# Evidence that Mifepristone, a Progesterone Receptor Antagonist, Can Cross the Blood Brain Barrier and Provide Palliative Benefits for Glioblastoma Multiforme Grade IV

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**Abstract.** *Background: Mifepristone, a progesterone receptor antagonist, has been found to provide palliative benefits for various types of spontaneous murine cancer in randomized controlled trials and in anecdotal reports from a variety of advanced metastatic human cancer not known to be associated with progesterone receptors. The theory of its mechanism is that it prevents the secretion of a progesterone-induced immunomodulatory protein in the tumor microenvironment, or in the tumor cell itself, called the progesterone-induced blocking factor, which inhibits natural killer cells from attacking the cancer cell. Many anticancer chemotherapeutic agents fail to cross the blood–brain barrier and thus prove ineffective for brain cancer. The objective of the present study was to determine if mifepristone could provide palliative benefits to a patient with end-stage stage IV glioblastoma multiforme. Case Report: A 43-year-old male with end-stage stage IV glioblastoma multiforme was exclusively treated with mifepristone 200 mg orally daily. Results: The patient showed definite palliative effects for several weeks and his life was significantly extended beyond pre-treatment predictors. Conclusion: It appears that mifepristone does cross the blood–brain barrier and could be considered for palliative therapy of other patients with chemotherapy-resistant brain cancer.*

The prognosis of patients with malignant glioma remains extremely poor despite surgery and improvements in radio- and chemotherapies. Therapeutic treatment with chemotherapeutic agents, *e.g.* temozolomide or 1,3-bis(2-chloroethnyl)-1-nitrosurea carmustine wafers or tipifarnib have not significantly improved patient survival (1-3).

It has been hypothesized that an immunomodality protein expressed by gamma delta thymic (T) cells with up-regulation of progesterone receptors will be produced after these cells have been exposed to a high concentration of progesterone. It has been hypothesized that this protein, known as the progesterone-induced blocking factor (PIBF) suppresses natural killer cell activity in the tumor microenvironment and thus provides one mechanism allowing cancer cells to escape immune surveillance, similar to the immunosuppressant effect that this protein has on natural killer cells during normal pregnancy (4-6). This hypothesis was supported by the demonstration of *PIBF* mRNA expression in all human leukemia cell lines tested in one study, including T-cell leukemia, seven myeloid leukemia and 10 B-cell leukemia cell lines (7). In that same study, 4 out of 10 leukemia cell lines tested for expression of this PIBF protein exhibited up-regulation of PIBF expression when extra progesterone was added to the culture medium, and down-regulation of PIBF expression was found with use of the progesterone receptor antagonist mifepristone (7).

The aforementioned study led to the evaluation of progesterone receptor antagonist therapy for possible palliative therapy for cancer. The first randomized controlled trials were attempted for spontaneous murine cancer. Mifepristone treatment was found to improve the length and quality of survival of mice with spontaneous leukemia not known to be associated with progesterone receptors (8). Subsequently gavaging with mifepristone compared to untreated controls was found to improve the length and quality of life in mice with solid malignant tumors including lung, testicular, and prostate cancer (9, 10).

Based on these cell line and murine studies, the United States Food and Drug Administration granted permission on a

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case-by-case basis to allow mifepristone therapy to be given for palliation in patients with very advanced cancer who have exhausted all other treatment options. The first type of cancer without known progesterone receptors treated in humans with mifepristone for palliation was metastatic adenocarcinoma of the colon (male and female) and the drug seemed to provide a very good palliative effect in both (11). Subsequently palliative benefit was demonstrated in thymic epithelial cell cancer, transitional cell carcinoma of the renal pelvis, pancreatic cancer and malignant fibrous histiocytoma (12).

Many anticancer chemotherapeutic drugs are not effective for brain cancer due to the blood–brain barrier, which often represents the robust P-glycoprotein-mediated efflux process from capillary endothelial cells in the cerebral circulation. The blood–brain barrier partially isolates the brain from the peripheral environment. Anatomically, the barrier is created by the presence of impermeable tight junctions between endothelial cells and by a relative absence of transendothelial conduits for the passive diffusion of soluble molecules. Because of the blood–brain barrier, lipid-insoluble molecules must utilize either ion channels or specific transport systems to gain entry to the central nervous system.

Mifepristone has been found to be effective in treating one type of brain tumor – meningioma (13-15). However, meningiomas lie outside of the blood–brain barrier. It is not clear if mifepristone can gain access to the brain through the blood–brain barrier and provide palliation for brain cancer. Described herein is a case report of a 43-year-old male with very advanced, highly-invasive grade IV glioblastoma multiforme treated with mifepristone.

## Case Report

A 43-year-old male suddenly presented with a three-week episode of severe protracted headaches. A computed tomographic scan and magnetic resonance imaging were performed which showed a large cerebral mass involving the frontal, parietal and temporal lobes, and the basal ganglia. Surgical resection found a large grade IV glioblastinoma multiforme tumor arising originally from the temporal lobe. Despite radiation and chemotherapy, repeat magnetic resonance imaging two months later showed progression of the tumor, with metastasis to the spinal cord. Because of the multifocal nature of the tumor, the patient was advised that he was not a candidate for any further therapyand that death would likely be within two months.

Oral mifepristone at 200 mg daily was started two months after receiving this terrible prognosis, when he was advised that death was imminent. At the time of starting the mifepristone, the patient was sleeping for most of the day and was not able to carry-out a normal conversation. Within two weeks of taking mifepristone, the patient became much more alert and was able to carry-out intelligent conversations. Before starting the medication, he was paralyzed from the neck down and his hands were in a clenched position. After two weeks of therapy, he was able to open his hands.

His paralysis did slowly progress such that after about three months on mifepristone, he had difficulty in breathing. Because he had trouble swallowing, mifepristone was stopped. the patient died two weeks later.

## Discussion

These data suggest that mifepristone can cross the blood–brain barrier and thus could be used for palliative therapy of advanced brain cancer. It is hoped that the publication of this case report will generate interest in a larger randomized controlled trial. Possibly other progesterone receptor antagonists with less anti-glucocorticoid receptor activity, *e.g.* ullipristal could be tried for malignant glioma and could prove even more effective.

Mifepristone has been found to be effective in treating certain tumors known to possess progesterone receptors, *e.g.* breast cancer (16-19). The reason for trying mifepristone for menengiomas was that they were also found to possess progesterone receptors (13). The only other tumor known to have progesterone receptors is prostate cancer. The reason for using mifepristone for malignant glioma and a variety of other cancer types not known to possess progesterone receptors is that even without abundant progesterone receptors, a tumor may secrete progesterone or a progesterone-like substance that is able to generate PIBF production either intra-cytoplasmically in the tumor, or by gamma/delta T-cells in the tumor microenvironment (4, 5). The hypothesized secretion of progesterone may seem problematic. However, there are data that most tumors secrete human chorionic gonadotropin (hCG), which can stimulate progesterone (20-22).

mRNA for *PIBF* has not only been found to be increased in all human leukemia cell lines tested but has also been found to be expressed in many normal tissues, and its level is significantly higher in the various tumors relative to normal tissue counterparts (23). The predominant form of the PIBF protein is 90 kDa (7, 23). The 90-kDa protein seems to be encoded by 18 exons of the predominant *PIBF* mRNA. Exons 1-5 and 17-18 transcript encodes for PIBF of 34-36 kDa (23, 24). The ~35 kDa PIBF isoform contains the *N*-terminal 223 and *C*-terminal 75 amino acids (23).

The centrosome is the primary microtube organizing center in animal cells. Disturbed centrosome duplication causes unequal segregation of chromosome and ultimately tumorigenesis. The 90kDa protein is predominantly located in the centrosome, whereas the 34-36 kDa splice variant, the main secreted form, is predominantly found in the cytoplasm (23). A number of proteins shown to be involved in tumor

genesis are associated with the centrosome. Interestingly other tumor-suppressing proteins, *e.g.* breast cancer antigen-1 (BRCA1) and p53 have the same centrosomal location as PIBF (25-29).

Further studies are required to determine if the 35-kDa isoform of PIBF described by Lachman *et al*. in the cytoplasm of cancer cells is identical to the 34-kDa form that rises precipitiously in females or males exposed to progesterone (24). Even if not identical, this protein, similarly to the 34-kDa secreted form, may be up-regulated by progesterone and be inhibited by progesterone receptor antagonism, thus, explaining the ameliorative effect of mifepristone even on tumors not known to have progesterone receptors.

The original hypothesis was that tumors may direct gamma/delta T cells in the tumor microenvironment to make the 34-kDa protein PIBF similar to that found in high levels in pregnancy states related to progesterone secretion and thus inhibit natural killer cell cytolytic activity in the tumor microenvironment. Based on the intracellular location of the 34-kDa PIBF splice variant, the possibility exists that intracellular progesterone production by tumor cells directs the parental 90 kDa protein to produce more of the intracellular 35-kDa PIBF protein, and this in turn protects the tumor cell from immune destruction. Now that a highly sensitive PIBF assay has been developed, it will be interesting to see if, similar to the pregnancy or post-ovulatory states, an increased serum PIBF level will be found and thus be a tumor marker. However, if most of the 34-36 kDA PIBF protein remains in the cytoplasm of the tumor cell, the tumor may still respond to drugs that inhibit progesterone receptivity even without being detected in the serum (30).

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