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Progesterone and Glucocorticoid Receptor Modulator Mifepristone (RU-486) as Treatment for Advanced Cancers

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Abstract

The fetal placental unit has paternal proteins which would normally result in immune rejection of fetus. Thus, to allow growth to 266 days, the mother must develop immunosuppressive proteins, cytokines, etc. to allow progression to a full-term baby. One of these essential immunomodulatory proteins is called the progesterone induced blocking factor (PIBF). Probably, the mechanism involved allowing the progesterone receptor antagonist mifepristone to cause termination of a pregnancy is by blocking the PIBF protein. There is good evidence that cancerous tumors borrow some of the same mechanisms as the fetus to escape immune surveillance, including the PIBF protein. Research data suggest that this protein is made and excreted by embryonic cells, mesenchymal cells, and trophoblast cells of the fetal placental unit to block the killing effect of natural killer cells and T-cells in the fetal microenvironment. Cancer cells do the same. Indeed, there is good evidence that mifepristone, a drug approved for pregnancy termination, can significantly improve length and quality of life in patients with various advanced cancers.

Keywords: progesterone induced blocking factor, metastatic cancer, progesterone receptor antagonists, natural killer cells, membrane progesterone receptors

1. Introduction

A certain minimal level of progesterone must be maintained from ovulation until delivery to allow the birth of a full-term live baby [1]. Progesterone (P), acting in conjunction with the P receptor, causes the production of a large number of various molecules needed for the development of an appropriate secretory endometrium to allow attachment of the blastocyst to the endometrium and adequate invasion to the proper depth of the fetal placental unit [1].

Some of the molecules induced are also needed to suppress rejection of the fetal semi-allograft. One of these immunomodulatory proteins has been termed the progesterone induced blocking factor (PIBF) [2]. There is evidence that PIBF is one of the most important immunomodulatory factors produced during pregnancy to inhibit immune rejection of the fetal semi-allograft [3, 4].

Progesterone-induced blocking factor is an immunomodulatory protein that can suppress or block various aspects of the immune system, especially, but not

limited to, natural killer (NK) cells [5, 6]. The blocking effect on cellular immunity, especially NK cell cytolytic activity, may be related, at least in part, to a shift from thymic helper (TH)-1 to TH2 cytokine dominance [7]. One mechanism by which PIBF can suppress NK cell cytolytic activity is by inhibiting degranulation of perforin granules, one mechanism used by NK cells to kill other cells [8].

The “parent” form has a molecular mass of 90 kDa and is localized in the centrosome [9]. Various splice variants of this nuclear protein lead to smaller intracytoplasmic molecules that have immunosuppressive activity [9]. The actual full-length protein contains 757 amino acids, and the 48 kDa N terminal part is biologically active [10]. The PIBF gene has been identified on chromosome 13 in the vicinity of breast cancer 1 (BRCA1) or BRCA2 or p53 [11, 12].

Progesterone-induced blocking factor rises precipitously in the serum after exposure to P (even in males injected with progesterone) and the source seems to be circulating gamma/delta T cells [2]. However, it seems that the main source of PIBF that allows the early feta-placental to escape immune surveillance are actually cells of the fetal placental unit namely embryonic cells, mesenchymal cells, and trophoblast cells [1, 9].

In 2001, Check et al. hypothesized that it is likely that cancer cells might “borrow” some of the same mechanisms to escape immune surveillance as the fetal-placental unit [13]. Based on their previous research with the PIBF protein, they considered that, whereas treatment for infertility or recurrent miscarriage should be aimed at increasing the production of the PIBF protein, theoretical treatment for cancer could be therapy aimed at suppressing the PIBF protein [13].

Support for this concept was provided by Lachman et al., who showed that many different types of cancer cells express this PIBF protein [9]. Though one may think that highly proliferating cancer cells may be the ones that have the classic nuclear progesterone present, the study by Lachman et al., found many of the cancers associated with PIBF were not known to be positive for the nuclear P receptor [9].

Based on this hypothesis, it was considered that a P receptor antagonist/modulator should cause suppression of PIBF production in rapidly growing cancer cells which could overcome the theoretical block of immune function of cellular immune cells in the tumor microenvironment.

Mifepristone was the first P receptor antagonist developed [14]. It was a derivative of the synthetic progestin norethindrone [14]. It was purposely developed to be an abortifacient to alter the endometrium and cause decidual necrosis and cause the trophoblast to separate from the decidua [14–16]. Mifepristone sensitizes the pregnant uterus and cervix to endogenous and exogenous prostaglandins increasing uterine contractility and helps to induce cervical softening [14–16].

Over the years other benefits of mifepristone, related to its anti-progesterone effect, have been developed, including treating uterine leiomyomata and endometriosis [17]. The anti-abortifacient drug comes in 200 mg tablets. Since mifepristone in higher dosages blocks the glucocorticoid receptor, it has been approved as a 300 mg tablet to treat Cushing’s syndrome [18].

Thus, we set up a study to determine if we could detect PIBF in various leukemia cell lines, and, if so, determine if adding mifepristone to the medium could reduce PIBF secretion. To do so we collaborated with Dr. Srivastava from the Roswell Park Cancer Institute, who for many years studied protein production by leukemia cell lines. Twenty-nine cell lines of diverse lineage were all found to express messenger (m) RNA for PIBF [19]. In fact, there was more mRNA dedicated to the production of the PIBF protein, by far, than any mRNA for any other protein previously studied in these leukemia cell lines [19]. Ten cell lines positive for mRNA for PIBF were tested for the PIBF protein using a much less sensitive assay for PIBF than is presently available. Four tested positive for the PIBF protein. Addition of progesterone to the

media of the cell lines up-regulated mRNA for PIBF and also the PIBF protein [19]. In contrast, the addition of mifepristone to the media down-regulated both mRNA for PIBF and the 35 kDa PIBF intracytoplasmic splice variant protein (similar in size to the PIBF splice variant in fetal-placental cells) [19].

Subsequently studies using other cancer cell lines supported the conclusions from the leukemia cell line studies. Kyurkchiev et al. found that glioblastoma multiforme also express the intracytoplasmic PIBF protein, but in this case the splice variant measured 57 kDa [20]. Gonzalez-Arenas et al. found, similar to the aforementioned leukemia cell line studies, adding P to the media up-regulates the 57 kDa intracytoplasmic splice variant of PIBF in glioblastoma multiforme cell lines [21]. Interestingly, in addition they added PIBF protein to the media and found that PIBF increased the number of U87 cancer cells on days 4 and 5 of treatment. This suggests that PIBF promotes proliferation of human glioblastoma cancer cells independent of an intact immune system, which would require a whole intact animal or human [21].

Mifepristone has been also found to inhibit the growth of cell lines or murine tumor transplantation from endometrial cancer, breast cancer, prostate cancer, gastric cancer, ovarian cancer, and lung cancer [22–27].

Goyeneche's group published some interesting findings concerning mifepristone and ovarian cancer cell lines. They have found that mifepristone inhibits ovarian cancer cell growth in vitro and in vivo [28]. They have published several studies showing the benefit of the combination of mifepristone and chemotherapy with cisplatin therapy or cisplatin-paclitaxel treatment of ovarian cell lines [29–31].

Based on these cell line studies, more support was provided that cancer cells may borrow some of the same escape mechanisms as the fetal-maternal unit to escape immune surveillance. Thus, therapy aimed to suppress these immune factors could lead to novel effective anticancer therapies [32]. Dr. Szekeres-Bartho, another pioneer in determining that the immunomodulatory protein, PIBF, plays a major role in allowing the fetus to avoid immune surveillance, in 2010 wrote a treatise entitled "PIBF: the double-edged sword. Pregnancy and tumor" [33].

In an opinion entitled "Pregnancy is a model for tumors, not transplantation," the renowned immunologist Kenneth Beaman, and his group, in 2016, stated "Nearly 65 years have passed since Peter Medawar posed the following question: "How does the pregnant mother contrive to nourish within itself for many weeks or months, a fetus that is an antigenic foreign body." Now, understanding of reproductive immunology has demonstrated that the HLA antigens in the placenta are non-classical and do not induce rejection. In the placenta and in tumors, 50% or more of the cells are cells of the immune system and were once thought to be primed and ready for killing tumors or "the fetal transplant" but these cells are not potential killers but abet the growth of either the tumor or the placenta. By examining the similarities of the placenta's and tumor's immune cells, novel mechanisms to cause tumors to be eliminated can be designed. Thus, 15 years later, the concept we published in 2001 is starting to be accepted by top immunologists in the field [34]. Though Beaman et al. do not refer at all to the PIBF protein, I recommend an article in gynecologic oncology to those readers wanting further knowledge into the immune similarities between pregnancy and cancer to open the door for other novel treatments of malignant tumors other than blocking the progesterone receptor [35].

2. Animal studies with mifepristone in cancers that are, and are not, known to Be associated with the classic P nuclear receptor

In humans, the progesterone receptor (PR) is expressed in prostate stroma. Reduced PR expression in cancer-associated stroma can be conducive to a tumor

microenvironment favorable for cancer cell invasion and tumor metastases [36]. Thus, if the presence of the PR somehow inhibits tumor invasion and metastases, treating with a PR antagonist may worsen the condition.

However, it may be that the loss of the PR receptor merely suggests a higher percentage of more aggressive cells, and thus, mifepristone, by suppressing PIBF, may inhibit prostate cancer proliferation. Indeed, gavaging mice with spontaneous prostate cancer with mifepristone (which on a weight basis was equivalent to 200 mg daily in humans) improved longevity of survival and body condition scores compared to placebo gavaged C57BL/6 mice [37].

Controlled studies were also performed in mice where there was no knowledge of the presence of the classic nuclear PR. Beneficial effect on longevity and quality of life (body conditioning score) were observed in 129 Pd/J mice with a strong predisposition for testicular cancer, in aldo-keto reductase/J mice with spontaneous lymphocytic leukemia and A/J mice with spontaneous lung cancer [37–39]. As an example, in A/J mice with spontaneous lung cancer, 67.4% treated with mifepristone survived 1 year vs. 27% of the controls [39]. Even more important, there were 66.7% of mice gavaged with the equivalent of 200 mg/day in humans with mifepristone who had no sick days (body conditioning score less than 4) vs. zero % for controls [39]. These murine carcinoma studies supported the concept that the benefit of mifepristone is not merely for cancers positive for the classic nuclear PR. If the mechanism of improvement did operate through the PIBF mechanism, the presence of the classic nuclear PR is not needed for production of PIBF expression by the tumor cells.

3. Case reports

Based on cell line studies and controlled animal studies, we wanted to determine if the mifepristone could provide increased longevity and/or improved quality of life in human patients with advanced cancer. Unfortunately, though physicians generally have the right to use drugs off-label, there was a restriction for mifepristone. This was not related to risk of the drug, but related to appeasing antiabortion groups who feared that the drug could find easy use to cause abortions. Thus, to use mifepristone as an anticancer drug, one needs to obtain from the Food and Drug Administration a compassionate use investigational new drug (IND) approval to use mifepristone to treat cancer.

3.1 Case 1

The first patient we treated with oral daily mifepristone 200 mg/day was a 46-year-old woman diagnosed with a rare thymic epithelial cell cancer. Over a one-year period following initial surgery and radiotherapy more cancerous lesions developed in the lung. There was no standard chemotherapy, but she was approved for experimental octreotide. However, the cancer still progressed. After starting mifepristone 200 mg/daily, though, her lung and mediastinum lesions did not regress, they remained stable. Clinically, she was feeling much better in that she had much less shortness of breath, much less cough and, marked improvement in fatigue. This clinical improvement persisted for over 2 years. Her oncologist decided that since the lesions were stable, this could be the opportunity to attempt a “cure” by a second course of radiotherapy to the mediastinum. She developed pulmonary fibrosis from this second course of radiotherapy. According to the thymic Cancer Carcinoma Society, she had survived the second longest time of any patient with this type of cancer [40]. Now, with more clinical experience, she would have

been advised against more radiotherapy and just continue the mifepristone. Most metastatic cancers will not be “cured.” The end point of treatment with mifepristone should be quality of life and increased longevity. This first case of our series of anecdotal cases treated with mifepristone first started treatment in 2004. It is important to note that thyroid epithelial cell cancer is not known to be associated with the classic nuclear P receptor.

3.2 Case 2

The second case of advanced cancer that we obtained a compassionate use IND to treat was a 61-year-old woman with a 6.5 cm invasive moderately differentiated adenocarcinoma of the transverse colon with extensive metastasis to the liver, peritoneum, ovary and uterus. She had marked ascites. The two largest liver metastases measured 3.1×1.3 cm and 2.3×1.9 cm. She was advised by her oncologist that even with chemotherapy she would only have a 15% chance of living 6 months.

After 1 year of mifepristone therapy 200 mg orally per day her carcinoembryonic antigen level had dropped all the way down to 1.6 ng/mL. After 18 months, there had not been any growth of her metastatic lesions nor did any new ones appear. She had no pain, no vomiting, and she stated her energy was great.

A CT-scan at 22 months showed some growth of the lesions. Nevertheless, she was pain free with good energy even at 27 months when ascites began to return (it had completely disappeared). She was still ambulatory at 30 months when she died.

Several years later talking to her sister we found out that at 18 months, to save money, she started taking the mifepristone every other day. Thus, this case helps to establish that the daily dosage should not be less than 200 mg/day. The case also supports the concept that mifepristone can prolong life and provide palliation for cancers not known to be associated with the classic P nuclear receptor [41].

3.3 Case 3

Another 43-year-old woman with stage IV metastatic colon cancer, who had progressed despite standard chemotherapy, began single agent mifepristone therapy. Similar to the aforementioned case, there was a halt to cancer progression, her energy markedly improved, and she had great relief of pain. After 18 months some of her metastatic lesions began to grow. She assumed that this was the end of her remission, so she stopped the mifepristone, and decided to try a new experimental drug. She died 3 months later [40]. Based on subsequent clinical experience, we would have advised her that even though the lesions are starting to grow again, mifepristone will still prolong a high quality of life, and will prevent rapid spread, thus advising her not to stop mifepristone.

3.4 Case 4

An 83-year-old man with rapidly growing stage IV colon cancer with metastases to his lungs, liver, peritoneum, and lymph nodes showed no improvement to either capecitabine or cetuximab. He was so weak that he could not get out of bed. Within 2 weeks of 200 mg mifepristone tablets daily obtained with compassionate use his energy returned, and he was able to resume normal function and go to restaurants and other social events and completely take care of himself (ECOG 0 now). His appetite also returned, and he was pain free.

After 4 ½ months of therapy none of his previously rapidly growing metastatic lesions grew with the exception of 1 lung lesion that grew 0.3 cm. He had no side

effects from treatment. Though he had no kidney metastases, he had pre-existing marked renal impairment. He became uremic. His wife was deciding on dialysis or not when he died of a sudden myocardial infarction [41].

3.5 Case 5

Sometimes, instead of the mifepristone therapy causing stable disease, or changing the pattern from rapid progression to slow progression, the lesions may show marked regression. This is evidenced by a 45-year-old woman who had widely metastatic leiomyosarcoma despite previous treatment with total abdominal hysterectomy and bilateral oophorectomy, letrozole (the tumor was estrogen receptor positive), and gemcitabine/docetaxel, and resection of lung metastases [40].

She was started on mifepristone 200 mg/day orally. This caused an almost total remission, with disappearance of almost all lesions, and those remaining had shown marked decrease in size. After 6 months, some lesions began to appear, but they were still very small. Nevertheless, without experience with the nature of this drug, the oncologist opted to stop mifepristone and place her in an experimental trial. She died within 1 month from complications of this new drug [40].

3.6 Case 6

Another case of very rapidly growing advanced cancer showing complete remission following ingestion of 200 mg/day oral mifepristone was an 80-year-old woman with a history of chronic lymphocytic leukemia who developed sudden onset respiratory failure with a po_2 of 72 mmHg. Chest X-ray revealed many lung lesions with a radiographic diagnosis of probable advanced lung cancer with multiple metastatic lesions. Her serum sodium was 118 mmol/L. She refused a surgical diagnosis or chemotherapy based on the presumptive clinical diagnosis of small cell lung cancer with the syndrome of inappropriate anti-diuretic hormone (SIADH) and the bleak prognosis, even with chemotherapy [42].

She sought an alternative treatment and agreed to mifepristone therapy 200 mg orally daily. Within 1 month her po_2 returned to 99-100 mmHg without supplemental oxygen. Her serum sodium increased to normal at 145 mmol/L. Her CT-scans showed complete disappearance of all lung lesions even 5 years after initial diagnosis. There did remain, however, a ground glass appearance in the lungs. She died 5½ years later at the age of 85.5 from an acute myocardial infarction, not from lung cancer [42].

Interestingly, though we know that PIBF is secreted by leukemia cell lines and is suppressed by mifepristone, this woman's CLL slowly progressed while her rapidly growing presumed small cell lung cancer had a complete remission [19]. This could suggest that mifepristone acts better on rapidly growing cells than slowly growing cancers. Of course, it is possible that the mifepristone helped keep the CLL slow growing, but that could simply be related to the normal situation of slow progression with CLL even without treatment. It should be noted that lung cancer, whether small cell or non-small cell (which is still possibly the type of cancer this woman had though small cell was more likely because of the clinical picture) is not known to be associated with nuclear P receptors.

Many cancer therapies are ineffective for brain metastases or primary brain cancers because they cannot cross the blood-brain barrier. There is anecdotal evidence that mifepristone can cross the blood brain barrier and provide palliative benefits for primary brain cancer and brain metastases.

3.7 Case 7

A 43-year-old male with a 3-week history of severe protracted headaches was found to have a large glioblastoma multiforme grade IV that originated in the temporal lobe but involved also the frontal, parietal and temporal lobes and metastases to the spinal cord. Despite surgery, radio and chemotherapy, the tumor rapidly progressed. He was not considered a candidate for any other therapy. At the time of starting mifepristone therapy, he was paralyzed from the neck down and his hands were fixed in the clenched position. He slept most of the day, and when awake, was not able to carry out conversations [43].

Within 2 weeks of treatment with 200 mg oral mifepristone daily, he became much more alert and was able to carry out intelligent conversations. He was now able to open his clenched fists and move his hands. He continued treatment for 3 months and remained alert. However, his paralysis slowly progressed to the point where he was having trouble breathing and swallowing. The mifepristone was stopped, and he died 2 weeks later [43].

3.8 Case 8

Another case demonstrating that mifepristone can cross the blood brain barrier to thwart brain metastases from progressing is a case of a 68 year old male with stage IV metastatic non-small cell adenocarcinoma lung cancer with brain metastases who was referred by his oncologist for mifepristone therapy [44]. Based on the experimental data with efficacy of mifepristone inhibiting growth of cancer cell lines, the beneficial effect in controlled various murine carcinomas, and the anecdotal benefits in individual causes with various advanced cancers following single agent mifepristone therapy the FDA approved our investigator imitated study entitled “A phase II study of treatment with oral mifepristone as salvage therapy in patients who have failed two or more previous chemotherapy regimens” (www.clinicaltrials.gov).

He had no tumor markers that could provide him targeted therapy. His cancer progressed despite 3 rounds of multi-agent chemotherapy including carboplatin/avastin/docetaxel, pemetrexed, and gemcitabine. In October of 2015 he had a seizure and magnetic resonance imaging indicated a 1 cm right frontal lobe metastatic lesion. He received palliative stereotactic radiotherapy to the brain lesion which was completed in November 2015.

With deteriorating symptoms, for example, dyspnea on exertion and fatigue and with no other treatment options available (PD-L1 marker was negative and checkpoint inhibitors were not approved for PD-L1 negative patients at this time), he was referred for our FDA study.

In all previous cases, the 200 mg mifepristone tablets were obtained from Danco Inc. at a cost of about \$500 per month. For the FDA approved investigator-initiated study, we decided to use mifepristone 300 mg tablets daily because the company Corcept, Inc. which manufactures the 300 mg tablet for treatment of Cushing’s syndrome (though the dosage is generally much higher than 300 mg to block the glucocorticoid receptor) was willing to provide the drug free to approved patients.

His clinical symptoms improved significantly within 1 month of treatment with single agent oral mifepristone 300 mg daily. He was ECOG 1 at the start of therapy and after 1 month was ECOG zero. He remains ECOG zero after 4.8 years of treatment, and for the majority of visits, he answers his 43 questions on the quality of life evaluation as “not at all” (the best answer that could be given). There has been no evidence of growth of his previous brain metastases or any new lesions by MRI testing.

One additional important piece of information that his case provides. His meta-static lesions remained stable for 1.5 years. But after 1½ years, some lesions began to grow slowly. His oncologist, based on his experience with other anticancer agents, thought that once disease progression began, it usually accelerates rapidly. He thus suggested to the patient that he stop the mifepristone, and consider nivolumab or pembrolizumab, which had at this time been tried on some patients who were PD-L1 negative, or consider another biopsy to determine if a new tumor marker could be found that would allow targeted therapy. The patient feeling so good on mifepristone therapy and feeling so poorly on all of his previous chemotherapy regimens, opted to take our advice and continue on the mifepristone therapy. Now 3.5 years later and still feeling great, he is very satisfied with his decision not to stop mifepristone therapy [44].

This case exemplifies the mistakes, from lack of experience, that we alluded to in some of the previous case reports, that is, one should not stop the drug if there is the start of tumor progression. There is still a good chance the drug will provide continued extension of a good quality life. Naturally, if a new therapy is likely to be more effective than the mifepristone therapy, then it would make sense to try the new agent. But it makes no sense to try a completely new experimental drug with unknown side effects, as tried by some of the previous described cases. Furthermore, experience suggests that mifepristone inhibits metastases, but cessation of therapy results in rapid spread. This progression can be so rapid that it could be too late to resume mifepristone therapy if the new anticancer therapy is not working.

Therapy with mifepristone could be considered hormonal therapy, but because its hypothesized mechanism is that it removed a block (i.e., PIBF), and thus allows the cellular immune system (especially NK cells) to attack cancer cells, it could also be considered a form of immunotherapy. The question arises as to whether the drug would be effective in cancers positive for the programmed cell death protein ligand 1 (PD-L1) marker where there was initial response to immunotherapy with a check-point inhibitor but where the tumor was now showing resistance.

3.9 Case 9

We did describe a case of a 66-year-old woman with stage IV non-small cell lung cancer, who not only had the PD-L1 marker, but also her cancer was positive for the epidermal growth factor receptor (EGFR). When her cancer began progressing following chemotherapy with carboplatin, pemetrexed and bevacizumab regimen and the carboplatin and docetaxel regimen, she was started on a targeted therapy for the EGFR marker, erlotinib [45]. At that time, there was only first-generation tyrosine kinase inhibitors.

When her cancer progressed despite erlotinib, she was treated with 11 cycles of the check-point inhibitor nivolumab. It was stopped after 11 months because it was apparent the drug was no longer inhibiting her cancer progression. She qualified for the investigator-initiated study, and thus she was treated with the 300 mg oral daily dose of mifepristone [45].

After 18 months of oral 300 mg single agent mifepristone therapy, there had been no cancer progression based on lung CT scans performed every 2 months. In fact, some lesions were actually smaller. She was considered ECOG 1 at the start of mifepristone therapy. At the end of 1 year, she was still ECOG 1 with a good quality of life and normal physical activity.

After 1 year, her pre-existing severe chronic obstructive pulmonary disease (COPD) worsened and she required supplemental oxygen to keep her po₂ above 80 mmHg. Based on her COPD, but not her cancer which still had not progressed, at

18 months from initiation of treatment, she was an ECOG 3. She died 2 months later from pneumonia.

Thus, this patient not only showed that mifepristone can prolong life and provide a good quality of life not only in a patient whose lung cancer is positive for the PD-L1 marker, but a person who also has the EGFR mutation [45].

Anecdotal cases are important, but more influential to other physicians would be a larger series. Even better would be a controlled trial with sufficient power, and the very best, a study that has all these qualifications, but is also multi-centered. The FDA approved the aforementioned investigator-initiated study for 40 patients. It is not considered ethical to have patients with such severe disease and subject them to placebo controls. Thus, the study was to evaluate in a larger series the efficacy of mifepristone therapy for advanced lung cancer and compare outcome to historical controls, that is, from quality of life to life expectancy, when dealing with a similar group of patients with lung cancer that has stage IV and failed at least two chemo or immunotherapy regimens.

We were allowed two principal investigators. However, as an investigator-initiated study with no funds provided to the principal investigator by a pharmaceutical company or a grant, we could not find a principal investigator who treats a larger population of patients with lung cancer. Thus, we became, by default, the only principal investigator. Unfortunately, it is not totally clear to us as to the reasons, but despite our efforts we have only recruited the two aforementioned patients that were treated in this investigator-initiated study. Perhaps some of the fault lies in making the criteria for registering too harsh, but most of the problem is that we have not been referred very many patients to even screen for the study. Even the physician who referred us our first case who still is doing so well after almost 5 years of single agent mifepristone therapy, plus years with no side effects, has not referred us another patient [44]. We asked him if he had more patients and he stated that he could send us 40 patients in 1 year, but patients do not want to travel 100 miles every month to receive the medication. This seem unbelievable but this was also related to us by an oncologist whose research with us involving PIBF helped him get into medical school, where the patients would only have to travel only 15 miles. He was supposed to be our first principal investigator, but his associates objected. Even our own well renowned cancer facility at our institution turned down the opportunity to be a principal investigator and has never referred one patient for treating cancer whether they had lung cancer for this investigator-initiated study, or for compassionate use for other cancers. From what we have ascertained, they refer the patients to hospice when they are at the stage eligible for our study. Yet they kindly refer to us many patients to consider oocyte freezing or embryo banking before potential ovary damaging therapy.

3.10 Cases 10 and 11

Actually, there were two patients with lung cancer that we screened that would have qualified for the investigator-initiated study. They both had stage IV non-small cell lung cancer positive for the EGFR mutation that were at the end of targeted therapy (erlotinib, afatinib, and osimertinib) because the lesions were progressing. They both responded very well to single agent mifepristone. Their case reports were accepted for presentation at the 2020 American Association for Cancer Research ("Improvement in quality and length of life following treatment with mifepristone in women with stage IV non-small cell lung cancer positive for the EGFR mutation that previously progressed on targeted therapy"). Because our study was not recruiting very well, we advised these two patients to try compassionate use 200 mg mifepristone, where the drug can be shipped to their

homes, rather than travel thousands of miles monthly to receive the medication gratis as required by the study design.

3.11 Case 12

There were two other abstracts accepted by the annual 2020 AACR meeting. The title of one tells it all – “Treatment with oral mifepristone enables a patient with end-stage pancreatic cancer, in hospice, on a morphine drip, to restore a decent quality of life.” The only other patient who we treated with mifepristone from pancreatic cancer, similar to the aforementioned patient, demonstrated a marked relief of her severe pain that had been present despite opiates. However, her husband, a physician, was informed by a major oncologic center of a new phase I research study. He quickly brought his wife there for treatment and she died 2 days later from cardiac complications of the new drug [40].

3.12 Case 13

A third abstract accepted for the 2020 annual AACR meeting is entitled “Palliative benefits of oral mifepristone for metastatic osteosarcoma.” This shows the wide diversity of different advanced cancers that have responded to extremely well tolerated oral mifepristone, frequently providing the patients their best quality of life even when their cancers had not been as advanced. The reason is that even in less advanced stages, many of these patients suffered from side effects of chemotherapy or even immunotherapy.

Pancreatic cancer and fibrous osteosarcoma are not known to be associated with the nuclear P receptor. Other patients with some rare advanced cancers have demonstrated significant palliative benefit following mifepristone therapy include a malignant fibrous histiocytoma in a 23-year-old male and an extremely aggressive transitional cell carcinoma of the renal pelvis [40].

4. Clinical studies using mifepristone to treat cancer

4.1 Cancers positive for the classic progesterone nuclear receptor

The presence of the classic nuclear P receptor in breast cancer tumors has been known for at least 40 years [26]. The thinking in those days was that the presence of the hormone receptor may be needed for the tumor to proliferate. Thus, intervening with the hormone receptor interaction may inhibit cancer growth while not creating serious adverse effects in the patient as long as the hormone-receptor interaction was not essential to life or well-being.

Based on the beneficial effects of blocking the estrogen receptor with selective estrogen receptors, that is, tamoxifen, it is not surprising that mifepristone was evaluated for treating advanced breast cancer with the thought that the interaction of progesterone with the classic nuclear progesterone receptor could somehow allow tumors, for example, breast and ovarian cancer to proliferate.

Mifepristone is a type II progesterone receptor antagonist which promotes DNA binding and also promotes progesterone receptor phosphorylation [46]. Mifepristone was given to advanced stage tamoxifen resistant women (second line setting) and the authors reported a complete or partial response in about 10% [47]. However, 6 of the 11 showed stable disease [47]. Another small study found an objective response rate of 18% [48]. For first line, mifepristone for untreated metastatic breast cancer, a 10% objective response rate was observed [49].

The main method of evaluating efficacy of anticancer treatments 25–40 years ago, and even today, is inhibition of disease progression. Thus, the improvement did not seem adequate enough compared to other “more encouraging therapies”. Thus, interest waned in treating advanced breast cancer with mifepristone. Subsequently, more experience with mifepristone therapy for a variety of advanced cancers will show that although sometimes the treatment will cause a very good objective remission, the majority of the time the drug provides significant palliation and extension of a higher quality life while it slows disease progression.

For ovarian cancer not only is the classic nuclear progesterone receptor present but it also predicts a favorable outcome [50]. For similar reasoning as with breast cancer, mifepristone was given about 20 years ago to patients with ovarian cancer who had persistent lesions or recurrent lesions despite one round of chemotherapy [51]. Mifepristone 200 mg/day was given daily and continued until disease progression was found. They were treated for a mean of only 2 months. For 34 patients there was a response in 26.5% (9% complete and 17.5% partial) [51]. A second study of this drug conducted 10 years later showed a partial response in 42% of patients [52]. Again, the drug was stopped if there was any evidence of progression. The median time of treatment was 2 months [52]. From what we know today, if they would have continued the drug, the ovarian cancer may have progressed slowly while the patient maintained a high-quality extension of life [53].

5. Discussion

Should biopsy specimens be tested for PIBF to see if a given patient should be treated with mifepristone?

We do not think it would be unreasonable to see if a given specimen produces PIBF, but can we be sure that the tests are sensitive enough to deprive a patient the potential great benefit of treatment with mifepristone?

Can measurement of serum PIBF be helpful in determining if the cancer is responding to mifepristone or if mifepristone therapy is no longer working?

There have been developed more sensitive and specific serum PIBF assays [2]. However, based on measurement of serum PIBF in patients with gynecologic cancers or breast cancers that are P receptor positive, or even associated with breast cancer antigen 1 or 2, the serum level of PIBF may not be helpful for these purposes [54, 55]. It is the PIBF in the tumor microenvironment that seems to be most important, and this, of course, would be difficult to measure.

The 200 mg daily dosage of mifepristone does not appear high enough to block the glucocorticoid receptor. So, another important question, is if it is the action of mifepristone on blocking the P receptor that leads to its efficacy in treating cancer why does it seem to work in cancers that are not associated with the classic nuclear P receptor?

The evidence supports the fact that it acts on membrane P receptors. Activation of the nuclear P receptor initiates transcription, which is a slower process, whereas rapid activation of the membrane P receptor is a more rapid signaling action [46].

Do cancers need to secrete P to activate the membrane P receptor?

It is possible that at a certain stage cancer cells can make P or a P-like substance sufficient to interact with membrane P receptors. There is evidence that a large variety of cancer cells express the human chorionic gonadotropin (hCG)-beta subunit gene [56]. Activation of the hCG beta subunit gene to produce hCG could lead to local P production by the cancer cells. Alternatively, there may be some other mechanism to activate the membrane P receptor to make PIBF. Even with this

scenario, mifepristone could still block the effect of this theoretical non-P membrane P receptor agonist.

Does mifepristone only work when the cancer is at the stage of rapid metastasis?

It is possible that all cancers have mRNA to produce PIBF, but only at a certain level, that is, perhaps stem cell level is the membrane progesterone receptor is activated and PIBF is manufactured. Thus, it is possible that activation of tumor secretion of PIBF only occurs at the stage when it is ready to rapidly metastasize. About 20% of meningiomas are associated with the classic nuclear P receptor. However, a large study comparing mifepristone vs. placebo for unresectable tumors did not find any therapeutic benefit for mifepristone vs. placebo [57]. This could be because meningiomas are slow growing tumors and the PIBF mechanism is only seen with rapidly growing tumors. However, it is also possible that some meningiomas are considered benign. Thus, maybe it is the ability to make PIBF that is one factor allowing the tumor to follow a benign vs. malignant course. One benefit of this large study was to demonstrate a very good safety profile for mifepristone with few side effects [57].

Since a compassionate use IND is required by the FDA, that organization is reluctant to grant an off-label use unless all “standard” treatments have been exhausted. Thus, most of the study subjects in our center have been patients with very advanced cancers where there are few, if any, reasonable treatment options.

One exception is a man, who at the age of 58 was found to have bilateral renal cell carcinoma with metastases to local lymph nodes [42]. Renal cell carcinoma can be multifocal, and even when several lesions are present, the tumor is generally not extremely aggressive. Today the recommendation is renal sparing surgery and to remove the tumors every time one reaches a certain critical size [58–60]. But 16 years ago, the recommendation was bilateral nephrectomy.

Since there were no chemotherapy or immunotherapy agents 16 years ago for renal cell carcinoma, and the patient did not want to become a dialysis cripple, the FDA approved a compassionate use IND for oral mifepristone following a laparoscopic hemi-nephrectomy with retention of a kidney with three lesions left untreated.

After 10 years of single agent treatment, there were no new tumors. The three lesions previously noted on the left kidney remained stable [42]. After 10 years his diabetes caused kidney failure and the start of dialysis. Thus, he had the 1½ kidneys removed. After 2 years of hemo-dialysis, he was approved for a kidney transplant. He is still doing well 16 years from initial diagnosis [42].

This case showed that mifepristone can also work to inhibit tumor growth even when not at the rapidly growing cell stage. Whether this is specific only for renal cell carcinoma, or applies to other malignancies, needs to be determined. Thus, perhaps one should consider using mifepristone in earlier stage metastatic cancers following tumor remission following treatment with chemotherapy or immunotherapy to possibly inhibit recurrence or negate the need to treat with another chemotherapy or immunotherapy regimen with morbid side effects.

One final thought. Frequently, once a tumor has widely metastasized chemotherapy or even immunotherapy may frequently extend life somewhat at the expense of significant side effects from treatment. Mifepristone therapy is devoid of major side effects, and thus may provide possibly a longer higher quality life than “approved therapy.” The treatment of patients with cancer has provided huge profits both for the pharmaceutical companies and the treating institutions. So realistically it is unlikely that mifepristone therapy will become popular in capitalistic societies.

However, in some countries needed to provide effective, yet inexpensive treatment, one could consider offering patients oral government provided mifepristone rather than expensive chemo or immunotherapy agents. The cost of a mifepristone pill in China is 50 cents. In fact, since growth of tumors is still consistent with a prolonged good quality life, one could save money on expensive diagnostic tests to monitor progression. Possibly mifepristone could be considered first line therapy for metastatic disease with consideration of other therapeutic modalities only if health deteriorates despite mifepristone therapy.

Since the drug is available as a generic already, it is unlikely any pharmaceutical company will invest in larger studies to prove its efficacy. Hopefully, the published anecdotal cases, and the easing of the requirements for compassionate use, will encourage other clinicians treating patients with advanced cancer to try the drug and publish their findings. If enough treating physicians request compassionate use IND for mifepristone use, perhaps the FDA will eventually drop the requirement of compassionate use IND, facilitating the use for treating physicians around the world. Many countries, similar to the United States, at this time also restrict the use of mifepristone solely for the purpose of therapeutic abortions, and in some countries, it is completely illegal, at least at the relatively inexpensive price for the 200 mg dosage to use this drug. The use of the 300 mg dosage that does not require a compassionate use IND is cost prohibitive. Possibly the manufactures may one day reduce the price considerably or it will be manufactured by a generic company at a much lower price when the patent expires. Perhaps at a lower cost, insurance companies will be happy to pay for off-label use of mifepristone realizing how much cheaper it is for cancer therapy than conventional chemo or immunotherapy regimens.

As previously mentioned, clinical trials with mifepristone for cancers associated with the classic nuclear P receptor were “disappointing” and thus clinical trails were not pursued. When these studies were initiated 20–30 years ago, the hope was that metastatic cancer can be “cured.” It is now realized that the best hope for advanced cancer is a truce with extension of a better quality of life. Also, at that time the goal of therapy was to induce a tumor response as evidenced by complete or partial tumor regression. We think if they had used the endpoints of quality and length of life, they would have had the satisfaction of treatment as we have had in these anecdotal cases. The majority of cases do not show tumor regression but stable disease and improved quality and length of life.

As far as side effects, the drug has been well tolerated. In higher dosages mifepristone can, by blocking the glucocorticoid receptor, lead to higher serum cortisol levels which acts on the mineralocorticoid receptor leading to hypokalemia. One has to be careful when using other drugs that can interfere with the metabolism of mifepristone leading to hypokalemia. We had one unreported case of a woman adding mifepristone to her ongoing treatment with alpelisib, which in itself can cause hypokalemia. Whereas the combination led to hypokalemia, neither drug by itself caused it. She was taking just the 200 mg dosage of mifepristone.

Similarly, case number 9, who was taking the 300 mg dosage, did develop hypokalemia when she was switched to another bronchodilator for her COPD, but reverted back to normal when it was stopped. She was taking the 300 mg dosage of mifepristone [45].

One man with stage IV non-small cell lung cancer became more somnolent when adding mifepristone to his fentanyl that he was using for pain. Though we advised him to reduce the dosage of fentanyl, he chose to just stop the mifepristone and died 2 weeks later. He had only taken the mifepristone for 2 days.

Conflict of interest

The authors declare no conflict of interest.

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