Long-term High-quality Survival with Single-agent Mifepristone Treatment Despite Advanced Cancer

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Abstract. Case Report: We show long-term high-quality survival following single-agent treatment with a progesterone receptor antagonist in two cases of advanced metastatic cancer. Because no biopsy was performed (patient refused) the exact type of lung cancer was not determined but the majority of oncologists who evaluated the patient thought that the rapid onset and syndrome of inappropriate anti-diuretic hormone was more consistent with small-cell lung cancer. The US Food and Drug Association granted a compassionate-use investigational new drug approval for use of single-agent 200 mg mifepristone orally/day to a moribund woman with never-treated metastatic lung cancer and a male with bilateral renal cell carcinoma who had undergone only a unilateral hemi-nephrectomy. Both had long-term high-quality survival (5 years for the patient with lung cancer with complete remission of all lung lesions, and 12 years for the male patient with kidney cancer). Neither patient had any side-effects from mifepristone therapy. Conclusion: These cases helped influence the US Food and Drug Association in granting an investigator-initiated investigational new drug study on advanced non-small cell lung cancer.

A hypothetical model for potential tumor immunotherapy based on the knowledge of immune mechanism responsible for the fetal semi-allograft escaping immune surveillance was published in 2001 (1). Logically, it makes sense that malignant tumors may ‘borrow’ mechanisms already in existence in normal pregnancy to similarly prevent immune rejection (1).

Immune fetal tolerance requires a balance between regulatory T-cells, effector T-cells and co-stimulatory pathways (2). The programmed cell death (PD)-1–PD1 ligand (PD1L) negative co-stimulatory pathway has been found to be essential for inducing and maintaining fetomaternal tolerance (3). This has led to the development of biological agents using antibodies targeting PD1 (also known as B7 homolog-1 or B7H1) and PD1L as immunotherapy for cancer, including non-small cell lung cancer and melanoma (4).

Another critical protein used by the fetal semi-allograft is known as the progesterone-induced blocking factor (PIBF) (5). The full-length protein consists of 757 amino acid residues. The parent compound, measuring 90 kDa, resides in the nucleus at a centrosomal position. A 34 kDa form is found in the serum and is believed to be caused by the interaction of progesterone with its receptors (PR) on γ/δ T-cells without the need for an allogeneic stimulus (7). An intracytoplasmic splice variant of the parent compound seems to be of similar size to the serum protein (8).

Adding progesterone to the media of human leukemia cell lines up-regulates intracytoplasmic PIBF expression, whereas adding the PR antagonist (or modulator is probably a more accurate term) mifepristone down-regulates intracytoplasmic PIBF expression (9). PIBF seems to be present in the cytoplasm of all rapidly growing cells, which would include fetal cells and cancer cells but not normally dividing cells (8). Thus, the PIBF protein seems to be a logical target to suppress in order to allow the normal body to immunologically destroy cancer cells (10).

In contrast to suppressing the PD1–PD1L negative co-stimulatory pathway to suppress tumor growth, which is also needed to suppress immune attack of normal cells (and thus anti-PD1 and -PD1L therapy are associated with a high frequency of autoimmune complications, e.g., severe Crohn’s disease), theoretically, suppressing PIBF should be associated with few side-effects because it is not needed in
cells growing at a normal speed. Reported below are two cases that had marked extension of expected life-span, marked improved quality of life, and no side-effects while being treated with mifepristone monotherapy.

**Case Report**

*Case 1.* An 80-year-old woman was admitted to the Intensive Care Unit for respiratory failure. Chest x-ray revealed many lung lesions most consistent with lung cancer with multiple lung metastases. She was subsequently admitted several more times with very low arterial pO2 levels and her serum sodium progressively decreased to 118 mmol/l. The radiological and clinical diagnosis was probable advanced lung cancer with the syndrome of inappropriate antidiuretic hormone (SIADH) from ectopic tumor production of arginine vasopressin. The patient refused surgery or chemotherapy but did agree to experimental use of oral mifepristone at 200 mg daily. Her pO2 returned to 99-100 mmHg within 1 month and her serum sodium level returned to normal. Six weeks later, all her lung lesions had gone by computed tomographic scan. The patient’s PO2 remains 96-98 mmHg, and her most recent computed tomographic scan continued to show no tumors 5 years after initial treatment. Her treatment had been approved by the US Food and Drug Association (FDA) on a compassionate basis.

*Case 2.* A 58-year-old male with bilateral renal cell carcinoma with metastasis to local lymph nodes received FDA approval to use 200 mg daily mifepristone on a compassionate basis because at that time there was no chemotherapy that was known to be effective. The patient refused bilateral nephrectomy, agreeing to only laparoscopic right hemi-nephrectomy in order to remove the largest lesion, leaving the left kidney intact. The left kidney lesions did not recede, but remained stable for 10 years, and no new lesions appeared on bi-annual computed tomographic scans. After 10 years of therapy, diabetes caused this patient to go into renal failure. He then underwent a bilateral nephrectomy and subsequently a kidney transplant. The patient is still fine after 12 years from diagnosis.

Neither patient has reported any side-effects from long-term use of mifepristone at 200 mg daily. The male with renal cell carcinoma is still taking 200 mg/day mifepristone. The female with lung cancer recently died of an acute myocardial infarction at the age of 85 years and she was lung cancer-free up to the time of death and continued her daily dosage of 200 mg/day mifepristone.

**Discussion**

These two cases demonstrate significant long-term survival, and improved quality of life, and in one of these, a prolonged disease-free interval with single-agent mifepristone therapy. These two patients received no other chemotherapy, radiation therapy, or immunotherapy. The patient with lung cancer did not even have any surgical treatment, and the patient with renal cell carcinoma underwent incomplete surgery.

These are not unique cases in that mifepristone immunotherapy has been given to other patients with advanced cancer with permission from the FDA on a compassionate basis because no other therapies were available. Significant palliation was observed in a variety of other types of cancer (11-13).

On the basis of the aforementioned patients with lung cancer in this present report, and similar improvement in a controlled study of mice with spontaneous lung cancer, the FDA has granted an investigator-initiated investigational new drug approval for studying the use of single-agent mifepristone for patients with stage IIIB or stage IV non-small cell lung cancer having failed to stop progression despite two rounds of chemotherapy/immunotherapy (14,15). Of course with the presence of SIADH, our patient with lung cancer could have had small cell lung cancer.

Due to the fact that mifepristone in dosages well above the dosage needed to cause abortion of a fetus failed to lower serum PIBF levels, Check et al. hypothesized that the benefit of the progesterone receptor modulator mifepristone for various cancers is related to suppressing the conversion of the 90 kDa parent nuclear-associated protein to the 34-36 kDa intracytoplasmic splice variant of PIBF (16,17). Nevertheless, the PR may be involved in other ways to allow cancer cells to escape immune surveillance (17).

Although it is possible that PIBF could also help fetal and cancer cells escape immune surveillance by suppression of natural killer cells in the tumor microenvironment, the suppression of intracytoplasmic PIBF by mifepristone, but not circulating PIBF, seems to detract from this hypothesis (9, 17, 18). Serum levels of PIBF are not elevated in gynecological or breast cancer even if PR-positive (19, 20).

To date, the data are limited by small numbers restricted to anecdotal cases. Mifepristone seems to be very well tolerated in 200-300 mg dosages. As far as we are aware, there has not been one individual treated with this drug for cancer who has not shown some benefit (11-13). In some cases the drug may induce complete remission, as in the aforementioned patient with lung cancer, and in some instances inhibit more tumors from forming and thwart growth of pre-existing lesions without complete regression, as in the case of renal cell carcinoma described.

Hopefully these reports will stimulate interest in other researchers to corroborate or refute this initial positive anecdotal experience. If corroborated, hopefully, interest could be generated in performing large prospective clinical trials for a variety of treatment-resistant cancer types.
References


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