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Prolonged High-Quality Life in Patients with Non-Small Cell Lung Cancer Treated with Mifepristone Who Advanced Despite Osimertinib

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ABSTRACT

Though representing only, a minority of cases of non-small cell lung cancer (NSCLC), the presence of the epidermal growth factor receptor (EGFR) mutation is associated with a better prognosis than other types of lung cancer, because the tumor responds well to targeted therapy especially with third generation tyrosine kinase inhibitors (TKI). The objective of the present case study was to determine if the use of the progesterone modulator mifepristone could extend a high quality of life, by targeting the progesterone induced blocking factor (PIBF), that seems to be present in most malignant tumors, especially when they are advanced. Two such patients, no longer responding to the third generation TKI osimertinib, were treated with 200mg oral mifepristone while remaining on osimertinib. These patients have enjoyed a high quality of life and are ECOG-zero, after approximately 1 ½ and 2 years of mifepristone therapy. Based on other experiences using single agent mifepristone, the patients are probably responding to single agent mifepristone, without much contribution from the osimertinib. Nevertheless, since the two drugs were well tolerated together, one may consider starting both drugs simultaneously when there is advanced NSCLC with the EGFR mutation. Mifepristone has demonstrated in previous reports increased quality and length of life in patients with advanced chemo-resistant NSCLC with no tumor markers, advanced NSCLC positive for programmed death factor-1 and progressing despite nivolumab, advanced small cell lung cancer, and now NSCLC with the EGFR mutation progressing despite the third generation TKI Osimertinib.

Keywords

Epidermal growth factor receptor mutation, Membrane progesterone receptor, Mifepristone, Non-small cell lung cancer, Progesterone induced blocking factor, Progesterone receptor modulator, Tyrosine kinase inhibitor third generation.

Introduction

Non-small cell lung cancer (NSCLC) generally carries a poor prognosis with about a 15% 5-year survival. However, there are certain subset groups of NSCLC with a better prognosis related to having either certain mutations or translocations producing molecules that promote cancer growth, that respond well to drugs targeting these molecular drivers, leading to increased length of survival, and better quality of life than NSCLC without these mutations and translocations [1].

One of the mutations is the epidermal growth factor receptor (EGFR), which may be present in about 15% of NSCLC tumors (1). These may respond to drugs known as tyrosine kinase inhibitors (TKIs), although, after a while, eventually resistance to these EGFR-TKIs is inevitable [2,3].

There have been many different mechanisms identified of irreversible, acquired resistance, e.g., amplification of the MET receptor tyrosine kinase gene, EGFRT790M gate keeper mutation, fibroblast growth factor receptor signaling, and even histological conversion to small cell lung cancer [4-8]. Pharmacologic research has been dedicated to the development of TKIs that are less likely to acquire resistance, starting with the first generation TKIs, erlotinib and gefitinib, second generation TKIs, afatinib and dacomitinib,

and third generation TKIs, osimertinib. One of the advantages of osimertinib over first and second generation TKIs, is that it can overcome resistance related to EGFRT790M [9,10].

The hope for further pharmacological efforts is to develop 4th generation TKIs capable of overcoming other resistance mechanisms. Until that happens, there does not seem to be any "conventional" viable options for patients where osimertinib is losing efficacy.

Until these 4th generation medications are developed, one treatment option would be to use a drug that targets a different tumor associated receptor that produces a different molecule needed for lung cancer progression.

There is a unique immunomodulatory protein known as the progesterone induced blocking factor (PIBF), that helps the fetal-placental semi-allograft to escape immune destruction by the cellular immune system, especially natural killer cells [11,12]. In 2001, it was hypothesized that cancer may utilize this same PIBF protein to escape immune surveillance [13]. Membrane progesterone receptors, rather than nuclear progesterone receptors, seem to be involved in the production of this unique protein, which does not have any amino acid homology to any known protein [14].

Thus, it was considered that drugs that would block the progesterone receptor could lead to suppression of the PIBF protein, thus promoting innate immune destruction of the cancer cells. Subsequent cancer cell line studies and prospective controlled studies on various spontaneous murine carcinomas provided support for the hypothesis of the key role of PIBF in allowing cancer cells to proliferate and metastasize [15-18].

One of the controlled murine cancer studies compared A/J mice bred to have a high frequency of spontaneous lung cancer gavaged with mifepristone (the equivalent in a weight basis of humans receiving 200mg per day of mifepristone), to controls gavaged with olive oil (the vehicle in which the mifepristone was dissolved). The results showed that 66.7% of mice treated with mifepristone survived 1 year, vs. 27% of the controls. Even more impressive, 66.7% of mice gavaged with mifepristone had no sick days, vs. zero % for controls (body conditioning score <4) [19].

Based on these cancer cell line studies and controlled animal studies, the Food and Drug Administration (FDA) allowed the off-label use of oral mifepristone for patients with advanced metastatic cancer, in which no more reasonable treatment options existed on a case by case basis. Although mifepristone was already on the pharmaceutical market, because it was approved as an abortifacient, but to satisfy groups with antiabortion sentiments, the drug requires a compassionate use investigator drug (IND) approval for its use by treating physicians. More support for the concept that blocking the progesterone receptor, and thus the PIBF, was provided by the demonstration that mifepristone significantly improved length and quality of life in people with a variety of very advanced metastatic cancers that progressed on chemo or immunotherapy [20-22]. In all cases the mifepristone was obtained on a compassionate use basis.

One 80-year-old woman was admitted to the intensive care unit with a serum PO2 of 72 mmol/L. The radiologic and clinical diagnosis was possible advanced small cell lung cancer, based on symptoms of sudden onset and the syndrome of inappropriate anti-diuretic hormone, with a serum sodium of 118 mmol/L. She refused biopsy, but agreed to take oral mifepristone daily, rather than any other chemotherapy, based on the poor prognosis and the lack of side effects of mifepristone. Within a short time, her PO2 returned to 98 mmol/L, without oxygen, and her serum sodium returned to normal. Subsequent lung CT scan showed disappearance of the large lung lesions, the remaining ones now showing only a ground-glass appearance. She continued to do well for 5 years. She died at 85 with a myocardial infarction [23].

Based on experimental data suggesting a positive benefit of mifepristone in suppressing growth of cancer cell lines, improvement of length and quality of life in controlled murine cancer studies, and similar benefit anecdotally in advanced human cancers, the FDA approved an investigator-initiated study for 40 patients with stage IIIB, or IV NSCLC, that had progressed despite a minimum of two courses of chemo or immunotherapy, to treat with single agent mifepristone. Though all previous human studies had been conducted with 200mg of mifepristone daily, the study dosage was to be 300mg daily, because Corcept Inc. agreed to provide the drug free to patients. Their drug is approved for treating hyperglycemia of Cushing's syndrome. Higher dosages of mifepristone will also suppress the glucocorticoid receptor.

The two patients described herein originally consulted us for consideration to be in the investigator-initiated study. Though they would have qualified, based on circumstances that will be described, we suggested that they be treated with the 200mg dosage, after obtaining a compassionate use IND.

Case Report

Case 1

A 59-year-old woman, who suffered from upper back pain and dyspnea on exertion, was found to have stage IV non-small cell lung cancer. At the time of initial diagnosis, she was found to have innumerable tiny lung nodules (miliary pattern), with bone metastases, and a single metastatic lesion to the left occipital lobe of the brain.

The tumor biopsy revealed non-small cell adenocarcinoma of the lung. The tumor was positive for the EGFR exon leu 858 any mutation.

The brain metastasis was treated with palliative radiotherapy. She began targeted therapy, directed against the EGFR mutation, with the first generation TKI drug, erlotinib. She remained stable for 1½ years when her lung nodules started to increase in in size.

Erlotinib was stopped and the third generation TKI drug, osimertinib, was started. After 6 months, osimertinib was no longer effective, and she had increased symptoms of dyspnea on exertion, which returned to the same level it had been prior to erlotinib therapy.

She was started on single agent oral mifepristone 200mg per day. Her dyspnea on exertion markedly improved within 1 month of treatment. Though, the osimertinib did not seem to be working, her oncologist, a world-renowned specialist in lung cancer, wanted her to remain on osimertinib, in addition to the mifepristone.

Though she was feeling great at 6 months on mifepristone treatment, and her lung lesions were stable, her oncologist informed her that he had available a couple of spots for her to become part of an investigational study, but she would have to stop the mifepristone. She asked our opinion, and we advised her to remain on the mifepristone, since stable disease with marked quality of life is the usual presentation.

After 1½ years of mifepristone single agent therapy, her pulmonary nodules remained stable with no new brain lesions. She was considered ECOG1 prior to mifepristone therapy, she is now ECOG zero.

Though Case 1 originally consulted us to be part of the investigator-initiated study using 300mg/day mifepristone, the requirement for the study would be to return once a month to receive the medication. She lived 2000 miles away. We advised her to instead take the 200mg dosage, which we obtained with compassionate use, since the 200mg dosage can be shipped directly to her home.

Case 2

A 46-year-old woman presented with headaches, difficulty with executive function, and memory loss. She was diagnosed with stage IV non-small cell lung cancer following excisional biopsy with extensive lung lesions and brain metastases.

An MRI of the brain revealed innumerable supratentorial rim enhancing lesions, with one dominant left parallel lobe lesion measuring 3 x 2.1cm. This was treated with palliative radiotherapy.

CT scans showed innumerable bilateral pulmonary nodules with evidence of lymphocytic spread. She also had multiple bone lesions.

The tumor was positive for the EGFR 1 exon 19 mutation CE746/751 mutation. She was started on targeted chemotherapy with afatinib, a second generation TKI.

Eight months later, her pulmonary and brain lesions showed progression and afatinib was stopped. She had a second course of palliative radiotherapy to the brain.

The third generation TKI, osimertinib, was started 5 months after stopping afatinib. She did well, but after 10 months, the nodules showed mild increase in size.

Mifepristone was started at 200mg/day, and the osimertinib was continued. She was considered ECOG 1 when starting mifepristone. After 22 months of mifepristone treatment, she is ECOG zero, she feels good with no dyspnea on exertion, or headaches, or any cognitive impairment. Most of her pulmonary lesions are stable and some of them have decreased in size. There have been no new brain lesions.

She initially consulted us to be part of the investigator-initiated study using 300mg daily mifepristone. However, we thought that she could still derive some benefit from the osimertinib that she was still taking, so we advised her to obtain the 200mg mifepristone dosage with compassionate use care so she could remain on both drugs.

Discussion

These two case studies of NSCLC reported, herein, showed marked clinical improvement following mifepristone therapy, despite progressing with osimertinib. However, they were not the first cases of NSCLC treated with mifepristone. The first patient treated for NSCLC was in the investigator-initiated study using 300mg daily single agent mifepristone. He had stage IV NSCLC with brain metastases. He started out as ECOG-1 and he is now ECOG zero. He had no tumor markers allowing targeted therapy and he had failed 3 courses of multiagent chemotherapy. He felt very ill from side effects all during his courses of chemotherapy. After 5 years on single agent mifepristone he says he feels great and feels every bit as good as prior to his diagnosis of lung cancer [24].

The second (and last patient) on the FDA approved investigator-initiated study presented with stage IV NSCLC and was ECOG-2 at initial presentation. She had failed several chemotherapy regimens in addition to targeted therapy with the first generation TKI erlotinib because she was positive for the EGFR mutation. She even progressed with the check-point inhibitor nivolumab, because she also was positive for the programmed death factor-1 ligand 1 (PD-L1) receptor [25].

As mentioned, the above second case taking 300mg mifepristone, in the investigator-initiated study, did have the EGFR marker and the PD-L1 marker, but she was only treated with a first generation TKI erlotinib. One could argue that maybe if she was undergoing treatment today, possibly the third generation TKI osimertinib would be the better choice over mifepristone. Thus, the importance of the two new cases reported in this manuscript, is that the mifepristone worked despite progression with the third generation TKI osimertinib. At the time of death her lung cancer was stable (she died from complications of end-stage chronic obstructive lung disease). Possibly if she had shown progression after a period of time with mifepristone (which did not) treatment with osimertinib would have been an option [25].

The nuclear progesterone receptor was not present in either of the

two new cases presented in this manuscript. There is evidence that the demonstrated beneficial effect of single agent progesterone receptor modulator mifepristone, in suppressing cancer progression, works by interfering with membrane progesterone receptors, rather than nuclear progesterone receptors, resulting in suppression of the immunomodulatory protein PIBF, and thus allowing cellular immune destruction, especially by natural killer cells [26,27]. Many of the cancers benefitted by mifepristone are not known to be associated with the nuclear progesterone receptor.

Nevertheless, one could argue that since both patients remained on osimertinib, that possibly mifepristone helped to reactivate the efficacy of this third generation TKI. Since no pharmacological company is financially supporting the evaluation of mifepristone therapy for treating advanced NSCLC, a study comparing the efficacy of osimertinib vs. mifepristone for NSCLC with the EGFR mutation is highly unlikely. However, perhaps the Astra-Zeneca pharmaceutical company, who manufacturers osimertinib, might consider osimertinib vs. osimertinib plus mifepristone in advanced cancers of this type especially since the two reported cases demonstrated that the two drugs taken together were well tolerated. Today, most oncologists would start osimertinib in chemo-naïve EGFR mutation positive NSCLC [28]. One could also consider the combination in earlier disease before widespread metastases.

The two aforementioned patients with stage IV NSCLC that were part of the investigator-initiated study were treated with the 300mg dosage of mifepristone. At this level, the glucocorticoid receptor may be suppressed. Thus, one could argue that the beneficial effect of mifepristone may be related to suppressing the glucocorticoid receptor, rather than the progesterone receptor, and thus PIBF. Therefore, the importance of these two cases, reported here, is that they improved with the 200mg dosage of mifepristone, which is considered insufficient to block the glucocorticoid receptor, thus, lending more support to the PIBF hypothesis.

The fact that, similar to the majority of previous treated patients with mifepristone, the two patients described had stable disease, rather than showing objective remission, yet have had a great extension of a high quality of life, supports the concept that the goal of treating metastatic cancer should be aimed more at quality of life and longevity rather than tumor shrinkage (yet without a real extension of a high quality of life). One must consider regarding treatment options side effects of the treatment in choosing the appropriate therapy. Mifepristone is extremely well tolerated as demonstrated in a large study of treating meningiomas [29]. This has been our experience also.

Finally, since neither patient has shown any recurrence of brain metastases, these cases lend support to the likelihood that mifepristone can cross the blood-brain barrier, and be effective for primary and secondary brain lesions [22,24].

References

1. Hirsch FR, Scagliotti GV, Mulshine JL, et al. Lung cancer current therapies and new targeted treatments. Lancet. 2017; 389: 299-311.
2. Oxnard GR, Hu Y, Mileham KF, et al. Assessment of resistance mechanisms and clinical implications in patients with EGFR T790M-positive lung cancer and acquired resistance to osimertinib. JAMA Oncol. 2018; 4: 1527-1534.
3. Yang Z, Yang N, Ou Q, et al. Investigating novel resistance mechanisms to third-generation EGFR tyrosine kinase inhibitor osimertinib in non-small cell lung cancer patients. Clin Cancer Res. 2018; 24: 3097-3107.
4. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med. 2005; 352: 786-792.
5. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med. 2005; 2: e73.
6. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science. 2007; 316: 1039-1043.
7. Azuma K, Kawahara A, Sonoda K, et al. FGFR1 activation is an escape mechanism in human lung cancer cells resistant to afatinib a pan-EGFR family kinase inhibitor. Oncotarget. 2014; 5: 5908-5919.
8. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med. 2011; 3: 75ra26.
9. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015; 372: 1689-1699.
10. Jia Y, Juarez J, Li J, et al. EGF816 Exerts Anticancer Effects in Non-Small Cell Lung Cancer by Irreversibly and Selectively Targeting Primary and Acquired Activating Mutations in the EGF Receptor. Cancer Res. 2016; 76: 1591-1602.
11. Check JH, Szekeres Bartho J, O'Shaughnessy A. Progesterone induced blocking factor seen in pregnancy lymphocytes soon after implantation. Am J Reprod Immunol. 1996; 35: 277-280.
12. Check JH, Arwitz M, Gross J, et al. Evidence that the expression of progesterone-induced blocking factor by maternal T-lymphocytes is positively correlated with conception. Am J Reprod Immunol. 1997; 38: 6-8.
13. Check JH, Nazari P, Goldberg J, et al. A model for potential tumor immunotherapy based on knowledge of immune mechanisms responsible for spontaneous abortion. Med Hypoth. 2001; 57: 337-343.
14. Polgar B, Kispal G, Lachmann M, et al. Molecular cloning and immunologic characterization of a novel cDNA coding for progesterone-induced blocking factor published correction appears in J Immunol. J Immunol. 2003; 171: 5956-5963.
15. Srivastava MD, Thomas A, Srivastava BI, et al. Expression and modulation of progesterone induced blocking factor PIBF and innate immune factors in human leukemia cell lines by progesterone and mifepristone. Leuk Lymphoma. 2007; 48: 1610-1617.
16. Check JH, SanSoucie L, Chern J, et al. Evidence that progesterone receptor antagonists may help in the treatment

of a variety of cancers by locally suppressing natural killer cell activity. Clin Exp Obst Gynecol. 2007; 34: 207-211.
17. Check JH, Dix E, Sansoucie L. Support for the hypothesis that successful immunotherapy of various cancers can be achieved by inhibiting a progesterone associated immunomodulatory protein. Med Hypoth. 2009; 72: 87-90.
18. Check JH, Cohen R. The role of progesterone and the progesterone receptor in human reproduction and cancer. Exp Rev Endocrinol Metab. 2013; 8: 469-484.
19. Check JH, Sansoucie L, Chern J, et al. Mifepristone treatment improves length and quality of survival of mice with spontaneous lung cancer. Anticancer Res. 2010; 30: 119-122.
20. Check JH, Dix E, Sansoucie L, et al. Mifepristone may halt progression of extensively metastatic human adenocarcinoma of the colon-case report. Anticancer Res. 2009; 29: 1611-1613.
21. Check JH, Dix E, Cohen R, et al. Efficacy of the progesterone receptor antagonist mifepristone for palliative therapy of patients with a variety of advanced cancer types. Anticancer Res. 2010; 30: 623-628.
22. Check JH, Wilson C, Cohen R, et al. Evidence that mifepristone a progesterone receptor antagonist can cross the blood brain barrier and provide palliative benefits for glioblastoma multiforme grade IV. Anticancer Res. 2014; 34: 2385-2388.
23. Check JH, Check D, Wilson C, et al. Long-term high-quality survival with single-agent mifepristone treatment despite advanced cancer. Anticancer Res. 2016; 36: 6511-6513.
24. Check DL, Check JH. Significant palliative benefits of single agent mifepristone for advanced lung cancer that previously failed standard therapy. Med Clin Sci. 2019; 1: 1-5.
25. Check JH, Check D, Poretta T. 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. Anticancer Res. 2019; 39: 1923-1926.
26. Check JH. The role of progesterone and the progesterone receptor in cancer. Expert Review Endo Metab. 2017; 12: 187-197.
27. Check JH, Check D. Therapy aimed to suppress the production of the immunosuppressive protein progesterone induced blocking factor PIBF may provide palliation and or increased longevity for patients with a variety of different advanced cancers-A review. Anticancer Res. 2019; 39: 3365-3372.
28. Takeda M, Nakagawa K. First- and second-generation EGFR-TKIs are all replaced to osimertinib in chemo-naïve EGFR mutation-positive non-small cell lung cancer? Int J Mol Sci. 2019; 20: 146.
29. Ji Y, Rankin C, Grunberg S, et al. Double-Blind Phase III Randomized Trial of the Antiprogestin Agent Mifepristone in the Treatment of Unresectable Meningioma SWOG S9005. J Clin Oncol. 2015; 33: 4093-4098.