Research Article ISSN 2639-8478

Cancer Science & Research

Mifepristone May Be the Best Single Pharmaceutical Agent for Treatment of a Variety of Advanced Cancers

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Received: 15 August 2021; **Accepted:** 14 September 2021

Citation: Check JH, Check D. Mifepristone May Be the Best Single Pharmaceutical Agent for Treatment of a Variety of Advanced Cancers. Cancer Sci Res. 2021; 4(2): 1-6.

ABSTRACT

Rationale: *To provide evidence to support the provocative statement that the progesterone receptor modulator (antagonist) mifepristone may be the best single anticancer drug to use for advanced metastatic cancer.*

Objective: *A summary of cancer cell line studies, controlled treatment trials of several types of spontaneous murine cancers, and anecdotal human case reports that support the premise of this review, is provided. The concept suggests that the mechanism of action involves the suppression of an immunosuppressive protein called the progesterone induced blocking factor (PIBF) that requires stimulation of a membrane progesterone receptor for its production.*

Findings: *Cell line studies show that mifepristone can down-regulate PIBF production by many different leukemia cell lines and inhibit proliferation of cancer cell lines, e.g., ovarian cancer and glioblastoma multiform stage IV. Controlled murine studies found improved longevity and quality of life as monitored by body conditioning scores following oral gavage of mifepristone including leukemia, lung, testicular, and prostate cancer. Most importantly, mifepristone anecdotally has been found to provide extension of life and improved quality of life in patients with a large majority of advanced cancers that were no longer responding to any available anticancer drug options. These cancers include colon, kidney, small cell and non-small cell lung, pancreatic, thymic epithelial cell, transitional cell of the renal pelvis, grade IV glioblastoma multiform, fibrous osteogenic sarcoma, and leiomyosarcoma cancers. Of note, the majority of the cancers treated are not known to be associated with the presence of classical nuclear progesterone receptor.*

Conclusions: *Related to additional benefits of easy oral administration, low cost, low risk of short-term side effects, or immediate, severe, or delayed severe complications, and its efficacy despite starting it, in general, in late stages of advanced metastatic disease in patients previously treated with standard or experimental drugs, and its beneficial effects in a large variety of cancers, mifepristone may be the best single agent anticancer drug for the treatment of advanced cancers.*

Keywords

Progesterone induced blocking factor, Natural killer cells, Cellular immunity, Advanced cancer, Mifepristone

Introduction

What criteria would be a requirement for a drug to be considered the best single drug to treat metastatic advanced treatment resistant cancer? Table 1 list 10 criteria that in the authors' opinion could

constitute the ideal anticancer drug for treating metastatic cancers.

Table 1: Ten criteria for the ideal anticancer drug for advanced cancers.

1) Efficacy for the majority of patients with advanced cancers.
2) A drug that can keep the cancer in check providing significant palliation and increased longevity even when the newest most effective drugs are no longer working.
3) The drug will cross the blood-brain barrier and thus treat metastatic cancer to the brain or primary brain cancer.
4) The ideal drug should be well tolerated and thus have no short-term side effects that even though not life threatening or causing serious morbidity detracts from the patient's quality of life, e.g., nausea and vomiting, rashes, etc.
5) Lack of increased risk for serious complications that may cause other medical conditions that magnify suffering or even lead to death from these complications.
6) Oral administration should be ideal thus allowing patients with cancer to maximize his/her time with the family instead of hospital clinics or the hospital itself or even multiple visits to the oncologist.
7) The ideal drug should be resistant to tumor mutation and thus provide long-term rather than short-term palliation.
8) The ideal drug targets a molecule that is not needed for normal function of various other organ systems thus leading to greater likelihood to achieve ideal drug goal of numbers 2 and 5.
9) Low cost of medication allowing the majority of patients even without insurance to afford the drug.
10) A drug that would significantly reduce the cost of healthcare for patients with cancer in other ways than the low cost of the drug itself.

Criteria 1

In the author's opinion, one characteristic would be a drug that would be efficacious not just for one type of cancer, but for a large variety of cancers.

Cancer cells rapidly grow. The premise of most chemotherapeutic agents in the past (but are still presently used) is the hope that these drugs stop the cancer cells from growing but spare most organs where rapid cell growth is not present. Unfortunately, there are no chemotherapy drugs working on rapidly growing cancer cells that completely spare normal cells of the body. Thus, significant side effects frequently occur with significant risk of infection, suppression of bone marrow production, and even may aid in the development of other cancers.

Modern concepts of anticancer therapies are to identify specific molecules needed for certain critical pathways needed for either the cancer to proliferate or avoid immune surveillance. These drugs would target the critical molecules that "hopefully" would not be so critical for cells from normal tissue. Many of these new agents can provide increased length and quality of life to patients with cancer. Unfortunately, frequently they only treat one type of cancer, and frequently only a small percentage of one type of tumor, e.g., third generation tyrosine kinase inhibitors, e.g., osimertinib, for a small percentage of patients with non-small cell lung cancer (NSCLC) that have the epidermal growth factor receptor (EGFR) mutation.

There are some agents, e.g., the checkpoint inhibitors, nivolumab or pembrolizumab that may benefit more than one type of cancer. However, only some of these cancers utilize the PD-L1 molecule to escape immune surveillance. These newer agents have less side effects than the older chemotherapeutic agents have, but still have significant risks, e.g., autoimmune disorders.

To develop an anticancer drug that would fulfill the number one criteria it would target a molecule that is needed by most cancers to proliferate or escape immune surveillance that is not required by the normal body cells for normal function. Ideally, the best molecular pathway to target would be one that is needed by the fetus to grow, but not be needed once the baby is born, or for normal function in adult life or a physiological function that is not essential for normal quality of life.

Such a molecule may well exist. A unique immunomodulatory protein has no amino acid homology to any other known protein. This protein is called the progesterone induced blocking factor (PIBF) [1]. Though, it has a function of allowing the fetal semi-allograft to escape immune surveillance, it is thus only needed for fetal survival and not the adult person.

Cell line studies have demonstrated that PIBF, especially the 90 kDa parent form, may be needed for rapid proliferation of fetal and cancer cells alike [2-5]. However, its main function may be to suppress cellular immune reactivity in the fetal and tumor microenvironment [1,6,7]. For example, PIBF stabilizes perforin granules and granzymes, thus negating the cytotoxicity of natural killer (NK) cells [8]. Furthermore, it may aid in causing a shift from a TH1 to TH2 cytokine dominance [6,7,9].

Though it has been the recent trend to create monoclonal antibodies against critical key factors needed for tumor proliferation, but not normal cell growth, the majority of the oncology community has not yet embraced the PIBF concept. To the authors' knowledge, attempts to create therapeutic monoclonal antibodies against PIBF is not in the oncology pharmaceutical pipeline despite this concept being published in 2001 [10].

Production of PIBF depends on interaction with a membrane progesterone (P) receptor rather than the nuclear P receptor [11]. Thus, the possibility existed that in lieu of a monoclonal antibody, one may inhibit PIBF secretion by treating with a P receptor antagonist, e.g., mifepristone. Indeed, mifepristone was found to down regulate PIBF secretion by 29 different leukemia cell lines [12].

With cell line evidence of benefit of mifepristone, controlled studies involving various murine spontaneous cancers were evaluated. Significant improvement in longevity and quality of life (as evidenced by body conditioning scores) were demonstrated [13-15].

Mifepristone had been tried about 25 years ago to see if it could provide benefit to patients with cancers positive for the classical nuclear P receptor, e.g., breast and ovarian cancer. Though the drug did stabilize the disease, in those days the emphasis was more on tumor regression than longevity and palliation, so these studies were discontinued since tumor regression was found only in a minority of cases [16,17]. Mifepristone was used because it was believed that the classic nuclear P receptor may play a role in the progression of these cancers [16,17].

The murine data evaluating spontaneous cancers not known to be associated with the classical nuclear P receptor was important because the results showed that mifepristone does not require the nuclear P receptor to work in suppressing cancer, but probably suppresses PIBF production by blocking membrane P receptors [13-15].

Significant improvement in longevity and/or quality of life following single agent mifepristone therapy was demonstrated in a large variety of very advanced human cancers not known to be associated with the classical nuclear P receptor that were refractory to any further conventional therapies as summarized in Table 2.

Table 2: Advanced treatment resistant cancers without the classical nuclear P receptor that showed significant palliation and longevity following mifepristone therapy.

- Colon cancer [18,19].
- Transitional cell carcinoma of the renal pelvis [19].
- Leiomyosarcoma [19].
- Thymic epithelial cell carcinoma [19].
- Multifocal renal cell carcinoma [20].
- Glioblastoma multiforme stage IV [21].
- Pancreatic cancer [22].
- Fibroblastic osteogenic sarcoma [23].
- Small cell lung cancer [24].
- Non-small cell lung cancer (NSCLC) no tumor markers [25].
- NSCLC positive for the PD-L1 marker [26].
- NSCLC positive for the EGFR mutation [27].

Thus, the first criteria of the ideal anticancer single agent criteria seems to be realized by the demonstration of a large variety of advanced cancers, resistant to standard therapies, that respond to mifepristone as evidenced by marked palliative benefits, and significant extension of life (years, not just months).

There are new drugs on the market that will also provide extension of life and improved quality. However, these newer agents can only be used for a minority of cancers that have certain specific tumor markers.

Two of these new agents include nivolumab, a check-point inhibitor, for tumors positive for the PD-L1 marker and osimertinib, a third-generation tyrosine kinase inhibitor, for the uncommon NSCLCs that have the EGFR mutation [28,29]. Evidence of the efficacy of mifepristone was demonstrated by prolonged extension of a high quality of life in patients with NSCLC that had progressed despite nivolumab or osimertinib [26,27]. Thus, mifepristone can work even when these newer highly touted, targeted drugs no longer provide clinical benefit.

Criteria 2

Thus, the second characteristic of the ideal single agent anticancer drug that it is efficacious even when the newest very effective anticancer drugs are no longer effective has been fulfilled.

Criteria 3

The ideal single agent should also cross the blood brain barrier. The cases of NSCLC demonstrating marked palliation and increased longevity all had brain metastases, which never progressed while on therapy [25-27]. Also, there is evidence that mifepristone can benefit very advanced glioblastoma multiforme stage IV [21].

Criteria 4

The ideal single agent anticancer drug should be well tolerated. Treating a large number of patients with meningiomas with mifepristone showed that there are very few side effects at the 200mg daily dosage [30]. The drug was very well tolerated with no significant side effects when used as a single agent in the cases treated by the present authors. It can, however, cause hypokalemia when combined with certain other anticancer drugs that inhibit the metabolism of mifepristone, thus emphasizing its anti-glucocorticoid properties [31].

Criteria 5

The ideal anticancer drug should not cause organ damage while taking the drug that can lead to death or significant morbidity from organ damage, e.g., liver and kidney failure, or bone marrow suppression. No such complications have been found in the patients treated to date.

Criteria 6

The ideal single agent anticancer drug should have easy administration. Mifepristone is taken as a single daily pill avoiding hospitalization or long hours in oncology clinics with administration of intravenous medication, or painful intramuscular injections.

Criteria 7

The ideal drug would target molecules that are resistant to tumor mutation, thus allowing the cancer to escape from sensitivity to the anticancer drug. The demonstration of longevity of life with slow or no tumor progression despite extensive metastases in very advanced cases suggests that the PIBF pathway seems to be recalcitrant to tumor mutations.

Criteria 8

Another ideal aspect of mifepristone, acting as an immunosuppressant, is that, in contrast to other immunosuppressive agents, it targets a protein that is not essential for normal immune function, but one that allows onco-fetal cells to proliferate.

Thus, it does not cause generalized immune suppression leading to infection or development of other cancers or remove a block that allows attack of normal tissue, i.e., promoting autoimmune disease while taking the drug. Some of these newer better tolerated drugs can cause complications that are not evident while taking the drug but may occur even years later after the drug had been stopped, e.g., autoimmune disease or other cancers. This would not be likely with mifepristone because there are no likely long-term complications from blocking the P receptor other than the possibility of endometrial hyperplasia or endometrial cancer. However, these complications were not evident in the large study of mifepristone therapy for meningiomas [30].

Criteria 9

Compared to other anticancer agents, mifepristone is much less expensive, which allows patients without insurance to be treated even when there are limited financial resources. In some countries it costs .50 cents per pill. In the USA it costs $15.00 per pill.

Criteria 10

Though there are some cases, e.g., the woman with small cell lung cancer and the woman with leiomyosarcoma, where all metastatic lesions seem to disappear, in the majority of cases of patients taking mifepristone there may be partial remission. However, the rate of growth is markedly decreased leading to the patient feeling much better, and living much longer, despite slow progression of the cancer [1,19,24]. Thus, not only would the low cost of the medication tremendously drop health care cost for treating patients with advanced cancer, but one could stop very expensive monitoring procedures, e.g., MRI's, CT scans, etc. Showing progression would not lead to stopping the drug, since there are no other options, thus why spend the extra money to monitor (unless for research where grants should cover the expense)? Though not continuing to monitor disease progression at first may sound like heresy, it is the same concept involved in the more and more popular option of sending the patient for hospice. Hopefully, those reading this manuscript will consider the option of trying single oral agent 200mg per day mifepristone to possibly allow further extension of a decent quality of life with little suffering, as opposed to hospice, which, while a humanitarian method to mitigate suffering, basically ends a normal functional life.

Conclusions and final thoughts

Though the experience with mifepristone has been anecdotal, some of the responses have been dramatic in very end-stage cancer cases. The majority of cases have shown some significant beneficial effects, even in some cases that were within 1-2 weeks of expected death. Nevertheless, proof of efficacy requires larger studies. Hopefully, this manuscript will stimulate interest in some oncologists to conduct such a study in some types of cancer evaluating efficacy of mifepristone, and hopefully confirm the efficacy of P receptor antagonist therapy.

In summary we presented 10 characteristics of what we thought were required for a drug to be considered as an ideal single agent anticancer drug. We believe that the published anecdotal cases strongly support the conclusion that mifepristone may be such an ideal drug. Based on the severity of the cancer, with few treatment options for unresectable disease, our first choice would be pancreatic cancer to be evaluated in a larger study [22].

Since PIBF and the P receptor are needed for the fetus to escape immune surveillance, the original development of mifepristone was an abortifacient drug, and the only approved use of the 200mg pill is to terminate pregnancies. To satisfy pro-life factions the United States Food and Drug Administration (FDA), and other governmental agencies in other countries, there were restrictions given as to which doctors who can prescribe this drug. Thus, these restrictions have made it difficult for an oncologist, or other treating physician, to prescribe the drug off-label for advanced cancer. Thus, most of the cases described required a compassionate use Investigator New Drug (IND) approval from the FDA and some of cases were part of an FDA approved investigator study for NSCLC. Thus, in almost every instance, the patients' cancers were very advanced with no more viable treatment options.

One possible exception was a man with multifocal renal cell carcinoma, who was not advanced, but was given permission by the FDA to use mifepristone because he did not want a bilateral nephrectomy and hemodialysis, as recommended by his oncology group. There were no chemotherapy agents for this cancer at this time. He is now 19 years from his initial start of mifepristone and still feeling well [20]. This brings up the question as to why not allow the option of starting mifepristone with early metastatic disease and use the other more toxic agents only if mifepristone no longer seems efficacious. Only about 10% of patients with advanced cancers are able to be provided with commercial anticancer agents because either their insurance does not cover the drug, and thus the patient cannot afford it, or there are no available treatment options to provide significant palliation benefits or extension of life, or they are not eligible for various reasons to be part of an experimental drug trial.

Experimental drug trials are important to aid in the development of more effective anticancer drugs. The development of these drugs and final approval are a boom to the economy and the pharmaceutical industry. They can be also very profitable to the oncology team performing the clinical trial with huge renumeration from pharmaceutical companies per patient registered. Patients are desperate when advised there are no more clinical options other than the hope that as yet an unproven drug may be beneficial, and thus subject themselves to the risk of significant side effects that are frequently without benefit.

Of course, the authors consider these clinical trials important for the progression of medicine. However, the ethical option would be to at least present the option of safe, inexpensive, mifepristone therapy especially if there have been at least some anecdotal evidence of its efficacy in their type of cancer, and if that fails, consider an experimental drug trial.

Although one of our suggestions to reduce health costs would be to forego expensive testing for disease progression while on mifepristone, nevertheless, we would suggest that a minimum requirement for the patient to continue therapy would be to fill out at least a quarterly quality of life form that is appropriate for their type of cancer.

Acknowledgement

The murine animal studies were approved by the Institutional Review Board (IRB) and ethical committee of the Cooper Hospital. Extreme consideration was taken to prevent suffering of mice and the guidelines of the University Animal Care Committee were precisely followed.

There were two IRBs used for human studies, The Chesapeake Review Board (approval number PR000011306) were used for patients that were part of a United States Food and Drug approved investigator initiated investigative new drug approval (IND entitled "A phase II study of treatment with oral mifepristone as salvage therapy in patients with advanced or metastatic non-small cell lung cancer (NSCLC) who have failed two or more previous chemotherapy regimens", www.clinicaltrials.gov). Patients with cancer other than NSCLC were approved by a Western IRB (protocol number 20121249, CIR 110).

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