimes they stopped mifepristone at the advice of their oncologist because the primary lesion was starting to slowly grow again so they wanted to try a new experimental drug trial. In each instance stopping the drug was followed by rapid spread of the cancer and death in a short time [20,26]. The drug costs $1300 per month and we are hoping that lack of funds does not lead to this patient with urothelial cancer to stop his medication.

In high dosages, mifepristone suppresses both PIBF and PGRMC-1 in cancer cell line studies [6,28]. However, mifepristone is not a pure PR antagonist but a PR modulator. Thus, in lower dosages, similar to what would be achieved by the 200-300mg daily dosage, mifepristone stimulates (PIBF) [29]. Thus, one hypothesis to explain the most common scenario seen with mifepristone treatment of advanced cancers i.e., inhibition of metastatic spread of cancer, but sometimes slow growth of the primary lesion, is that PIBF is needed for metastasis whereas PGRMC-1 is more required for local growth.

Thus for endocrinological research, potential improved efficacy could be provided by developing a selective progesterone receptor modulator (SPRM) that suppresses both PIBF and PGRMC-1, or a SPRM that does not block the glucocorticoid receptor allowing higher dosages of the SPRM to be given, or develop a monoclonal antibody type of immunotherapy to block PGRMC-1 plus mifepristone to block PIBF, or use other drugs in addition to mifepristone to block PGRMC-1 e.g., AG205 [30,31]. Immunoendocrine treatment of advanced cancer can improve the dwindling number of patients seen by clinical endocrinologists. Experience has shown that at this stage of cancer oncologists are no longer interested in the patient's treatment and are prone to merely refer them to hospice. So far, every patient treated with mifepristone has demonstrated some significant palliative ben-

efit and, in some cases, marked extension of lifespan. Furthermore, directing research to developing a PR antagonist for treating cancer may open grants and studies for research endocrinologists [26,32,33].

Conflict of Interest

None of the authors have had any remuneration or funding from any pharmaceutical companies or have any patents for any drugs or research grants. All studies referred to in this manuscript where Drs. Check or Neumann or Diane Check were authors or co-authors were self-funded.

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Statement of Patient Consent

The 73-year-old patients described in this report signed consent that his care could be published. Off-label use of mifepristone was approved by a western IRB. All cases mentioned were also approved by the United States FDA. The present case was the first one without FDA approval since this is no longer necessary to obtain mifepristone.

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