Journal of Nursing & Patient Care

Review Article A SCITECHNOL JOURNAL

A New Treatment Modality for Palliative Care Oncologists-Progesterone Receptor Modulators for very Advanced Cancer

Jerome H Check*

Department of Oncology, Cooper Medical School of Rowan University, 401 Broadway, United States of America

***Corresponding Author:** Jerome H Check, Department of Oncology, Cooper Medical School of Rowan University, 401 Broadway, United States of America; E-mail: laurie@ccivf.com

Received date: 23 February, 2024, Manuscript No. JNPC-24-128078;

Editor assigned date: 26 February, 2024, PreQC No. JNPC-24-128078 (PQ);

Reviewed date: 14 March, 2024, QC No. JNPC-24-128078;

Revised date: 21 March, 2024, Manuscript No. JNPC-24-128078 (R);

Published date: 29 March, 2024, DOI: 10.4172/2573-4571.1000048

Abstract

In the last 15 years, there has been several presentations at national and international cancer meetings and multiple publications showing marked palliative benefits with significant extension of life in patients with very advanced cancers especially those where the cancer is devoid of the classical nuclear progesterone receptor by treating the patients with the progesterone receptor antagonist/modulator mifepristone. The target appears to be the immunomodulatory protein known as the Progesterone Induced Blocking Factor (PIBF). This drug is very well tolerated and given as a simple daily oral pill. Unfortunately, oncologists seem to be reluctant to treat even end stage patients with cancer with an off-label drug. Thus, when the patient's cancer has extensively metastasized, and there are no other treatment options, the patient is referred to hospice to relieve pain and suffering while the patient's family and friends pray for a quick death. This perspective/commentary will show that the use of mifepristone, and possibly even better progesterone receptor modulators that could be developed, is the proper next step before preparing for death so that the patient can still look forward to a functional extension of life without suffering. The hope lies in the palliative care group to hopefully substantiate the efficacy of the drug and thus revolutionize the treatment of end-stage cancer.

Keywords: Cancer treatment; Reproductive Endocrinology and Infertility (REI); Oncologists; Palliative oncologists

Introduction

I will begin this long commentary/perspective with very provocative statements. There is already a drug available in the pharmaceutical market that can, and usually does, stop the progression of advanced metastatic cancer. This drug may even cause complete or marked regression of existing lesions. This drug is effective even when all known chemo or immunotherapies have failed to halt progression. This drug can provide not only a significant extension of life by years, despite the very advanced state of the cancer being treated, but may provide marked palliative benefits, including relief of pain, better energy, and better breathing. It is very safe, and is usually free of side effects. Furthermore, treatment with this drug does not require careful follow-up related to lack of hematological, renal, hepatic or cardiac side effects. Finally, it seems to be effective for all types of cancer.

I will continue with another provocative statement, this drug should be administered by palliative care specialists or palliative oncologists rather than traditional medical oncologists. I have reached the ripe old age of 77 and my present and only position at Cooper Medical School of Rowan University is as a professor of obstetrics-gynecology and division head of reproductive endocrinology and infertility, which I have held for 35 years.

So, some of the readers may at this point decide to stop reading right here, thinking why should I listen to a "senior citizen" about a significant treatment for cancer when he is neither an oncologist nor a palliative/hospice physician. It is my hope that those physicians, nurses, scientists, and other healthcare workers who read the entire lengthy (unfortunately) editorial will not only be convinced of the efficacy of this drug, but also agree that the most appropriate physician to prescribe this drug for cancer are palliative care/hospice physicians.

To hopefully enhance the credibility factor, I will briefly state some facts about my background. I was in a special program in college and medical school where I not only designed my own cancer research studies, but I had my own laboratory. Though while in college I did all the experimentation, in medical school, after acquiring funding from the National Cancer Institute, I had the aid of three research assistants who I trained. My focus was to try to make autologous tumor vaccines to treat spontaneous murine cancers by attempting to make their tumor cells more immunogenic. We actually did find beneficial effects of these tumor vaccines and published our findings of protection against spontaneous mouse mammary carcinoma in 1971 and subsequently in 1974 and 1979 concerning spontaneous and transplanted mouse lymphomas [1-4].

I planned to become a clinical oncologist but continue research that would have potential clinical benefit rather than discovering esoteric findings. I finished a residency in internal medicine while I continued my research. I decided to do a side study to determine if radiation therapy to the mediastinum could suppress cellular immunity because of damage to the thymus [5]. This study influenced a change in my career plans. This was a human study, and one of the patients, who I really liked, died from his stage IV non-Hodgkin's lymphoma. Devastated by his death, I was not sure that I could develop enough fortitude to harden myself against death. My stepdaughter is a palliative care/hospice physician and I admire her for how she can deal with dying patients.

Even before the death occurred, I had considered that there was a lot of similarity between malignant tumors and the fetal placental unit in that there is rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance. I thought if one could determine how the fetus escapes immune surveillance, despite the presence of paternal antigens, there was the possibility that malignant tumors may utilize some of the already existing mechanisms to allow survival of the fetal semi-allograft to allow survival of the cancer.

However, very little was known 40 years ago about the immunology of pregnancy. At the same time there was a new medical field starting called Reproductive Endocrinology and Infertility (REI). I thought maybe I should take training in OB-GYN to proceed with a fellowship in REI and conduct research as how does the fetus escapes immune surveillance, and then determine if the malignant tumor may utilize the same mechanisms. If a similarity was found, then therapy directed to blocking these factors may provide a less tedious, less expensive, and more universally available treatment rather than autologous tumor inoculation (which still has some clinical benefits in treating some human cancers even today).

While shifting from medicine to OB-GYN and during my fellowship in REI; I focused on trying to find immunomodulatory proteins that the fetus may produce to counteract the increase in cellular permeability caused by progesterone blocking dopamine to purposely increase cellular permeability. This increase in cellular permeability allows irritants to permeate the endometrium stimulating invasion by natural killer cells, macrophages, and cytotoxic T cells that are needed to remodel some of thick-walled uterine arteries to create thin-walled spiral arteries which subsequently allows nutrient exchange between mother and fetus [6]. From these studies a practical model was established to develop targets for anticancer therapy. This model will be constantly reshaped and revamped as new research findings are discovered. My own research studies were used for my Ph.D. thesis in reproductive biology entitled, "The role of progesterone in promoting implantation and preventing spontaneous abortion may be through the stimulation of immunomodulatory proteins."

The main immunomodulatory protein that we evaluated was called the Progesterone Induced Blocking Factor (PIBF) [7,8]. Thus, PIBF became the main protein to now conduct cancer research trying to determine if some malignant tumors may utilize the PIBF protein to escape immune surveillance. If so, then anti-cancer therapy could be developed to block this protein. Theoretically, this protein does not appear to be essential for normal life, just the life of a fetus. Thus, a hypothetical model could now be established as to how the malignant tumor could also utilize this PIBF protein to escape immune surveillance [9-11].

Theoretically, if this PIBF protein is utilized by malignant tumors, and with no evidence that multiparous women are more prone to cancer (perhaps the opposite) because of constant exposure to progesterone, it would seem more likely that the PR, rather than P itself, would be more involved in PIBF production, in contrast to pregnancy where exposure to P markedly enhances PIBF production by embryonic, mesenchymal, and trophoblast cells and gamma/delta T cells [12,13]. Thus, one potential therapy could be progesterone receptor antagonists, e.g., mifepristone, which was already available from the pharmaceutical industry for the use of pregnancy termination [14]. However, there were already trials using mifepristone to treat cancers known to be positive for the Nuclear Progesterone Receptor (nPR), e.g., breast cancer that showed benefit in some cases, but overall, the results were not nearly as impressive as selective estrogen receptor modulators e.g., tamoxifen [15].

In fact, there had been evidence that the presence of the PR may be protective against cancer progression and metastasis in some way, as evidenced by the increased virulence of breast cancer that is negative for the P Nuclear Receptor (nPR), or finding that when breast cancer has reoccurred or metastasized, the more aggressive cancer, that may have been PR positive initially, has now lost its nPR [16,17].

Thus, the next step would be to prove that at least some cancers may utilize PIBF to proliferate and metastasize by proving that cancer cells have both MRNA to produce PIBF, and even better, if one could actually determine that some cancers secrete the PIBF protein. The most feasible method to accomplish this goal would be to evaluate a cancer cell line that is not from a malignancy known to be positive for the nPR, in case one of the functions of the nPR is to silence PIBF production. Trying to start my own cancer cell lines *de novo* would be a daunting task that would take a huge amount of time, money, facility, and technical staff (none of which I had). So, I sought to find a scientist that already had cancer cell lines. I did find such a scientist, Dr. Srivastava at Roswell Park Cancer Center. We collaborated on methods to detect PIBF (I had developed a method to measure PIBF) and we thus subsequently studied whether multiple different human leukemia cell lines produced mRNA for PIBF and the PIBF protein.

The studies were conducted at Roswell Park (not at my institution). We determined that not only did these cell lines have mRNA for PIBF production, but we found that there was more mRNA devoted to PIBF production by multiple different leukemia cell lines than any of the mRNAs dedicated to making any other protein by these same cell lines that Dr. Srivastava evaluated over 40 years of his research. Just as important, these leukemia cell lines were found to be making the actual PIBF protein [18].

The next step was to see if mifepristone added to the cell culture medium could down regulate PIBF mRNA and PIBF protein production. We were so excited to find that mifepristone did, in fact, down-regulate mRNA for PIBF and the PIBF protein.

Cancer cell lines studies do not always reflect what happens in the intact human because of various interactions of cytokines, enzymes, and cell to cell crosstalk. Thus, the next step was to evaluate the efficacy of mifepristone treatment in mice who have a high frequency of developing spontaneous cancers that are not known to be positive for the nPR. I conducted these studies at my institution. We evaluated the effect of savaging these mice with a dosage of mifepristone, which on a weight basis, would be equivalent to a human ingesting a daily dosage of 200 mg/day. We evaluated mice with spontaneous leukemia, lung cancer, testicular cancer, and prostate cancer. We found that mifepristone significantly increased their lifespan, but just as important, improved their quality of life as determined by body conditioning scores [19-21].

With the exciting results of cancer cell line data, and the spontaneous murine cancer results, the next step would be to try it on humans with advanced cancer. There were a few hurdles, though, to overcome. The important stumbling block was that because of the sensitivity of mifepristone at the 200 mg dosage being approved as an abortion drug, the United States Food and Drug Administration (FDA), and governing agencies in many other countries, restricted the use of the drug to licensed abortionists to appease anti-abortion groups. Thus, to obtain mifepristone for off-label use for a patient with cancer, I would have to obtain each time from the FDA a compassionate use Investigative New Drug approval (IND). After obtaining Institutional Review Board (IRB) approval, we requested an IND for a patient with extensively metastatic colon cancer who was advised by her oncologist to either just prepare for death (which would probably occur in two to four weeks) or they could try a new chemotherapy regimen, but they would still give her no more than a 15% chance of living six months and significant side effects from this new drug. We provided the FDA with our data on mifepristone and leukemia cell line studies and data from the murine spontaneous

cancer studies, and we were granted the IND to treat this woman who was a family friend. Her case will be presented below [22].

Why palliative care specialists rather than oncologists are probably the best groups suited to treat advanced human cancer with mifepristone.

In this section, I will not only want to recount the efficacy of mifepristone for treating very advanced human cancers, but with each case hope to provide more and more credence to support my contention that the hope to mitigate suffering from advanced cancer for humanity with progesterone receptor antagonist/modulators lies in the hands of palliative care/hospice physicians and their team, not oncologists. The hope for widespread use of this drug will be to convince palliative care physicians to try mifepristone along with analgesics rather than oncologists because of various reasons including, sadly, economic reasons, who seem reluctant to recommend this therapy even if it will be administered by another physician. It is my hope to convince the palliative care oncologist that mPRs are needed for cancers to metastasize and proliferate (possibly through PIBF) and that PR modulators, e.g., mifepristone, will markedly improve quality and longevity of life. The reason for choosing palliative care specialists is that this is the group to which clinical oncologists refer their patients with advanced cancer when they no longer have any treatment options.

Adenocarcinoma of the colon

My first published human case with extensive end-stage cancer that I treated with oral 200 mg mifepristone was a 61-year-old woman whose primary adenocarcinoma of the transverse colon was resected. However, when subsequently the cancer had extensively metastasized to the liver, peritoneum, ovaries, and uterus associated with marked ascites, they told her she would probably live no more than one month, and that chemotherapy would probably not improve her lifespan very much.

She was a friend of my cousin, who knew of my cancer research, and she asked me if I could help her. At that time a physician could not use the drug off-label unless a compassionate use IND was granted by the FDA. When I received approval, she started single agent oral mifepristone.

Five weeks from starting mifepristone, she stated that she was feeling very well with no pain and good energy. Her ascites had disappeared. A CT scan showed no increase in either number or size of any of the lesions. Though initially her oncologist denied her treatment with chemotherapy, seeing more clinical improvement and stable disease, and a marked decrease in her Carcinoembryonic Antigen (CEA) level to 1.9 ng/ml, they decided to add chemotherapy with bevacizumab and 5 fluorouracil. Though she had mild side effects with these chemotherapy drugs (she had none with mifepristone), she was willing to stay on all three medications to hope for a cure.

Neither the patient nor the oncologist asked for my opinion. At 21 months on mifepristone (but three months on a 50% reduced dosage of mifepristone), the lesions started to grow for the first time. However, she was still feeling quite well with no pain and good energy. Nevertheless, the oncologist told her to stop the chemotherapy and the mifepristone [23].

Literature Review

Thymic epithelial cell cancer

Thymic epithelial cell cancer (not a thymoma) is a rare cancer. One of my patients, who I was treating for gynecologic problems, was diagnosed with this cancer at age 46. She had surgical excision followed by radiation therapy to the mediastinum and lung. Despite these treatments, the lung lesions continued to increase in size and number. She was symptomatic in that she complained of marked fatigue, dyspnea on exertion, and cough. There were no chemotherapy regimens at that time to treat this cancer, so she tried octreotide in a clinical trial. She stopped two months later because the octreotide did not thwart progression at all. She was very symptomatic at this time with marked fatigue and marked dyspnea on exertion. However, she would not quite be considered moribund or end stage cancer at this time. Nevertheless, the FDA approved a compassionate use IND for mifepristone.

Though the aforementioned patient with colon cancer was my first moribund patient with cancer that I treated, this 46-year-old woman was the first patient that I ever treated with mifepristone. During two years of single agent mifepristone therapy, she had marked improvement in her energy and shortness of breath and decrease in cough. Interestingly, the improved symptomatology occurred despite no shrinkage of any of the lesions. However, over two years there was very little growth of pre-existing lesions and no new ones appeared.

This case suggests that by blocking certain factors that involve the P receptor (possible PIBF), the cancer will at least arrest further growth and metastasis but not “cure” cancer once it metastasizes. Either the product made by the membrane PR contributes to the asthenia of cancer, or possibly the spread of cancer itself by blocking the membrane PR and its products makes the patient feel a lot better, not just for a short time, but years instead of weeks or months. Thus, it seems that this medication seems to be one that the cancer does not seem to find a way to mutate so easily, and thus the mifepristone continues to provide significant beneficial effects. This is a concept more likely to be understood by palliative care specialists rather than oncologists who would be more apt to stop treatment, even if the patient feels a lot better, if there is not obvious tumor regression. Even worse, the oncologist may decide to try a different anti-cancer drug or other therapy not likely to be effective, but cause significant side effects, and thus make the patient feel worse rather than better.

One more reason why the palliative care doctor, not the oncologist, should be the one designated for treating with mifepristone: once the oncologist turns the patient over to palliative care, the oncologist is no longer involved in the case. There is a certain “hypnotism” that influences the patients to go along with the advice from the oncologist, which for whatever reason, is not always in the patient’s best interests. This woman was my patient for over 15 years before she developed thymic epithelial cell carcinoma. She was doing so well on the mifepristone and would have probably would have broken the record for the largest lifespan with this dreaded cancer, yet she never asked for my opinion as to whether to do the second course of radiation therapy or not or to stop the mifepristone as recommended.

Transitional cell carcinoma of the renal pelvis

One of my patients, a Harvard physician, who was familiar with my cancer research, asked me if I could obtain mifepristone for a philanthropist who provided her with research funds to study and treat

human immunodeficiency virus in Africa. The patient was 73 years old, and the family was advised that he only had a week to live despite radical surgery for transitional cell carcinoma of the renal pelvis and two different courses of chemotherapy. I borrowed some pills from another patient that I was treating until I got him a compassionate use IND approval by the FDA. He was semi-comatose at the time of treatment partly from marked asthenia and partly from the cancer, and partly from high dosage opiates which only minimally reduced his pain.

He died two months later and initially I considered this case a failure with mifepristone. I thought the oncologist could not know for sure that he only had one week to live. Subsequently, from talking to his wife, and then about three months after his death his oncologist, I do consider this case as evidence of palliative benefits of mifepristone for this type of cancer.

Lesson to be learned from this case: 1) Even with death appearing imminent, there still may be benefit to treatment with mifepristone. 2) Once again, he noted that he felt much better with basically the same number of lesions, once the mechanism to allow continual spread was stopped. 3) This was now the third different type of cancer that had no other treatment options which responded to mifepristone. None of these tumors were known to be positive for the nPR. Assuming the main target for mifepristone benefit is suppression of PIBF, could this immunomodulatory problem be the one universal protein that all tumors need to proliferate? Is it possible that mifepristone or other PR antagonists will prove to be the only anti-cancer treatment that can have anti-cancer benefit for all cancers?

This case also supports the contention that this drug should be used primarily by palliative care specialists rather than oncologists. Oncologists do not seem to be interested in drugs that provide palliation rather than care. If this concept spread amongst the palliative care group and became a staple of treatment, they could as a group not only negotiate with the pharmaceutical company to reduce the price for patients with cancer, but may convince insurance companies to pay for the drug in lieu of many more expensive anti-cancer drugs. Though I was pleasantly surprised by the phone call from the oncologists, he only expressed his interest in participating in a clinical trial if some pharmaceutical company is sponsoring such a trial.

Probable small cell lung cancer

A moribund 80-year-old woman with advanced lung cancer is probably the case that best illustrates the benefit of mifepristone for advanced cancers, and why the drug should be in the hands of palliative care specialists. This case involved my mother-in-law. She developed sudden severe dyspnea on exertion and marked weakness. The chest x-ray and CT scan showed multiple lung lesions and bilateral pleural effusion with a PO_2 of 72 mm Hg and a serum sodium of 118 m. She refused a lung biopsy since the results would not change the management. The oncologist concluded that based on rapidly of symptoms, and presentation on first evaluation with extensive metastatic disease, and with the syndrome of inappropriate anti-diuretic hormone, she most likely had small cell lung cancer. The oncologist estimated that death would be within two weeks. She was advised to consult hospice.

I convinced her to try mifepristone. In the first month, she was feeling much better with much improved energy and no shortness of breath. After one month of single agent mifepristone therapy, her PO_2 was now 99 mm Hg and her serum sodium was 145 mmo/1 L.

She was the first case to demonstrate complete regression of all of her lung lesions; though the chest x-ray still showed a ground glass appearance. Her probable small cell lung cancer never returned while she continued 200 mg daily oral mifepristone daily. She died five years later at the age of 85 with a myocardial infraction [24].

Before my mother-in-law developed lung cancer, she had been under the care of a hematologist/oncologist for chronic lymphocytic leukemia. Her treatment that time was just observation. He was the physician who saw her in the hospital with probable SCLC. He never inquired about her outcome. When she was doing so well, after one year of single agent mifepristone, I wrote him a letter explaining how well she was doing. I also sent him some publications about our treatment of cancer with mifepristone. He never responded. When I was invited recently to write an article for a medical endocrine journal, I wrote about the endocrine paraneoplastic syndrome and mentioned the unique use of mifepristone to treat it using this case as an example [25]. Again, I sent him that publication, but still no response. Though I am sure that exceptions do exist, for some reason practicing clinical oncologists do not seem to be interested in learning about a new, extremely safe, very tolerable treatment for cancer that, through off label, is available for immediate treatment of their cancer patients. I have found that in my experience that the large majority of oncologists who observe their patients doing well on mifepristone (I always have them stay with their oncologists for follow-up) have never called me personally or requested publications. Thus, more support for the contention that mifepristone treatment should be rendered by palliative care specialists.

End stage pancreatic cancer

A 57-year-old man with end-stage pancreatic cancer was admitted to home hospice. He was started on opioids to reduce his severe pain. After one week of hospice, his sons heard from a friend about mifepristone. Upon his first visit, he was slumped over in a wheelchair, and he could barely talk.

Before I provide my thoughts as to how does this case support PR antagonist treatment better suited for palliative care specialists than clinical oncologists, I want to briefly mention another case of advanced pancreatic cancer [26]. A 58-year-old woman with stage 4 pancreatic cancer widely metastatic to her liver failed to show any response to chemotherapy. Despite palliative care, she was still in a great deal of pain [23].

Her husband, a physician, heard about our treatment with mifepristone. Within two weeks of taking mifepristone, her husband stated that her degree of pain markedly improved so that her requirement for narcotics dropped to less than a third of what it was before starting mifepristone. Her energy had also markedly improved. After one month, she hardly had any pain.

How do these cases support the argument that mifepristone therapy is best administered by palliative care/hospice physicians rather than oncologists? For the second case of pancreatic cancer, her palliative care team was thrilled by her marked improvement in energy and pain relief. Yet, the oncologist, hopefully cognizant about her great progress while taking mifepristone, convinced them to start a new experimental drug that never had been tried in humans. The oncologist was from a world-renowned cancer center. My conclusion is that his decision to try this new drug and stop mifepristone was not suggested

for the best interest of the patient, but the best interest of that physician and his institution

Malignant fibrous histiocytoma [23]

One of my patients asked me if I could treat her 23-year-old son who had a widely metastasized malignant fibrous histiocytoma. She was advised that he only had two weeks to live. However, despite narcotics, he still suffered from intense pain. Within two weeks of taking single agent mifepristone his pain markedly improved, so that the pain was only mild and quite bearable. His narcotics dosage was reduced to less than 25% of the dosage prior to mifepristone.

His energy returned and he resumed a functional life. After three and a half months of taking mifepristone, the pain started to intensify, and he died two weeks later. He did stay on the mifepristone until death. This was the first case where despite mifepristone providing definite palliative benefits and probably some extension of life, the cancer eventually spread rapidly and caused his death despite continuing the medication on a daily basis.

Clearly the palliative care/hospice team for cases like these are the ideal group to administer mifepristone so they can carefully titrate analgesics. There are some extremely expensive anti-cancer drugs that have significant side effects yet they would be highly touted if they could extend life by four months, as accomplished by mifepristone in this case. Nevertheless, the question arises as to whether despite hundreds of anti-cancer drugs on the pharmaceutical market, how many could not only extend life, but provide a good functional life with little pain started so close to death as seen in these patients, and in addition after all other therapies failed?

Glioblastoma multiforme Grade IV [27]

One of my patients heard that we were treating end stage cancer of various types with mifepristone, and asked if we could treat her 43-year-old boyfriend who had end stage grade IV glioblastoma multiforme. She was advised that death was imminent. He was paralyzed from the neck down and his hands stayed in a clenched position. He was sleeping most of the day and he was not capable of normal conversation.

Within two weeks of taking mifepristone, he became much more alert and was able to converse normally. He was now able to use his hands but otherwise remained paralyzed. After three months of taking mifepristone, though his energy level remained good and his mentation was still normal, he was still having some difficulty breathing and swallowing. He thanked us for the extra three months of life, stopped the mifepristone, went back to 100% hospice care and died two weeks later. Mifepristone can interfere with the metabolic clearance of fentanyl which could lead to lethal serum level of fentanyl. Thus, the palliative care specialist, knowledgeable about drugs to reduce pain would be the best suited physician to add other analgesics to reduce pain, if single agent mifepristone is not sufficient, to completely eradicate pain without using fentanyl. The most important new information that we learned from this case was that mifepristone can cross the blood-brain barrier.

Breast cancer [28]

I was familiar with this young lady since birth because she was one of the quadruplets delivered from a patient that I treated for infertility related to polycystic ovarian syndrome. At age 31, one of the quadruplets was diagnosed with stage III breast cancer with focal invasive ductal and lobular type that was positive for the Estrogen (E) and P receptors. Before starting chemotherapy, this young lady, who was not married, came for oocyte cryopreservation. Despite surgery, radiation therapy, tamoxifen, adjuvant chemotherapy and various other medications, including palbocilib, everlimas and fulvestrant, her cancer progressed locally and also metastasized distally to bone, liver, and bowel.

At the age of 37, she returned to have the frozen eggs thawed and fertilized and have the embryos transferred to her sister. (Another one of the quadruplets who had also been an infertility patient with us and who had a successful delivery). Her clinical oncologist was opposed to this telling her that she would be dead before her child was old enough to remember her name! Nevertheless, for whatever time she had left, she wanted to enjoy a child with her husband, and he was 100% in favor of having a child. Her sister subsequently did have a successful delivery.

During this time, I discussed with her, her mother, and sister (both nurses) about the possible use of mifepristone. They discussed this option with her oncologist who was not in favor of using mifepristone. As this point her tumor was only 40% positive for the ER and was negative for the PR.

Alpelisib was stopped and she stayed on mifepristone and her potassium returned to normal. After one month on single agent mifepristone, she stated that this was the best quality of life she has had in several years. Despite having a decent quality of life, her oncologist finally convinced her to stop the mifepristone and enter hospice because her tumor markers were increasing despite the treatment with mifepristone. She finally gave in, entered hospice, and died three weeks later at age 39 [28].

I think this case illustrates my contention, and frustration that for whatever reason, clinical oncologists are reluctant to use mifepristone, thus they tend to make poor decisions that do not appear to be in the best interest of the patient, at least when the cancer has become very advanced.

Metastatic fibroblastic osteosarcoma

My wife and I took a cruise to Cuba and we met a 48-year-old man, married to a nurse, who was ambulating with a walker. A conversation determined that he was suffering from metastatic fibrous osteosarcoma, and he was not doing well. We talked about the possibility of mifepristone therapy, and they subsequently made an appointment to further discuss and initiate the therapy.

At age 46, he was diagnosed with a 6 cm fibroblastic osteosarcoma of his right tibia. Following surgery, he was given a chemotherapy cocktail of doxorubicin, cisplatin, and high-dosage methotrexate for nine months. He suffered from many side effects during treatment. Despite this therapy, the tumor recurred in the same area as where previously resected, and now two metastatic lung lesions were found [29].

He had a second resection of the tibial lesion and was given iodamide and etoposide for nine months alternating with high dosage methotrexate. The chemotherapy was stopped because it did not halt growth of the metastatic lung lesions, and new right tibial tumors were found. Furthermore, Foundation I testing suggested that he may respond to targeted therapy with regorafenib. Nevertheless, CT scans eight months later after regorafenib showed continued disease

progression. He now had four lower left lung lesions and the right upper lung lesion increased in size. He also was found to have a metastatic lesion to the ischiorectal fossa, one in the right lower leg, and a large 5 cm lesion in the right pelvic fossa.

Though regorafenib was better tolerated than previous chemotherapies, he was suffering from significant neuropathy pain in his hands and feet as a side effect, plus somnolence. His oncologist suggested he stay on this therapy because there were no more treatment options, and perhaps the regorafenib reduced the rate of the spread.

The patient decided to be treated instead with oral mifepristone. The oncologist insisted that if he was to try mifepristone he must stay on the regorafenib. Radiologic evaluation for five months on combined therapy for the first time found no disease progression. The patient, against his oncologist's advice, stopped the regorafenib and the neuropathic pain disappeared three weeks later.

The patient was feeling much better on single agent mifepristone and was able to partake in the activities that he enjoyed most-national and international travel He did decide to have a radical resection of the mass in the ischiorectal fossa, his right pelvic lesions, and his right leg osteosarcoma.

His good quality of life persisted for four more years. However, there was now evidence of recurrence in the tibia. His medical oncologist advised him of a new drug for osteosarcoma, and suggested he try the new medication. He also advised to stop the mifepristone because one cannot be sure of drug interactions. Furthermore, this way they could evaluate the efficacy of the new drug. He was advised that if it was not working, the drug would be stopped, and mifepristone resumed.

His wife had remembered our conversation stating that once one stops the mifepristone the cancer will rapidly spread. She begged her husband not to stop the mifepristone. Nevertheless, he decided to give the new drug a try. The cancer spread rapidly, and he died three weeks later.

Though up to this point, I have described some near-death patients who had a dramatic improvement with mifepristone, who not only had palliative benefits, but longevity. Case reports only suggest that a given treatment can work, but perhaps only in a minority of cases. However, in my experience most end stage patients showed palliative benefits with extension of life. The man with the fibroblastic osteosarcoma was someone who was stage IV with no other treatment options, but who was not extremely close to death. This shows that mifepristone should be considered not necessarily as the last treatment option, but when there are no longer any good alternative treatment options. Patients may turn to palliative oncologists before continuing therapy with their clinical oncologist when word spreads through social media that there is another treatment option that seems to work in a large variety of cancers, and that allows you to be treated strictly as an outpatient, with very few visits needed. Even further testing of disease progression may not be needed. This would provide immense cost reduction for healthcare [30].

Non-Small Cell Lung Cancer (NSCLC)

Recounting these interesting cases of various types of advanced cancers that had very good palliative benefits from single agent mifepristone establishes the fact that PR antagonists/modulators can be a very effective treatment for advanced cancer. However, one does not know so far as to whether this response was found in a very small minority of cancer or the majority. I have recounted the stories of practically everyone that I have ever treated with the drug. I did not mention one woman with advanced breast cancer whose oncologist kept advising her not to take the drug who finally agreed to it, and she took one pill and died the next day. Another patient with Non-Small Cell Lung Cancer (NSCLC) cancer taking fentanyl was told that he should change the opiate. He did not heed our suggestion and took mifepristone and fentanyl together and became very somnolent. He elected not to continue the mifepristone rather than stop the fentanyl.

Nevertheless, to better convince the medical community to use this drug, demonstration of efficacy in a larger series would certainly be more credible. We applied to the FDA for an investigator initiated study to evaluate single agent mifepristone (in this case 300 mg per day because we got Corcept Inc. to provide the drug gratis for advanced non-small lung cancer). The 300 mg dosage is approved for Cushing's syndrome in the United States but not for abortion. Thus, its use does not require a compassionate use IND from the FDA, but it is cost prohibitive ($500 per pill).

The FDA approved a 40-patient study and two principal investigators. What happened next solidifies my position that oncologists are not interested in an anti-cancer drug unless there will be some financial reward for the oncology group rendering treatment. Corcept Inc was willing to provide the drug gratis but not to provide any financial support for the principal investigators. I had my doubts that I could receive a grant for this project, (off-label use is frowned upon) and I did not want to delay the study. I even implored the American Cancer Society and The American Society for Cancer Research to provide names of possible principal investigators. They did supply names, but all refused to be a principal investigator. Even my own medical school and hospital, with a large oncology division, turned down the opportunity to be a principal investigator. Thus, by default, I became the sole principal investigator.

Mifepristone was allowed to be given to a patient with stage III B or IV NSCLC which progressed despite a minimum of two rounds of chemotherapy and/or immunotherapy. The study was published in clinical trials. Gov. My first enrolled patient in the study was referred by the father of one of my OBGYN residents. This OB-GYN resident was cognizant of our work with mifepristone and advanced cancer because of her interest in becoming a reproductive endocrinologist/ infertility specialist. She had taken several electives with our practice.

The clinical oncologist referred a 68-year-old male with stage IV NSCLC with metastasis to the brain [31]. Despite several chemotherapy regimens, his lung cancer progressed with no other tumor markers present so there were no other treatment options. He also had a history of bladder cancer and Chronic Obstructive Pulmonary Disease (COPD) from heavy smoking. His main symptomatology was marked fatigue, dyspnea on exertion, and severe cough.

He still felt great after two and a half years. However, he had a consult with his oncologist, and he was advised that nivolumab had been approved for NSCLC even if the tumor marker called the Programmed Death-1 (PD-1) or programmed cell death ligand 1 (PD-L1) was not present. He suggested that since the primary lesion was growing, maybe he should stop the study. The patient, not the oncologist, asked my opinion. I suggested not to stop the mifepristone, and based on the nature of the study he could not add nivolumab. He could stop the study, add nivolumab, pay out of pocket for 200 mg of

mifepristone, but he chose to stay on single agent mifepristone. He died after five and a half years on mifepristone, still feeling good and having a normal functional life but he died of pneumonia during the early phase of the COVID pandemic. During his treatment, he never developed any recurrence of brain metastatic lesions or any new lung lesions.

For twelve months of single agent mifepristone therapy, she had a very good quality of life with full resumption of normal activities. Her quality of life began to slowly deteriorate after twelve months of mifepristone treatment, not related to tumor progression (which showed no progression and some tumor shrinkage) but related to worsening of her COPD. She died one and half years on mifepristone therapy not from cancer progression, but COPD [32].

Case 1 of NSCLC re-emphasizes my contention that despite observing marked clinical benefit, oncologists are quick to add another drug e.g., nivolumab, even though the data did not show a great response if PD-1 is not present or even with low positivity for the PD-1 marker [33]. He received all my monthly notes about the patient including reminders that stopping mifepristone therapy may result in very rapid tumor progression. I have never received another referral from this physician.

Enrollment into the study was poor. It was clear we would fall short of any type of large series, nowhere near the 40 approved patients. Thus, when a 59-year-old woman and 46-year-old woman decided to enroll to treat stage IV NSCLC positive for the EGFR mutation that usually responds so well to the third generation tyrosine inhibitor osimertinib, we advised them not to enroll in the study but apply for a compassionate use IND. Unfortunately, the cancer progressed with multiple brain metastases after one year of osimertinib. Though they would have to pay for the mifepristone, they would do all their treatment at home rather than travelling monthly to our office to be evaluated and to be provided the next month's allotment of pills. The cost of travelling for these women who lived 1000-2000 miles from our office would far exceed the cost of the drug ($600 per month with 50% reduction when a compassionate use IND is obtained.) They are both alive and doing well five years on single agent mifepristone [34].

Discussion

Small Cell Lung Cancer (SCLC)

A 59-year-old male consulted us because of rapid progression and poor quality of life despite standard chemotherapy and immunotherapy with Small Cell Lung Cancer (SCLC). Two months after starting mifepristone, there was evidence of regression of some of the metastatic lesions. However, more importantly, his quality of life returned to normal, which included skiing and scuba diving. His good quality of life continued for one year.

However, at the one-year mark, a CT scan showed slight growth of the right upper lung lesion but without pleural effusion, pleural nodularity or interlobular septal thickening that had been present prior to mifepristone therapy.

The oncologist convinced him to stop mifepristone and be treated with a new experimental drug that targets PD-L1. The cancer rapidly progressed and did not respond to the new drug [35]. He died three months later. He never called to ask to retry the mifepristone. I spoke to a friend of his, who thought he did not think his friend was in a state of proper mentation to consider going back on mifepristone once he started the new drug [35].

This case certainly provides more convincing evidence that biases and potential personal gains preclude most clinical oncologists from making the right decision as to what is best for the patient and not for themselves. There should be no such conflict for palliative oncologists.

Conclusion

My main objective of this commentary/perspective is not only to convince the palliative care/hospice community of the efficacy of using mifepristone for advanced cancers, but also why palliative care oncologists or simply palliative care physicians and team, are the hope in propagating the benefit of this very effective, and very well tolerated drug. It would seem that most clinical oncologists want to go for the “cure” of metastatic cancer. However, a “cure” for cancer once it is metastatic does not seem to be likely in the near future. Thus, the aim should be to extend the best quality of life possible and convert cancer to a tolerable, chronic disorder.

Hopefully, if the palliative/hospice community embraces this treatment concept, and more experience continues to demonstrate marked benefit, they will attain approval of the drug by government agencies for cancer use or convince third party insurance carriers that paying for mifepristone is a lot less expensive than most other anti-cancer therapies by far. At the worst, there are some patients who can afford $13,000 per year to live longer and have a better quality of life, or even better, if the manufacturer agrees to lower the price considering daily use for years instead of one single pill needed for pregnancy termination.

The hope is that demonstration of efficacy for a variety of cancers by the palliative care/hospice group will influence other physicians e.g., internal medicine specialists or family doctors, or even impressing the clinical oncologists, to try the drug earlier in the cancer disease state to provide maximum quality of life and longevity, especially if it can save multiple surgeries, radiation therapy, or other chemo or immuno-therapies with their associated side effects.

Related to FDA restrictions, we have only been given permission to treat one patient with cancer that was not advanced with mifepristone for multifocal renal cell carcinoma in both kidneys. At that time the recommendation was to treat with a bilateral nephrectomy with subsequent dialysis. This approval was given because this 58-year-old man did not want the consequence and impairment of his lifestyle on dialysis. There was no chemotherapy that had proven beneficial for treating this type of cancer at that time. The patient preferred a hemi nephrectomy of his largest lesion in the right kidney, and leave in the left kidney intact with three cancer lesions. Mifepristone prevented growth of these three lesions or any new ones to develop and he is now 78 years old still doing well [36]. This use suggests that mifepristone should be considered in earlier stages of cancer to prevent progression of metastases.

Acknowledgement

We would like to acknowledge Dr. Trina Poretta who has been our oncology advisor. We would also like to acknowledge Diane Check

and Carrie Wilson who have run the clinical studies, have obtained the the IND from the FDA and the IRB for the patients enrolled in the program. They have also participated in other manuscripts.

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