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Mifepristone Extends Both Length and Quality of Life in a Patient With Advanced Non-small Cell Lung Cancer that Has Progressed Despite Chemotherapy and a Check-point Inhibitor

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Abstract. *Case Report: Case 1 of an investigator-initiated study using oral single agent mifepristone to halt stage IV non-small cell lung cancer whose tumor was devoid of any targeted markers has remained ECOG zero and in good health for over 3 years. Case 2, reported here, is a 68-year-old woman with stage IV non-small cell lung cancer whose tumor was positive for the programmed death ligand-1 (PD-L1) marker. Her cancer progressed despite treatment with a check-point inhibitor (nivolumab), besides 3 rounds of multi-agent chemotherapy. After 1 ½ years of treatment with single agent mifepristone, her cancer remains stable (even some tumor regression) and her quality of life is only impaired by her pre-existing chronic obstructive lung disease, not her cancer. Conclusion: Mifepristone therapy may provide a method to halt metastatic lung cancer positive for the PD-L1 marker when check-point inhibitors are no longer effective.*

The progesterone receptor modulator, mifepristone, has been found to improve quality of life, and extend the length of life when used as a single agent treatment in patients with a variety of advanced metastatic cancers that have progressed despite standard therapy, or were not candidates for chemo or immunotherapy, even when the tumors were devoid of the classic nuclear progesterone receptor (1-4).

The hypothesized mechanism of action of mifepristone is that this progesterone receptor modulator suppresses a progesterone-associated immunomodulatory protein that is unique to rapidly growing cells in the fetal placental unit, including embryonic, mesenchymal, and trophoblast cells, and in rapidly growing cancer cells. This protein is called the progesterone induced blocking factor (PIBF) (5-8).

The parent protein of PIBF has a molecular weight of 90 kDa, consists of 757 amino acid residues (9), resides in the nucleus and is associated with the centrosome (9).

The parent PIBF protein is cleaved to generate various cytoplasmic proteolytic products that include the biologically active-N-terminal portion and have immunosuppressive activity (8, 9). For example, the 34-kDa intracytoplasmic isoform (similar in size to the circulating isoform found in the serum after exposure to progesterone in males or females), inhibits natural killer (NK) cell cytolytic activity by preventing degranulation of perforin granules (10).

Both, the messenger RNA (mRNA) and the 34-kDa isoform have been found in a high percentage of various human leukemia cell lines (11). Interesting, incubation with progesterone up-regulated both PIBF mRNA and protein, whereas the progesterone receptor modulator, mifepristone, down-regulated PIBF mRNA and protein (11).

Based on anecdotal evidence showing considerable palliation and increased longevity when used in treating a variety of cancers, and on controlled studies in spontaneous murine cancers, the United States Food and Drug Administration (FDA) approved an investigator-initiated investigative new drug approval (IND), to treat up to 40 patients with stage IIIB or IV non-small cell lung cancer, that had progressed despite a minimum of two chemotherapy or immunotherapy regimens ("A phase II study of treatment with oral mifepristone as salvage therapy in patients with advanced or metastatic non-small cell lung cancer who have failed two or more previous chemotherapy regimens") (www.clinicaltrials.gov) (1-4, 12-14). The study was approved by the Chesapeake Institutional Review Board (approval number Pr000011306).

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The first patient, presented at the 2017 meeting of the American Association for Cancer Research (AACR), had stage IV non-small cell lung cancer with brain metastasis. He has now completed 42 monthly treatment cycles of daily oral mifepristone 300 mg/day, is still ECOG zero, and his answer to all 43 questions on his quality of life questionnaire was "not at all". His lung lesions have not progressed, and some have regressed, and there has been no evidence of brain metastasis (15, 16).

The PIBF protein is not the only protein used by the fetal placental unit to escape immunosurveillance that is similarly used by cancer cells to escape immune surveillance (5). One such protein is known as programmed cell death protein 1 (PD-1). This PD-1 protein interacts with two ligands to balance regulatory T-cells, effector T-cells, and co-stimulatory pathways (17-19). This has led to the development of antibodies that target these check-point inhibitors, *e.g.*, PD-1 or PD-1 ligand (L)-1 (PD-L1) (20).

Two of these check-point inhibitors, known as nivolumab and pembrolizumab, are commercially available, and have made a tremendous impact in the prolongation of life in patients with metastatic non-small cell lung cancer (20-25).

The first patient in the aforementioned investigator-initiated study, was not considered a candidate for nivolumab or pembrolizumab because his tumor was devoid of the PD-L1 marker. The second case examined in this study, which is reported here, had non-small cell lung cancer that progressed despite multiple courses of chemotherapy or immunotherapy with nivolumab. This case report documents a positive response to single agent mifepristone, which activates the immune destruction of the tumor by inhibiting intracytoplasmic PIBF by blocking extranuclear membrane P receptors (7, 16).

Case Report

A 66-year old woman with chronic obstructive lung disease (COPD) presented with increased respiratory distress. Computerized tomography was suspicious for advanced lung cancer. Subsequent surgical biopsy revealed a non-small cell adenocarcinoma of the lung. Further testing concluded she was stage IV. The tumor was positive for the PD-L1 marker.

She was first treated with 4 cycles of carboplatin, pemetrexed, and bevacizumab in 2014. In 2015 she received 6 cycles of carboplatin and docetaxel. Still in 2015, she completed 6 cycles of erlotinib (the tumor was also positive for the epidermal growth factor receptor (EGFR) marker).

Starting at the end of 2015, she received 11 cycles of nivolumab. When her cancer disease subsequently progressed, nivolumab treatment was stopped. She met the inclusion criteria for the mifepristone study, and was started on 300 mg daily as single agent oral therapy.

After 18 months of single agent mifepristone therapy, there has been no disease progression based on CT scans performed every 2 months. In fact, some lesions have become smaller.

She was considered ECOG 1 at the start of mifepristone therapy. She was still considered ECOG 1 with a good quality of life and normal activity for 12 months. In the last 6 months her quality of life and activities have become decreased, not related to her lung cancer, but due to the progressively worsening COPD. In the last month she requires 4 liters of oxygen supplementation per minute to maintain a PO2 of greater than 80 with mild activity, and is considered ECOG 3. Other than shortness of breath, she has no other complaints.

Discussion

Similarly to the first case in this study, this second case of a patient with non-small cell lung cancer of stage IIIB or IV treated with mifepristone, demonstrated long lasting palliative benefits, and significantly increased longevity than what was predicted by the consulting oncologists (with no other treatment recommendations). Therefore, single-agent oral mifepristone, can, in some cases, stop progression of non-small cell lung cancer. However, such anecdotal evidence does not indicate whether this treatment is effective in only a small minority of cases, or in the majority. If the first two cases seemingly responded, but the next 30 did not, one would actually question whether the apparent positive outcome was merely fortuitous, and possibly represented some spontaneous remission, which sometimes occurs. It should be noted that so far these are the only two patients that have been recruited in the study.

Prior to the aforementioned investigator-initiated FDA approved study, there was another patient with advanced lung cancer who responded very well to single agent mifepristone therapy. She was an 80-year old with rapid onset respiratory distress who received 200 mg, rather than 300 mg, of the drug mifepristone. Her PO2 was 70 mmHg upon initial presentation, and her serum sodium was 118 mmol/l, consistent with the syndrome of inappropriate antidiuretic hormone. The chest x-ray and CT scan showed multiple lung nodules. She refused surgical biopsy, but the clinical presentation suggested small cell lung cancer (4). She had no previous treatment for her lung cancer, *i.e.*, neither surgery, radiation therapy, chemotherapy, or immunotherapy (4). One month after daily mifepristone treatment, her PO2 without extra oxygen, was 95 mmHg, and her serum sodium normalized at 145 mmol/l. Six weeks later, the CT scan showed regression of all nodules, but still showed a ground glass appearance. She remained in complete remission for 5.5 years, dying of a myocardial infarction at age 85.5.

This woman with probable small cell lung cancer had been advised that she probably had only two months to live. Thus, it seems highly likely that the complete remission for

5.5 years (and probably longer had she not had a myocardial infarction) was related to the mifepristone treatment, rather than to spontaneous remission. This case shows that mifepristone can correct the syndrome of inappropriate anti-diuretic hormone by causing tumor regression, since no other treatment for this condition was given (4).

The possibility exists that mifepristone would only be effective for those tumors positive for the PD-L1 marker, similar to check-point inhibitors. Case 1 of this investigator-initiated study showed that mifepristone is effective even when the PD-L1 marker is absent. Thus, mifepristone therapy could be recommended to patients, who are not likely to respond to check-point inhibitors, as first line "endocrine/immunotherapy".

Case 1 also showed that mifepristone may cross the blood-brain barrier and inhibit the progression of brain metastasis. It is possible that mifepristone is not effective for tumors that are positive for the PD-L1 marker. Alternatively, possibly the check-point inhibitors, and mifepristone may work in similar areas of the immune system, and thus not be effective for those patients progressing despite nivolumab, pembrolizumab or other check-point inhibitors. However, the case presented here, our second case, has shown that a patient who progresses despite both chemotherapy and immunotherapy with check-point inhibitors may still respond to mifepristone.

Most previous anecdotal cases were treated with a 200 mg dosage of mifepristone (1-4). The drug was very well tolerated consistent with extensive data from patients that used it for the treatment of meningiomas (26). The case presented here, similarly to the first case in the study, showed that the 300 mg dosage of mifepristone is also well tolerated and relatively free of side effects.

Hopefully, this case, added to the results of case 1, showing long-term high-quality survival, will generate interest in an oncologist who treats a large number of patients with metastatic non-small cell lung cancer to become a principal investigator, and thus expedite this study which has been approved for 40 patients by the United States FDA.

Conflicts of Interest

There are no conflicts of interest regarding this study.

Authors' Contributions

Jerome H. Check, M.D., Ph.D. is the principal investigator of this investigator-initiated study for the use of single agent mifepristone for the treatment of stage IIIB or stage IV non-small cell lung cancer and wrote the majority of the manuscript. Diane Check, B.S., M.T., is the project manager for the study, made major contributions to the writing of the manuscript. Trina Poretta, D.O., was the oncologist treating the patient and she reviewed the manuscript, made some revisions, but her main role, in addition to Diane Check, was writing the part of the manuscript that dealt with the clinical presentation of the patient.

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