



Short communication

Safety and efficacy of cyclin-dependent kinase inhibitor rechallenge following ribociclib-induced limiting hypertransaminasemia



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ABSTRACT

Cyclin-dependent kinase inhibitors (CDKIs) and endocrine therapy (ET) are the corner-stone of systemic therapy for patients with hormone-positive (HR+) HER2-negative metastatic breast cancer (MBC). However, limited data exist regarding rechallenge treatment strategies with CDKIs after limiting toxicity. In this report, we provide evidence of the safety and efficacy of sequential treatment with palbociclib or abemaciclib in 6 HR+/HER- MBC patients who experienced grade ≥ 3 ribociclib-induced hypertransaminasemia. Until results from large observational or randomized studies are communicated, empirical evidence may help make individualized decisions on CDKI rechallenge beyond ribociclib-induced unacceptable liver toxicity.

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1. Introduction

Palbociclib, ribociclib, and abemaciclib, are well-tolerated, orally active, cyclin-dependent kinase inhibitors (CDKIs), each approved for hormone-positive (HR+) HER2-negative metastatic breast cancer (MBC) following pivotal trials showing substantial progression-free survival (PFS) benefit in the first and second-line settings in combination with ET, while abemaciclib is also approved as monotherapy for pre-treated patients [1–6]. Although these drugs share a similar molecular mechanism of action and metabolism by the CYP3A4, they differ substantially in terms of half-life, IC50, and their binding avidity to different CDK molecules, which could contribute to the disparity in their toxicity profiles [7]. As reported by large randomized clinical trials (RCTs), neutropenia was the most common side effect of palbociclib and ribociclib, while diarrhea was the most frequent with abemaciclib. Hypertransaminasemia has emerged as a concern with ribociclib and abemaciclib, resulting in regulatory warnings and recommendations for monitoring liver function tests. It remains unclear whether liver injury might be due to toxic metabolites, immunogenic

intermediates, and/or on-target effects on hepatocytes. In this regard, grade ≥ 3 elevation of alanine and aspartate aminotransferases occurred in up to 11% and 6% of patients receiving ribociclib or abemaciclib in RCTs [2,4,8]. To date, the scarcity of data on cross toxicity and cross efficacy between CDKIs narrows the use of rechallenge strategies in patients who discontinued ribociclib due to liver toxicity.

2. Materials and methods

We retrospectively reviewed the case records of patients with HR+/HER2- MBC treated with ribociclib at the San Carlos University Hospital, Madrid, Spain, both in clinical trials and clinical practice, from January 2017 to May 2020. Patients in whom ribociclib was discontinued due to grade ≥ 3 hypertransaminasemia, and who subsequently received palbociclib or abemaciclib, were included in the analysis. The Common Terminology Criteria for Adverse Events (CTCAE, v5.0) was utilized. Drugs were prescribed at full doses unless otherwise indicated. This study was approved by the Ethics Committee of the San Carlos University Hospital and performed in accordance with the Declaration of Helsinki. Informed consent was waived due to its retrospective nature.

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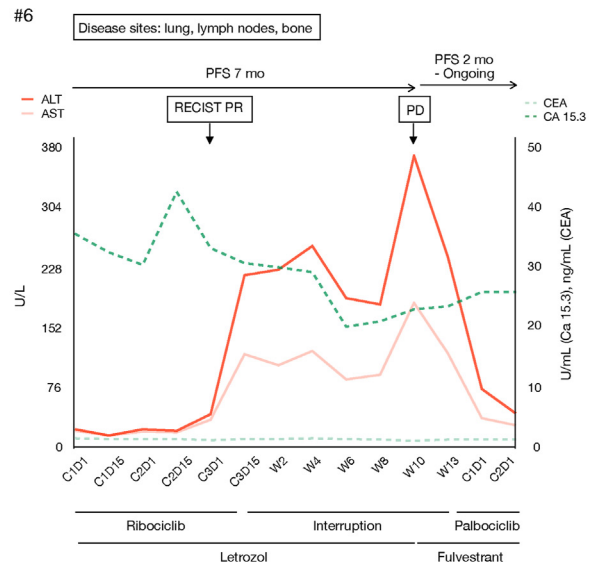
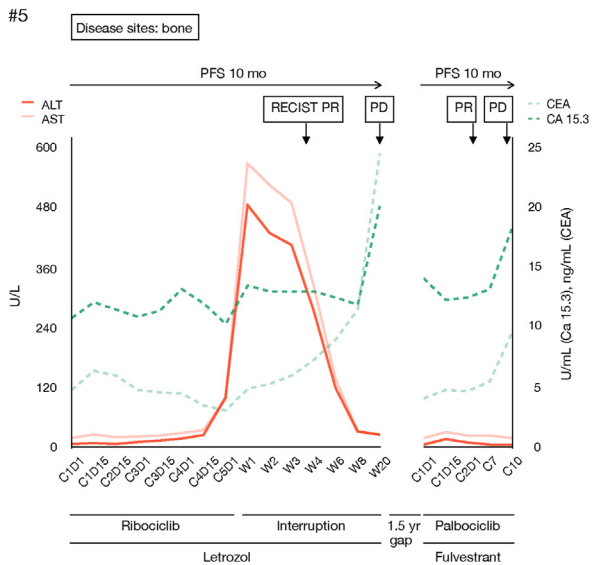
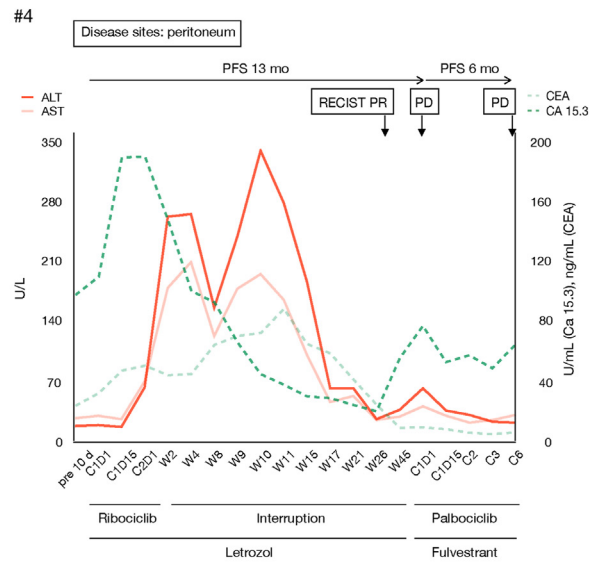
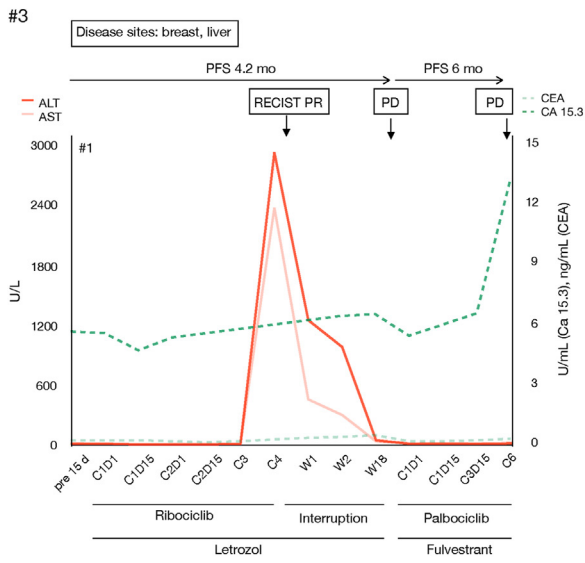
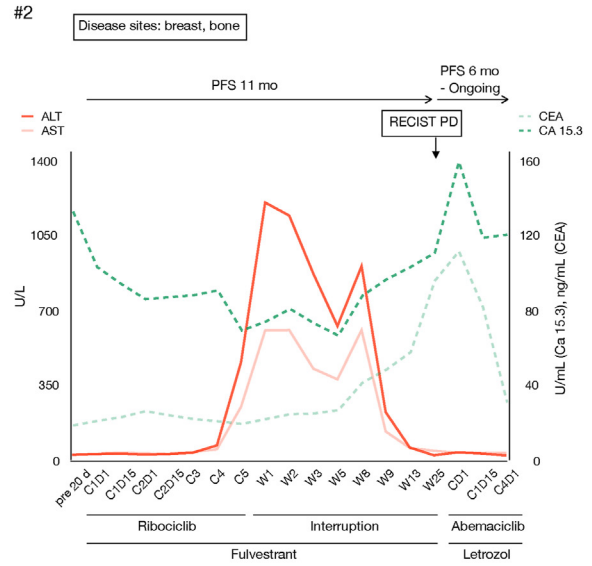
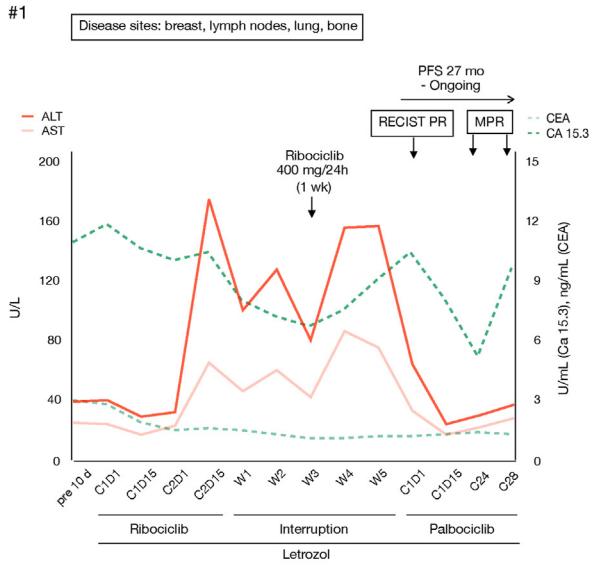


Fig. 1. Time course of serum liver aminotransferases, tumor markers CEA and Ca15.3, and tumor response by RECIST, in the 6 patients exposed to a rechallenge strategy with palbociclib or abemaciclib after ribociclib-induced limiting hypertransaminasemia. The different treatments choices are indicated below. The duration of the CDKI interruption/hormonal partner, and subsequent CDKI, is denoted by black solid lines. The box above shows the extension of the metastatic disease at the time of ribociclib initiation. ALT: alanine aminotransferase. AST: aspartate aminotransferase. CD: cycle and day of CDKI treatment. W: week. Mo: months. PFS: progression-free survival. PR: partial response. MPR: maintained partial response. PD: progressive disease.

3. Results

Sixty-four HR+/HER2- MBC patients were exposed to ribociclib in our institution during the investigation period. Hypertransaminasemia of any grade occurred in 14 patients (21.9%), of which grade ≥ 3 occurred in 7 patients (10.9%). Ribociclib was interrupted and reintroduced with dose reductions in 3 patients, while it was definitely discontinued in 7 patients. Six of them were subsequently treated with a different CDKI and composed the final cohort of the study. Median age was 49.5 years (range 45–61) and all patients were female and ECOG 0. Only 1 patient had liver metastasis and only 1 patient had bone metastasis exclusively. In 5 patients, letrozole plus ribociclib was prescribed as first line therapy for metastatic disease, and in 1 patient, fulvestrant plus ribociclib was initiated as fourth line therapy (Fig. 1). None of the patients had a history of previous liver disease, and neither received hepatotoxic concomitant medications. All patients stopped treatment because of toxicity, but none of them presented symptoms other than mild asthenia and gastrointestinal complaints.

The median number of cycles of ribociclib before treatment withdrawal was 4.5 (1.5–5) (Fig. 1). Liver toxicity reached grade 3 in 4 of the patients, and grade 4 in 2 of them. The median follow-up after treatment discontinuation was 19.5 months (7–36). Viral serology for hepatotropic viruses was negative, and an autoimmune liver disease panel including antinuclear antibodies and antibodies against parietal cells, LC1, LKM, M2, smooth muscle, and reticulon, was performed in 5 of the 6 patients displaying no abnormalities. No patient was biopsied. Patients #1, 2, 3, and 5 reached peaking values of transaminases early after treatment interruption (0–1 week), while it took 10 weeks for patients #4 and 6. Remarkably, patient #3 met criteria for the biochemical Hy's law (elevated bilirubin levels without cholestasis). The median time to recovery was 13.5 weeks (6–26). By maintaining the endocrine therapy partner as monotherapy beyond ribociclib withdrawal, 4 patients attained a partial response by RECIST and the median PFS was 10.5 months (7–13).

The drugs of choice for the rechallenge strategy were palbociclib plus fulvestrant in 4 patients, palbociclib plus letrozole in 1 patient, and abemaciclib plus letrozole in 1 patient. These regimens were initiated after progression to the remaining endocrine partner in 4 of the patients, right after normalization of transaminases in 1 patient, and 1.5 years later in 1 patient. No elevation of transaminases has been observed after a median follow-up of 6 months (2–27). In terms of efficacy, patient #1 remains on treatment with almost complete response after 27 months, while patients #3 and 4 progressed at 6 months of therapy, and patient #5 progressed at 10 months patients. Patients #2 and 6 have not been yet evaluated radiologically after 6 and 2 months of therapy, respectively.

4. Discussion

To the best of our knowledge, here we present the largest case series to date showing the safety and efficacy of utilizing palbociclib or abemaciclib in HR+/HER2- MBC patients who had experienced unacceptable ribociclib-induced hypertransaminasemia. The incidence of grade ≥ 3 hypertransaminasemia in our series was consistent with that reported by RCTs (10.9% vs 5–11%). In the MONALEESA trials, grade ≥ 3 hypertransaminasemia led to the

discontinuation of ribociclib/placebo. In grade 3 toxicity, however, the drug could be resumed at a lower dose level if grade ≤ 1 was restored in ≤ 21 days and in the absence of recurrences [2,5,8]. Only two individual case reports have been published addressing this issue, both of them describing young post-menopausal women with HR+/HER-bone-only MBC who received ribociclib plus letrozole as first line regimen and switched to palbociclib after grade ≥ 3 liver toxicity [9,10]. In both cases, administration of palbociclib did not elicit liver toxicity of any grade, and patients achieved durable responses after 1 year of follow-up. However, there is no evidence on the sequential use of CDKIs in women with MBC including visceral involvement or ≥ 1 previous lines of therapy. Also, it is unclear whether the continuation of the endocrine partner alone can negatively impact the efficacy of other CDKIs compared to immediate switching after liver function recovery.

Ongoing studies will shed light on this controversy, although specific prospective and randomized initiatives are required. We expect results from the phase II PACE (NCT03147287) and PALMIRA (NCT02732119) trials evaluating the activity of combinations including palbociclib in HR+/HER- MBC patients that have previously stopped responding to prior palbociclib. Similarly, the phase II portion of the TRINITY trial (NCT02732119) will report on the anti-tumor activity of ribociclib following progression on a CDKI.

We hope that these data can assist clinicians and their patients in making individualized decisions in such an ominous scenario as metastatic disease, in which the limited resources must be managed in a timely manner to obtain the maximum efficacy and prolong patient well-being as much as possible.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the San Carlos University Hospital and performed in accordance with the Declaration of Helsinki. Informed consent was waived due to its retrospective and descriptive nature.

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