

Ribociclib Improves Clinical Outcomes in Breast Cancer Brain Metastases: A Case Report

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Abstract

Ribociclib, an oral cyclin-dependent kinase (CDK) inhibitor, targets the cyclin D1/CDK4 and cyclin D3/CDK6 cell cycle pathway, which shows antineoplastic activity. In the MONALEESA trials (Mammary Oncology Assessment of LEE011's [Ribociclib's] Efficacy and Safety), ribociclib plus endocrine therapy resulted in significantly longer progression free survival (PFS) and overall survival (OS) compared with the endocrine therapy alone. It is plausible to think that the lipophilicity, volume of distribution, and size characteristics of the ribociclib molecule underlie its ability to cross the blood-brain barrier through fenestrated capillaries. This might explain its use in the treatment of brain metastases. We present the case of a 62-year-old woman with infiltrating ductal breast cancer grade GIII, who developed a metastatic breast cancer (estrogen receptor, 95%; progesterone receptor, 0%; ki67, 15%; human epidermal growth factor receptor 2 score, 1+) and disease residue at the pituitary level and other small lesions on the right (at the cerebellar level) and on the left (at the parietal level) of the brain. Systemic therapy with letrozole + ribociclib led to a reduction in the dimensions of sellar and suprasellar pathologic tissue and in the number of lesions. Combination therapy of ribociclib plus letrozole can lead to a promising response, with a reduction in the dimensions of the brain lesions. This allowed chemotherapy to be delayed, improving the patient's quality of life.

Keywords: Ribociclib; Pharmacokinetics; HER2-negative advanced breast cancer; Brain metastasis

Introduction

Ribociclib, an oral cyclin-dependent kinase (CDK) inhibitor, targets the cyclin D1/CDK4 and cyclin D3/CDK6 cell cycle pathway, which shows antineoplastic activity [1, 2]. Moreover, ribociclib inhibits phosphorylation of the retinoblastoma (Rb) protein, preventing CDK-mediated G1-S phase transition and blocking the cell cycle in G1 phase. As a consequence, it suppresses DNA synthesis and inhibits cancer cell growth [2].

The efficacy of ribociclib as treatment of choice for human receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2) negative metastatic breast cancer was first revealed in the MONALEESA ((Mammary Oncology Assessment of LEE011's [Ribociclib's] Efficacy and Safety; M2, M3, M7) randomized, double-blind, placebo-controlled phase 3 trials. In the MONALEESA trials, ribociclib plus endocrine therapy resulted in significantly longer PFS and OS compared with endocrine therapy alone [3].

Ribociclib, in combination with letrozole, was approved in the United States in March 2017 as an initial endocrine-based

therapy for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer [1].

Pharmacodynamics

Ribociclib (7-cyclopentyl-*N,N*-dimethyl-2-[[5-(piperazin-1-yl)pyridine-2-yl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidine) is produced by chemical synthesis [4]. Compared with similar compounds such as palbociclib and abemaciclib, ribociclib shows greater selectivity and higher lipophilicity [5].

Pharmacokinetics

Ribociclib exhibits slightly greater proportional increases in exposure (C_{max} and area under the curve) across the dose range 50 to 1200 mg. With repeated once-daily dosing, steady state was generally achieved after 8 days, and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range, 0.97–6.40) [6].

The pharmacokinetics of ribociclib are reported in Table 1.

Table 1: Pharmacokinetics of ribociclib

	Ribociclib
Molecular weight (g/mol)	434.55
cLog P	2.3
Half-life (h)	30–55
Distribution (L)	1090

Here, we present the case of a 62-year-old woman with infiltrating ductal breast cancer grade GIII, who developed metastatic breast cancer (estrogen receptor [ER], 95%; progesterone receptor (PR), 0%; ki67, 15%; HER2 score, 1+) and disease residue at the pituitary level and other small lesions on the right (at the cerebellar level) and on the left (at the parietal level) of the brain. In this patient, the systemic therapy with letrozole + ribociclib reduced the dimensions of sellar and suprasellar pathologic tissue and the number of lesions.

Case report

In September 2018, a 62-year-old woman underwent to left quadrantectomy and concomitant sentinel lymph node biopsy for infiltrating ductal breast cancer grade GIII (pT2N0(sn); ER, 80%; PR, negative; ki67, 40%; HER2 score, 0).

Four cycles of adjuvant chemotherapy with epirubicin and cyclophosphamide was started, followed by paclitaxel weekly for 12 weeks. After the first cycle of adjuvant chemotherapy, the patient showed grade 3 medullary toxicity and dental problems. For this reason, the treatment with epirubicin and cyclophosphamide was discontinued and the weekly treatment with paclitaxel was pursued. After the first administration of paclitaxel, the patient was hospitalized for 1 month. Pneumococcal pneumonia and complete hypopituitarism with partial diabetes insipidus from a suspicious pituitary macroadenoma were diagnosed. Due to the adverse events reported above, chemotherapy was discontinued.

Positron emission tomography/computed tomography (CT) images from March 2019 did not show any relapse. After 1 month (April 2019), she underwent trans-sphenoidal surgery to

remove the suspicious pituitary macroadenoma. On 29 April, the patient underwent an endocrinologic examination and therapy with cortisone acetate and desmopressin (Minirin) was started. The histologic examination performed on 7 May showed metastatic breast cancer (ER, 95%; PR, 0%; ki67, 15%; HER2 score, 1+). Based on these results, on 18 May, the patient underwent magnetic resonance imaging (MRI) of the brain, which showed the presence of disease residue at the pituitary level and other small lesions on the right (at the cerebellar level) and on the left (at the parietal level). Brain lesions were in pituitary, right cerebellar, and left frontoparietal sites (total of 4 metastatic lesions).

Stereotactic radiosurgery treatment was excluded, and stereotactic radiant treatment on the brain lesions (2500 cGy on the pituitary lesion and 2700 cGy on the right cerebellar lesions and left fronto-parietal lesions) was performed from 11 June to 17 June, 2019. In July 2019, systemic therapy with letrozole + ribociclib was established.

In December 2019, brain MRI and CT total body were performed, showing a reduction in the dimensions of sellar and suprasellar pathologic tissue and in the number of lesions, in both the right cerebellar site and the left posterior frontal site. The clinical improvements are reported in Figure 1. The patient has continued regular therapy with ribociclib and letrozole, and the disease remains in remission after 2 years to date.

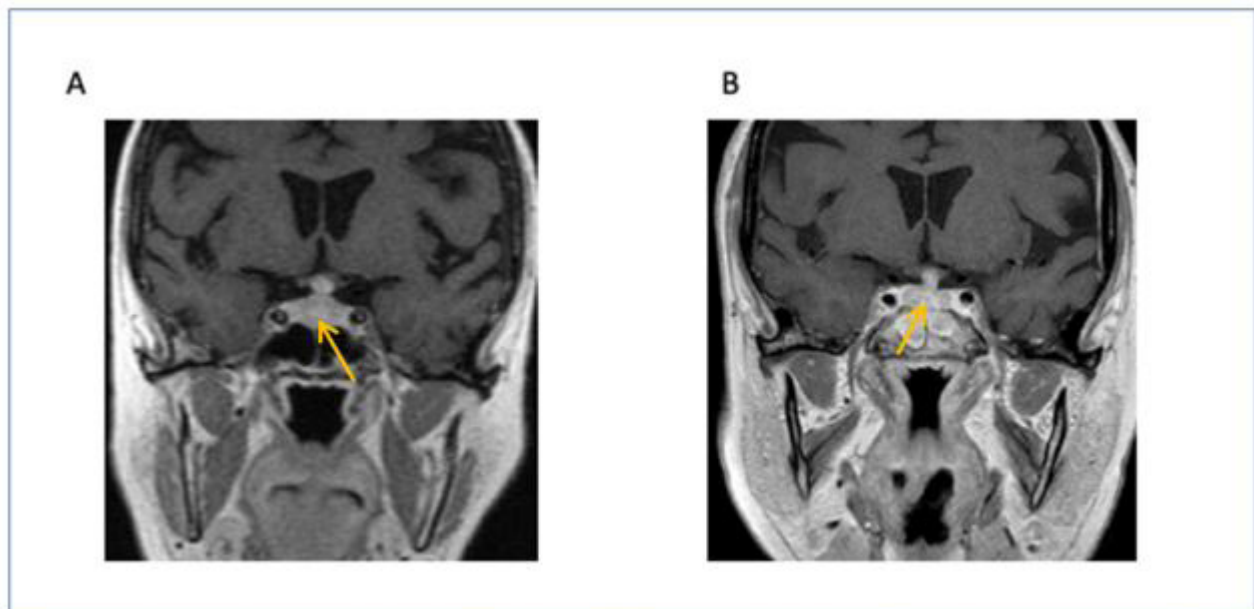


Figure 1: Clinical improvement as a result of the ribociclib plus letrozole treatment. (a) Time of diagnosis: macronodular expansive process with endo- and supra-saddle development with marked elevation of the sellar diaphragm and extension into the chiasmatic cisterna with a clear imprint on the chiasm in the median location. (b) Improvement after the treatment: reduction in the macronodular expansive process

Discussion

Ribociclib (7-cyclopentyl-*N,N*-dimethyl-2-[[5-(piperazin-1-yl)pyridine-2-yl]amino]-7*H*-pyrrolo[2,3-*d*]pyrimidine) is produced by chemical synthesis [4]. Compared with similar compounds such as palbociclib and abemaciclib, ribociclib shows greater selectivity and higher lipophilicity [5]. The mechanism of action of ribociclib results in 50% inhibition (IC_{50}) values of 0.01 (4.3 ng/ml) and 0.039 μ M (16.9 ng/ml) for CDK 4 and 6 in biochemical assays, respectively [6]. The clinical efficacy and safety of ribociclib have been evaluated in various clinical trials. The mechanism of action of ribociclib results in 50% inhibition

(IC_{50}) values of 0.01 (4.3 ng/ml) and 0.039 μ M (16.9 ng/ml) for CDK 4 and 6 in biochemical assays, respectively [6]. The clinical efficacy and safety of ribociclib have been evaluated in various clinical trials.

The MONALEESA-2 trial was a randomized, placebo-controlled, phase 3 trial that evaluated the efficacy and safety of ribociclib combined with letrozole for first-line treatment in 668 postmenopausal women with HR-positive, HER2-negative recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease. Patients were randomized to receive ribociclib (600 mg/day on a 3-weeks-on,

1-week-off schedule) plus letrozole (2.5 mg per day) or placebo plus letrozole. Investigator-assessed PFS was evaluated as the primary endpoint. Results showed that the duration of PFS was significantly longer among patients receiving ribociclib plus letrozole than among those receiving placebo plus letrozole, with a higher rate of myelosuppression in the ribociclib group [7]. On June 2021, 47 patients were still on treatment and the results have been published. The authors described a statistically significant and clinically meaningful benefit in OS, with an improvement of >12 months for ribociclib plus letrozole group versus the placebo plus letrozole group [8].

The MONALEESA-7 trial was a randomized, double-blind, placebo-controlled, multicenter phase 3 clinical study on the treatment of pre- and perimenopausal women with HR-positive, HER2-negative advanced breast cancer. Patients were randomly assigned to receive either ribociclib or placebo in addition to endocrine therapy (goserelin and either a non-steroidal aromatase inhibitor or tamoxifen). The study aimed to evaluate OS and included 672 patients. The results showed significantly longer OS with ribociclib plus endocrine therapy than with endocrine therapy, with no concerns regarding toxic effects [9].

More recently, the MONALEESA-3 study analyzed the second interim analysis of OS. Patients were randomized 2:1 to receive either ribociclib or placebo in addition to fulvestrant as first-line or second-line treatment. Survival was evaluated. The results showed that ribociclib plus fulvestrant had a significant benefit in OS compared with placebo plus fulvestrant in patients with HR-positive, HER2-negative advanced breast cancer [10].

The pharmacokinetics of ribociclib were investigated in patients with advanced cancer on oral daily doses of 50 mg to 1200 mg. The time to reach C_{max} (T_{max}) after oral administration of ribociclib is between 1 and 4 h. Ribociclib exhibits slightly greater proportional increases in exposure (C_{max} and area under the curve) across the dose range 50 to 1200 mg. With repeated once-daily dosing, steady state was generally achieved after 8 days, and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range, 0.97–6.40) [6]. However, the absolute oral bioavailability has not yet been determined [4]. Its human protein binding is $\pm 70\%$, equally distributed in plasma and red blood cells. The estimated apparent volume of distribution is 1090 L, and it has been determined using population pharmacokinetic analysis [11, 12].

Ribociclib is primarily metabolized by CYP3A4 into three major circulating metabolites, M4, M13, and M1. After a half-life of 32 h [13], excretion is greater in feces than in urine with 69.1% and 22.6% of the dose recovered, respectively [4]. It is plausible to think that the lipophilicity, volume of distribution, and size characteristics of the ribociclib molecule underlie its ability to cross the blood–brain barrier through fenestrated capillaries. This might explain its use in the treatment of brain metastases [5].

BC is one of the most frequent causes of brain metastasis, with an estimated incidence of 10%–30% [14]. The development of brain metastases requires the invasion from the primary tumor into surrounding tissue, extravasation into blood colonization, and growth at a distant site [14]. Survival of patients with brain metastasis mostly depends on the therapy.

This case report highlights the opportunity to improve both local and systemic PFS for more than 24 months, even when the patient undergoes various local treatments, such as surgery or stereotactic body radiotherapy.

Conclusion

This case report shows that a combination therapy of ribociclib plus letrozole can lead to a promising response, with a reduction in the dimension of brain lesions, allowing chemotherapy to be delayed and improving patients' quality of life.

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Contribution statement

All authors contributed to the research, development and content of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest: SG declares that she has no conflict of interest. MP declares that she has no conflict of interest. CM declares that she has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent for this type of study, formal consent is not required.

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