Efficacy of the Progesterone Receptor Antagonist Mifepristone for Palliative Therapy of Patients with a Variety of Advanced Cancer Types

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Abstract. *Background: Mifepristone has been demonstrated to improve longevity and quality of life in mice with spontaneous murine cancer without progesterone receptors and in human colon cancer. The present study evaluated the palliative effect of mifepristone in a variety of different types of human cancer. Patients and Methods: Mifepristone was given at 200 mg daily orally with permission from the Food and Drug Administration to people with widely metastatic human cancer no longer responsive to other chemotherapy regimens. Results: Improvement in pain and energy and/or length of life was found in thymic epithelial cell carcinoma, transitional cell carcinoma of the renal pelvis, leiomyosarcoma, pancreatic carcinoma, malignant fibrous histiocytoma and another case of adenocarcinoma of the colon. Conclusion: Our data demonstrate a palliative role for the use of mifepristone in cancer therapy. Progesterone receptor antagonists should be given a therapeutic trial in larger controlled studies of various malignancies in humans.*

There are data suggesting that the fetal semi-allograft escapes immune surveillance from natural killer (NK) cells with the help of a 34 kDa protein known as the progesterone-induced blocking factor (PIBF) (1, 2). This PIBF protein is expressed by T-cells (3). There is evidence that expression of PIBF is the result of the interaction of a high concentration of progesterone generated at the maternal fetal interface with a progesterone receptor that develops on T-cells from exposure to an allogeneic stimulus (4).

In 2001, a hypothesis was presented suggesting that various malignancies may 'borrow' the PIBF mechanism to inhibit natural killer cell activity at a local level against certain tumor antigens that would normally evoke immune surveillance by NK cells (5). The hypothesis suggested that cancer cells could evoke PIBF expression by T-cells either through some alternative pathway that did not involve progesterone production or a pathway that involved progesterone secretion (5).

If PIBF is generated independently of progesterone, then anticancer therapy could potentially still be achieved by monoclonal antibody therapy directed against PIBF, especially since this protein is not essential for normal human function. Monoclonal antibody therapy has its limitations. However, if PIBF were found to be somehow related to progesterone secretion, then a more effective and relatively non-toxic therapy may be achieved by using a drug that blocks progesterone receptors.

A theoretical pathway of progesterone production by cancer cells was provided by the demonstration of human chorionic gonadotropin β subunit gene expression in cell lines of cancer cells of different types of origin (6). Evidence that at least white blood cell cancer can express PIBF was provided by demonstrating that all 29 human leukemia/lymphoma B-cell, T-cell, myeloid cell and fibroblast epithelial cell lines demonstrated messenger RNA for PIBF (7). Even more interesting, was the demonstration that adding progesterone to the media caused up-regulation of the expression of the PIBF protein by three cell lines expressing the protein and that adding the progesterone receptor antagonist mifepristone reduced PIBF protein expression (7).

Subsequently, it was demonstrated that gavaging mice prone to spontaneous leukemia could improve length and quality of life compared to controls (8). It would not seem likely that solid cancer cells are able to express PIBF, but more likely that they may direct T-cells in the tumor microenvironment to express the PIBF protein. Thus, if the allogeneic stimulus of tumor antigens causes the induction of progesterone receptors on T-cells similar to pregnancy, and if tumor cells enable progesterone production possibly

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related to the secretion of hCG, the interaction of a high local concentration of progesterone with the progesterone receptors could enable local PIBF expression in the tumor microenvironment from the T-cells. The PIBF secreted could then inhibit NK cell activity in the tumor microenvironment.

If this mechanism does exist, then the use of a progesterone receptor antagonist may be able to block the interaction of progesterone with its receptor and thus inhibit PIBF expression. Theoretically, suppression of PIBF would remove the block from NK cells and thus allow NK cells to inhibit tumor progression.

Mifepristone therapy was found to improve longevity and quality of life in mice with a variety of spontaneous solid tumors not known to be associated with progesterone receptors, *e.g.* lung, prostate and testicular cancer (9-11). Marked improvement in the length and quality of life was also reported in two patients with extremely advanced widely metastatic colon cancer resistant to chemotherapy, treated with mifepristone (12).

In light of these data, especially the improved quality and length of life in various types of spontaneous animal cancer, we applied for permission to the United States Food and Drug Administration to treat end-stage advanced cancer patients (both male and female) with mifepristone to see if treating patients with a variety of cancers with mifepristone can produce palliative effects similar to those demonstrated with spontaneous murine cancers treated by mifepristone. The study would also try to determine if the palliative effects of progesterone receptor antagonist therapy are restricted in humans to adenocarcinoma of the colon, or whether other responsive human cancers would be found.

Patients and Methods

Permission from the Food and Drug Administration was obtained to use off-label mifepristone at 200 mg orally daily in patients with advanced cancer having failed standard chemotherapy or having a type of cancer with known resistance to standard chemotherapy. The immediate and subsequent response to this therapy was recorded.

Sometimes the drug was used alone and sometimes with some other type of palliative therapy that the patient was already taking. Tumor progression was determined by standard testing *e.g.* computed tomography (CT) scans at the direction of their specific oncologists. Since this was not a funded study, the oncologists had no obligation for their patient to have monitoring *e.g.* CT scans at certain intervals to determine if the medication caused any tumor regression. Frequently, the patients had such advanced disease that they were close to, or already in a hospice, and the oncologists did not believe that further evaluation of tumor progression was worth the inconvenience to the patient, or increased insurance costs. Thus the main end-point was the difference in length of life following therapy compared to that predicted by the oncologist and whether the patient reported any subjective improvement in symptoms *e.g.* pain and energy. Of course if tumor progression was monitored, we included the results in the study. The patients or their caretakers were called every two weeks and were questioned specifically about improvement in pain, energy and whether any increased social activity was noted.

Patients were monitored for serum cortisol after two weeks of treatment and then monthly thereafter until death to be sure the drug did not cause adrenal insufficiency.

Results

Mifepristone 200 mg per day was approved by the FDA for the following types of stage 4 malignancies with extensive metastases that had failed to respond to conventional chemotherapy for that particular tumor: thymic epithelial cell carcinoma, transitional cell carcinoma of the renal pelvis, leiomyosarcoma, colon adenocarcinoma, pancreatic adenocarcinoma, and malignant fibrous histiocytoma. All patients reported significant decrease in pain and improved energy within 2 weeks of starting the medication. No one reported any side-effects.

Thymic epithelial cell cancer. A 46-year-old woman with thymic epithelial cell carcinoma reported feeling very well for 2 years while taking mifepristone. She was the first human case that we treated. She had a prior history of surgery and radiation therapy to the mediastinum and lungs. She had failed to respond to octreotide. No lesions disappeared following mifepristone treatment, but there was very little growth over 2 years. Her oncologist decided to irradiate the mediastinum again. She developed pulmonary fibrosis as a complication of the radiation. She was advised to stop taking mifepristone by her oncologist when she began her second course of radiation therapy and died 2 months later. According to the Thymic Cell Carcinoma Society she had survived the second longest time of any patient with this type of cancer.

Transitional cell carcinoma of the renal pelvis. A 73-year-old man with transitional cell carcinoma of the renal pelvis had a radical cystoprostatectomy and nephroureterectomy in an attempt to resect the tumor. Extremely rapid and extensive metastases ensued and disease progression rapidly continued despite treatment with paclitaxel and cisplatin, then carboplatin and gemcitabine. The family was advised that he had no more than one week to live. After taking mifepristone, not only was his life extended to eight weeks but his quality of life significantly improved as shown by a marked improvement in energy and a decrease in pain. A CT scan performed six weeks after treatment showed no growth of any of the metastatic lesions and the disappearance of some. His disease had been so aggressive that each prior CT scan had shown marked progression of disease without any benefit with his two prior chemotherapy regimens. The only time interval where cancer progression was halted and even reduced was during his 2 months on mifepristone.

Leiomyosarcoma. A 45-year-old woman with widely metastatic leiomyosarcoma surgically treated by total abdominal hysterectomy was found to have lung metastases two years later. Following right lung tumor resection, letrozole was given because the tumor was estrogen receptor positive. The letrozole did not halt new lung metastases so she was treated for 5 months with 7 cycles of gemcitabine/docetaxel. Despite this therapy, progression of the lung metastases continued and tumors were resected in both lungs. The patient then underwent bilateral oophorectomy. The cancer progressed despite treatment. She was then treated with mifepristone. For the first time the lesions decreased in size dramatically and had mostly disappeared. Furthermore, she regained her energy and her breathing improved. After six months some lesions started to reappear. Seeing this, her oncologist concluded the cancer was now refractory to mifepristone and stopped the medication and started her on some other chemotherapy regimen (not known). She died of complications from this new regimen.

Colon cancer. A 43-year-old with stage 4 metastatic colon adenocarcinoma, having failed standard chemotherapy regimens, started mifepristone. Similarly to the previously described women with stage 4 metastatic colon cancer, there was a halt to disease progression and her pain markedly improved, as did her energy (12). After 1 ¾ years some lesions began to grow again. She assumed that this was the last of her remission so she stopped taking mifepristone, and died 3 months later.

Pancreatic cancer. A 58-year-old woman had stage 4 pancreatic adenocarcinoma widely metastatic to her liver which had shown progression with gemcitabine and erlotinib, and hence she had been on palliative treatment with capecitabine plus oxaliplatin. However, despite therapy she was in great pain. Within 2 weeks of starting mifepristone, her requirement for narcotics dropped to less than a third. Her energy also improved. She continued with significant pain relief for another 2 weeks. She was then approved for another chemotherapy regimen, which required her to stop taking mifepristone. She died within 2 weeks related to complications of the new chemotherapy regimen.

Malignant fibrous histiocytoma. A 23-year-old male with widely metastatic malignant fibrous histiocytoma was in extreme pain unrelieved by extensive use of narcotics. He was told that he had only 2 more weeks to live. Within a week of mifepristone, the pain markedly diminished and he required less than 25% of his previous narcotic dosage to achieve quite adequate relief of pain. His energy markedly improved and he had returned to a functional life. He had lived with much improved energy and much less pain for 3 ½ months before the pain started to intensify. He died after 4 months of mifepristone therapy.

None of the patients showed evidence of decreasing serum cortisol levels with mifepristone. If anything the levels increased somewhat but not significantly. Since mifepristone is a glucocorticoid receptor blocker, suppression of serum cortisol would not be expected. Probably future studies should not include serum cortisol monitoring.

Discussion

Although clinical experience is limited, to date, all patients with a variety of very extensive cancer types have demonstrated some type of improvement in clinical symptoms or slowing of the progression of disease following treatment with mifepristone. There were few, if any, side-effects of the medication (reduced price courtesy of Danko pharmaceutical). Because it is an off-label use third party payers do not reimburse for the mifepristone therapy. It costs about $450 per month.

Mifepristone is a synthetic 19-norsteroid that has a high affinity for both progesterone and glucocorticoid receptors resulting in a competitive inhibition of both types of hormones (13, 14). At a certain dosage symptoms of adrenal insufficiency, *e.g*. weakness occurs. The decision to use the dosage of 200 mg/day was based on the demonstration of some response as far as shrinkage of some tumors known to be progesterone receptor positive, but without significant side-effects (15-19).

In the murine studies we conducted in mice with tumors that were not likely to be positive for progesterone receptors, the improvement was not in the disappearance of tumors but in increased longevity and much improved body conditioning scores (8-11). Similar observations were noted in two patients with extensively metastatic colon cancer, *i.e*. improved longevity, improved quality of life, a halt to the rapid progression but no disappearance of metastatic lesions (12). It is interesting that in a phase II trial of mifepristone for untreated metastatic breast cancer known to be positive for progesterone receptor, the conclusion was that mifepristone had only minimal activity (19). The parameters evaluated were complete regression of metastatic lesions (no patients), partial response, *i.e*. some disappearance or shrinkage of tumors (3 women), stable disease in 11 and progressive disease in 14 (19). Thus compared to other agents, these responses were disappointing in this supposedly ideal group (19).

However, based on our observations, we believe that the response to progesterone receptor antagonists should not be judged on tumor regression, but on an improvement in quality of life, length of life and disease stabilization rather than remission. Thus, it may serve more in a palliative than a curative role, at least as a single agent.

Interestingly, using the same dosage of 200 mg/day, the breast cancer study found lethargy and nausea in 68%,

anorexia in 29%, vomiting in 29%, hot flashes in 50%, and skin rash in 32% (19). None of the patients in the present study had these complaints. However, they were not given quality of life questionnaires with these specific complaints. They were merely asked questions concerning their energy, pain and whether there were any significant side-effects. All patients had some improvement in the first two categories and no one complained of side-effects. We were concerned that 400 mg/day may induce significant glucocorticoid deficiency side-effects and could lead to symptoms of adrenal insufficiency, *e.g.* nausea, anorexia, weakness, confusion and abdominal pain. Since the main objective was palliation, we elected not to try this higher dosage.

Our studies of human leukemia cell lines showing mRNA for PIBF in all cell lines tested leads us to suspect that the palliative effect of mifepristone was acting on the progesterone receptor and not on the glucocorticoid receptor (7). However, the nature of this study does not allow us to draw any conclusions as to the mechanism of action of mifepristone in these cases. To best distinguish whether the palliative effect is related to progesterone receptor antagonism *vs.* glucocorticoid receptor antagonism, one might try treating with a more pure progesterone antagonist, *e.g.* onapristone (20). Onapristone has induced tumor responses in primary breast cancer positive for progesterone receptors (20). Our preference would have been to use onapristone rather than mifepristone. However, only mifepristone was commercially available. Higher dosages may be possible if one develops the proper pure progesterone antagonist.

The possibility exists that mifepristone blocks the receptor for cortisol, but not for some of the synthetic glucocorticoids, *e.g.* prednisone or methyl-prednisone. If this is found to be true, one could consider higher dosages of mifepristone with the addition of synthetic glucocorticoids and possibly synthetic mineralocorticoids.

In the United States mifepristone is a restricted drug. It can only be used by licensed abortionists. One needs special permission from the Food and Drug Administration to use it off-label. Approval can only be obtained for cases where no known approved therapy exists or the patient has proven resistant at this time to standard therapy. It is hoped that this study could stimulate interest in trying mifepristone for various cancers in other countries than the United States where the anti-abortion politics are not so strong that it is very difficult to freely prescribe this drug even if the end-point is termination of cancer and not pregnancy.

The case of thymic epithelial cell cancer had come for her annual gynecologic examination and mentioned that she was diagnosed with this very rare cancer for which there appears to be no adequate chemotherapy. Unfortunately radiation therapy had failed to halt progression. She was advised of our theory that some types of cancer may 'borrow' a mechanism from normal pregnancy that is used to escape natural killer cell surveillance. She was also advised of our preliminary positive data showing that a treatment with mifepristone seemed to prolong length and quality of life in the mice with various cancers that were treated.

We said we could apply to the FDA for permission to use this drug. We chose 200 mg per day because this dosage had been safely used in other conditions, *e.g.* Cushing's syndrome and meningiomas without causing adrenal insufficiency unlike 400 mg/day. The FDA approved her use of the drug not because she was end-stage, but because there was no other chemotherapy known to halt the tumor (she failed to respond to the experimental use of octreotide).

Since she was under the continued observation of her oncologists and had CT scans at two month intervals in her case we had the opportunity to observe her progress for two years. The lesions did not grow or increase in number, whereas they had been growing and increasing in number for six months prior to therapy. She had prior symptoms of mildly diminished energy, which she reported improved for the two years she was on the mifepristone and she maintained normal activities.

She was the first human case that we treated. She was still nervous that the mifepristone though halting tumor progression, did not induce a remission. A consultation with a different radiation therapist led to the attempt to 'eradicate' the cancer with a second course of radiation therapy which ultimately led to complications and her death. Besides the halt in tumor progression, the fact that she lived longer than almost all other cases with this cancer suggests that the mifepristone did have some palliative benefit.

The man with the extremely aggressive transitional cell cancer of the renal pelvis quality of life had deteriorated so much that he was in hospice. We certainly could not ask the patient to fill out a standard quality of life form. Sometimes predictions of imminent death are not accurate and a patient who lives two months instead of one week could happen by chance alone. However, the fact that for the first time metastatic lesions decreased in size or disappeared and he showed significant improvement in energy makes us believe he was benefited by the mifepristone therapy.

The leiomyosarcoma was the only cancer that showed almost complete remission with mifepristone therapy. The previous failure to respond to other chemotherapy and anti-estrogen treatment leaves little questions that this tumor responded to the progesterone receptor antagonist. The end-point used for this patient was observation of disease progression by CT scans.

The end-point of assessment in the case of colon cancer was the demonstration of failure of any growth of metastatic lesions or appearance of any new ones by CT scan whereas the disease had progressed with prior chemotherapy. Though she was not administered a formal quality of life questionnaire, our phone interview (she lived in a different

state and we did not make her physically come to our office but allowed her to be monitored by her local oncologist) concluded that she had a marked improvement in energy and pain similar to the findings of the aforementioned cases of colon cancer similarly treated (12).

The 58-year-old woman with pancreatic cancer was under hospice care. Questions regarding her pain and energy were answered by her husband, who was a physician. He was amazed with the quick improvement in pain and energy once treatment started. Since we advised him that based on animal and human experience we think this medication only has palliative benefit, he opted to try a new chemotherapy regimen intending cure, which unfortunately produced complications that led to her death.

The 23-year-old male with metastatic malignant fibrous histiocytoma was told he had terminal disease. We were all extremely happy when he showed a dramatic improvement in his symptoms, especially pain and energy, with therapy. We were disappointed, however, that his life was not extended past four months. He had been told that he would probably die within one month.

When we applied for funding for larger formal human studies we were refused, with the suggestion to resubmit after obtaining some preliminary human data. Based on these anecdotal experiences, we have been finally able to obtain a grant to study the effects of mifepristone on stage 4 non-small cell lung cancer, which has failed two different standard chemotherapy regimens. This will be a phase 2 salvage study. The primary end-point will be progression free survival. The efficacy/safety endpoints will be response rate, overall survival (the expected survival is 2 ½ months for this group) toxicity assessment and quality of life as assessed by lung cancer symptom scale (LCSS).

The FDA would not allow the evaluation of a group with less severe disease. Lung cancer was chosen because the oncologists at our institution have an interest in studying this group. We have no anecdotal experience with humans with lung cancer, but mice with spontaneous lung cancer responded very well to this therapy.

There probably are some countries where the political issues of using an 'abortion' drug may not be as much of an impediment for using mifepristone in treating cancer. It is hoped that the sharing of our anecdotal experiences, suggesting a significant palliative effect of this type of therapy, may generate interest in larger studies of end-stage patients with other cancers or the use of this drug, or other progesterone receptor antagonists for less advanced cancers. Perhaps this treatment when administered at earlier disease stages could show an even greater ameliorative effect, either alone or in combination with other therapies. Hopefully, this study will stimulate other cancer centers to design controlled studies for a variety of cancer types.

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