Mifepristone May Halt Progression of Extensively Metastatic Human Adenocarcinoma of the Colon – Case Report

JEROME H. CHECK, EBONY DIX, LYNN SANSOUCIE and DIANE CHECK

Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, The University of Medicine and Dentistry of New Jersey, Medical Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Camden, NJ, U.S.A.

Abstract. Background: Mifepristone, a progesterone receptor antagonist has been found to improve the length and quality of life in various spontaneous murine cancer models including tumors without progesterone receptors theoretically by inhibiting an immunomodulatory protein that suppresses natural killer cell function in the tumor microenvironment. Materials and Methods: Mifepristone 200 mg per day by mouth was given to two patients with stage 4 colon cancer with extensive metastases. Results: Both patients not only survived far longer than expected but had marked improvement in their quality of life similar to mice. Though the metastatic lesions did not disappear, no new ones appeared for a long time and the ones present did not grow. The drug was extremely well tolerated. Conclusion: The use of progesterone receptor antagonists may present a novel immunotherapy to help fight cancer. A larger controlled study is needed.

There are data supporting the concept that the fetal semi-allograft escapes natural killer (NK) cell surveillance by promoting the local production of an immunomodulatory protein known as the progesterone induced blocking factor (PIBF) (1-5).

There was a hypothesis that various tumors may use a similar mechanism involving PIBF to escape immune surveillance by NK cells (6). Data were presented demonstrating that all 27 human leukemia cell lines tested expressed messenger ribonucleic acid (RNA) for PIBF (7).

In fact, in many of these leukemia cell lines the amount of mRNA for PIBF was greater than for any other protein known to be made by the leukemia cells (7).

Even if PIBF is made by leukemia cells, and even if it is important in inhibiting NK cell cytolytic activity against the tumor cells, the mechanism could be independent of progesterone. In pregnancy, the allogeneic stimulus of the fetus induces de novo progesterone receptors on gamma delta T cells (8). The interaction of progesterone (P) with the P receptor on gamma/delta T cells leads to the expression of the PIBF protein (1, 2).

There is evidence that the expression of PIBF induced by tumor cells may be influenced by progesterone. One study showed that in leukemia cell lines that expressed PIBF the addition of P to the medium upregulated the expression of PIBF (7). Even more importantly, the addition of mifepristone, a P receptor antagonist, caused a downregulation of PIBF expression (7).

Leukemia cell lines have a two fold advantage when studying expression of PIBF. The allogeneic stimulus of foreign antigens on the leukemia cells according to the theory can induce de novo P receptors on the leukemia cells similar to the induction of P receptors on normal gamma/delta T cells in pregnant women when exposed to an allogeneic stimulus (2). If somehow the leukemia cells could also secrete progesterone or a P-like substance, then the possibility exists that the leukemia cells with P receptors induced may be able to express the PIBF protein.

Whether PIBF plays a role in the avoidance of immune destruction in clinical cancer settings remains to be determined. Indeed, there are murine data suggesting that mifepristone can extend length and quality of life in a spontaneous leukemia model (9). The next question is whether solid tumors can direct local gamma/delta T cells in the tumor microenvironment to express PIBF and thus inhibit local NK cell response. Mifepristone has been also shown to improve length and quality of survival in a spontaneous murine lung cancer model (10).

Mifepristone has also been shown to inhibit murine breast cancer; however in this case there could be a direct effect on the tumor cells which may have P receptors (perhaps P may be needed for some direct growth process) (11). Thus the murine
lung cancer model may be more supportive of the concept that
the benefit of mifepristone may be through an immunologic
mechanism involving the tumor microenvironment allowing
NK cells which had been previously suppressed to now attack
tumor cells.

When cancer has widely metastasized, death and suffering
is usually imminent. Present day chemotherapy, under these
circumstances, will usually provide no more than a few
weeks to months extension of life and exert only a small
palliative effect. Two cases of colon cancer with extensive
metastasis are presented where mifepristone treatment was
added to or following standard chemotherapy and were
associated with extended and improved quality of life.

Case Report

Case 1. Mifepristone 200 mg orally per day was given to a
61 year old woman who had a 6.5 cm invasive moderately
differentiated adenocarcinoma of the transverse colon with
extensive metastases to the liver, peritoneum, ovary and
uterus. The two largest liver metastases measured 3.1×1.3 cm
and 2.3×1.9 cm. She began mifepristone 200 mg orally daily
1½ months after surgery. Her disease seemed to stabilize on
the mifepristone in that 5 weeks after initiation of therapy
she was feeling very well with no pain and good energy. A
CT scan showed no increase in either number or size of any
lesions. At this point she decided to add treatment with
bevucizumab and 5 fluorouracil because they were known to
have a lower rate of side effects than other chemotherapy
drugs used for this type of cancer.

After 1½ years from the original diagnosis the woman
claimed to feel strong, carried out normal every day
activities, and there had not been any growth of any of the
metastatic lesions nor any new ones appeared. Her
carcinoembryonic antigen (CEA) level after one year was
only 1.3 ng/mL. After 21 months the lesions began to grow.
She had good energy and was pain free until 27 months
when ascites returned. She was still ambulatory when she
died following 30 months of treatment with mifepristone.
During treatment her CBC and serum cortisol levels
remained normal.

Case 2. A second case of colorectal cancer was also treated
with mifepristone 200 mg daily. An 83 year old man had a
previous resection of a large bowel lesion of adenocarcinoma
that had metastasized to his lungs, liver, peritoneum and
lymph nodes. He was started on capecitabine 500 mg a.m.,
100 mg p.m. which continued when cetuximab was added at
250 mg/m² for 6 weeks then 200 mg/m² weekly. The latter
drug was added because of progressive disease. These
therapies were stopped after 2 months because the disease
was progressing rapidly despite therapy. His CEA level was
104 ng/mL. A large lesion appeared on his chest arising from
bone and soft tissue extending from upper-sternum to mid-
lower sternum. He was so weak that he was bed-ridden.
After starting mifepristone 200 mg daily his energy markedly
improved within 2 weeks. He was able to resume normal
activity including going to restaurants and race tracks and his
appetite returned. In 4 ½ months of treatment no new
metastases were noted on MRI testing and only 1 metastatic
lesion in the lung grew 0.3 cm. He reported no side effects
from treatment.

He started getting confused but repeat MRI testing failed
to show any brain metastases. It was found that his pre-
existing renovascular disease (no renal metastases) became
worse and he was uremic. Dialysis was considered but he
died from an acute myocardial infarction before that could
be instituted.

This work has been approved by the appropriate ethical
committee related to the institution in which it was performed
and these subjects gave informed consent to the work.

Discussion

If one treats enough cancer patients there is always someone
who defies the odds and lives longer without suffering than
anyone expected even without any therapy. Thus one cannot
say for sure that the improved length and quality of survival
of these two patients with extensive metastatic colon cancer
was because of mifepristone therapy and thus possibly their
improvement may have been merely fortuitous.

The possibility also exists that the amazing quality of life
with very low serum CEA levels in case 1 may have been
related to the bevucizumab and 5 fluorouracil therapy though
these drugs were not expected to thwart progression of
disease so long and so effectively. Furthermore, her first
treatment was exclusively the mifepristone for 5 weeks and
she was doing extremely well at that time. The bevucizumab
and 5 fluorouracil were added not because of progressive
disease but with the apparent halting of the rapid progression
it was hoped that the addition of these two drugs might
improve her odds of longer and better quality of survival.
She had initially refused chemotherapy based on the side
effects mentioned and the poor prognosis given despite
chemotherapy.

Certainly one has to consider as another very likely
possibility that the improved quality and length of the
survival of these two patients may have been related to
mifepristone administration. If so, monotherapy with the
progesterone receptor antagonist may have been sufficient or
it may have augmented the therapeutic effects of
bevucizumab and 5-fluorouracil.

There are no data suggesting that colon cancer cells have
P receptors. Thus, if in fact mifepristone had a beneficial
effect in these cases of metastatic colon cancer, the
mechanism would probably not be related to suppressing a
direct beneficial effect of P on tumor growth. If more studies do confirm improved survival with colon cancer following mifepristone treatment, the absence of known P receptors in the tumor cells would make the hypothesized mechanism of action more likely: abrogating select immune tolerance against NK cells in the tumor microenvironment by suppressing the PIBF protein made by local gamma/delta T cells (6). According to the hypothesis, the allogeneic stimulus of the colon cancer cells would induce P receptors on gamma/delta T cells. The colon cancer cells would secrete either P or a P-like steroid that interacted with the P receptor on the gamma/delta T-cell and thus allowed the expression of the PIBF protein. The PIBF protein, in turn, inhibited the cytolytic action of NK cells in the vicinity of the colon cancer cells (6).

Thus the postulated mechanism of suppression of tumor growth by the mifepristone was to negate the effect of the hypothesized P substance secreted by the colon cancer cells that would interact with P receptors on gamma/delta T cells and thus allow PIBF expression which would inhibit NK cells in the tumor microenvironment. Thus removing the block against NK cell activity would allow the NK cells to inhibit tumor growth.

Since the responses of these cases despite the caveats are consistent with animal data, it is hoped that this case report may prompt interest in human clinical trials of mifepristone for cancers not known to be hormonally dependent or even the use of more potent and specific progesterone receptor antagonists. It should be noted that the drug was extremely well tolerated with no side effects. Hopefully the murine data along with this case report will spark interest in performing a larger controlled clinical trial in humans not only with adenocarcinoma of the colon but other tumors as well.

References


