Mifepristone (or RU-486)

Mifepristone is a synthetic steroid compound a progesterone receptor antagonist with potent glucocorticoid receptor antagonist activity, effectively blocks cortisol activity at the level of the receptor,

The compound is a 19-nor steroid with substitutions at positions C11 and C17 (17 beta-hydroxy-11 beta-[4-dimethylamino phenyl] 17 alpha-[1-propynyl]estra-4,9-dien-3-one), which antagonizes cortisol action competitively at the receptor level.

It improves morbidities associated with Cushing's syndrome. Common adverse effects include hypokalemia, vaginal bleeding, and symptoms of adrenal steroid withdrawal [1].

Evidence suggests that female sex hormones play a role in the meningioma tumorigenesis. In particular, progesterone, has a receptor (PR) that is highly expressed in the majority of grade I meningiomas. Multiple meningiomas (diffuse meningiomatosis) are less frequent, but have a higher female predominance and a higher PR expression. They are, therefore, attractive candidates for anti-PR therapy.

The presence of the progesterone receptor (PR) in meningioma tissue has been confirmed by previous investigations. Studies have shown that the antiprogesterone drug, mifepristone, is a potent agent that inhibits the growth of cultured meningioma cells and reduces the size of meningiomas in experimental animal models and humans. However, these studies have not fully examined the relationship between the antitumor effects of an antiprogesterone agent and the expression of the PR.

The computational repositioning of existing drugs represents an appealing avenue for identifying effective compounds to treat diseases with no FDA-approved pharmacotherapies. Here we present the largest meta-analysis to date of differential gene expression in human vestibular schwannoma (VS), a debilitating intracranial tumor, and use these data to inform the first application of algorithm-based drug repositioning for this tumor class. We apply an open-source computational drug repositioning platform to gene expression data from 80 patient tumors and identify eight promising FDA-approved drugs with potential for repurposing in VS. Of these eight, mifepristone, a progesterone and glucocorticoid receptor antagonist, consistently and adversely affects the morphology, metabolic activity, and proliferation of primary human VS cells and HEI-193 human schwannoma cells. Mifepristone treatment reduces VS cell viability more significantly than cells derived from patient meningiomas, while healthy human Schwann cells remain unaffected. Our data recommend a Phase II clinical trial of mifepristone in VS [2].

1991

Fourteen patients received mifepristone in daily doses of 200 mg for periods ranging from 2 to 31+ months (greater than or equal to 6 months in 12 patients). Five patients have shown signs of objective response (reduced tumor measurement on computerized tomography scan or magnetic resonance image, or improved visual field examination). Three have also experienced subjective improvement (improved extraocular muscle function or relief from headache). The side effects of long-term mifepristone therapy have been mild. Fatigue was noted in 11 of the 14 patients. Other side effects included hot flashes in five patients, gynecomastia in three, partial alopecia in two, and

cessation of menses in two. Long-term therapy with mifepristone is a new therapeutic option that may have efficacy in cases of unresectable benign meningioma [3].

1992

Ten patients were treated with 12 recurrent or primary “inoperable” meningiomas, all of whom had shown recent neuroradiological and/or ophthalmological evidence of tumour growth. They received 200 mg mifepristone daily for 12 months. Most patients initially had complaints of nausea, vomiting and/or tiredness. In four patients prednisone (7.5 mg/day) was given after which these side-effects subsided. CT scan analysis of tumour size, showed progression of growth of five meningiomas in four patients, stable disease in three patients with three tumours and regression of four tumours in three patients. A decrease in the complaints of headache and an improved general well being was observed in five patients. Two patients died during the treatment period from unrelated causes. Mifepristone treatment resulted in control of tumour growth (= stable disease) in six of 10 patients who had shown recent evidence of tumour growth. In three of these six patients consistent tumour shrinkage was observed [4].

1994

A study examined the antitumor effects of mifepristone and a new potent antiprogesterone agent, onapristone; a correlation between the antitumor effects of these antiprogesterones and the presence of PR's in meningiomas in vitro and in vivo was also investigated. Meningioma tissue surgically removed from 13 patients was used in this study. In the in vitro arm of the study, mifepristone and onapristone exhibited cytostatic and cytocidal effects against cultured meningioma cells, regardless of the presence or absence of PR's; however, three PR-negative meningiomas showed no response to any dose of mifeprestone and/or onapristone. In the in vivo arm, meningioma cells, embedded in a collagen gel, were implanted into the renal capsules of nude mice. Antiprogesterone treatment resulted in a marked reduction of the tumor volume regardless of the presence or absence of PR's. No histological changes in the meningioma cells suggestive of necrosis or apoptosis were detected in any of the mice treated with antiprogesterones. These findings suggest that mifepristone and onapristone have an antitumor effect against meningioma cells via the PR's and/or another receptor, such as the glucocorticoid receptor [5].

2001

Two randomized phase III trials have been undertaken on symptomatic unselected meningiomas but were inconclusive, and only one abstract has been published with no clear conclusion [6].

2006

Long-term administration of mifepristone is feasible and clinically well tolerated, with generally mild toxicity. However, endometrial hyperplasia was noted in several patients. In view of the association between long-term treatment with tamoxifen (another agent that can induce an unopposed estrogen effect) and endometrial cancer, this observation will require further investigation and screening. Minor regression of meningioma that can result in significant clinical benefit is suggested in the male and premenopausal female subgroups of patients [7].

2014

Touat et al., treated three consecutive women with multiple meningiomas with mifepristone (RU 486).

The treatment was well tolerated, and they observed an important and long-lasting clinical (3/3) and radiological response (2/3) or stabilisation. All the three patients are now stable after five to nine years of treatment.

These encouraging results strongly support a prospective clinical trial in this preselected population [8].

2019

Cohan et al., retrospectively assessed 4 patients treated with mifepristone from multiple medical practices with hypercortisolism due to BMAH had who either failed unilateral adrenalectomy, declined surgery, or were poor surgical candidates.

Mifepristone induced clinical improvement and remission of the signs and symptoms of hypercortisolism in all the described patients with BMAH. The median treatment duration at the time of efficacy response assessment was 5 months (range: 3-18 months). Improvement in cardiometabolic parameters was observed as early as 2 weeks after treatment was started. All patients achieved improvements in glycemic control and hypertension and had significant weight loss. The most common adverse event observed with mifepristone therapy was fatigue. Increases in thyroid-stimulating hormone level occurred in 2 patients.

Mifepristone can be an effective alternative to surgery in patients with hypercortisolism due to BMAH [9].

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