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Toxicities Associated with Metformin/Ritonavir Combination Treatment in Relapsed/Refractory Multiple Myeloma

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Introduction

Despite significant advances in the treatment of multiple myeloma (MM), the disease remains incurable for the vast majority of patients. Active multiple myeloma is usually treated using steroid-based induction therapy with combinations of proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), and, increasingly, monoclonal antibodies (mAbs). Although these agents are included in the majority of frontline and subsequent treatment regimens for MM, studies show that patients eventually develop refractory disease to these regimens, leading to poor prognoses (1-3). Ideally, a second-, third- or fourth-line MM

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treatment regimen would act through unique mechanisms that do not overlap with prior treatment regimens, and have a tolerable safety profile, in a potentially heavily pre-treated patient population.

The surface glucose transporters of multiple myeloma cells are upregulated and constitutively active (4). Published studies have shown that ritonavir, a protease inhibitor used along with other medications to treat HIV/AIDS, reversibly inhibits the glucose transporter GLUT4, providing the rationale to study ritonavir in MM therapy (5, 6). Because cells engage in compensatory metabolic circuitry to evade perturbations in metabolic pathways, we investigated the combination of ritonavir with the anti-diabetic drug metformin, which targets mitochondrial complex 1. In an animal model, metformin with ritonavir substantially and synergistically reduced multiple myeloma tumor burden (7). *In vitro* and *in vivo* work revealed that the ritonavir/metformin combination resulted in suppression of the AKT and mTORC1 pathways, which regulate the synthesis of MCL-1, a member of the pro-survival BCL-2 family. In cell lines and mouse models, co-treatment led to suppression of pAMPK and pAKT, which are key nodes regulating cellular metabolism..

There is considerable clinical experience of both agents. The combination of ritonavir and metformin has been safely administered to non-diabetics with HIV for the treatment of antiretroviral-therapy-induced insulin resistance and lipodystrophy (8). Additionally, in a retrospective review of multiple myeloma patients, the use of metformin correlated with an increase in overall survival when compared to that in patients on insulin or analogues (9). To further explore this combination, we designed a prospective pilot study to evaluate the ability to administer this regimen in relapsed/refractory MM (RRMM).

Case Report

The primary objective of the pilot study was to assess the safety, tolerability, and feasibility of metformin/ ritonavir combination therapy in patients with RRMM (clinicaltrials.org, [NCT# 02948283](https://clinicaltrials.gov/ct2/show/study?term=NCT02948283)). The metformin dosage was increased at three-day intervals up to a maximum of 1000 mg twice daily extended-release metformin and combined with up to 800 mg twice-daily ritonavir. For both agents, doses were escalated to the planned dose or to the subject's own maximum tolerated dose (see Supplemental Information). Eligible subjects had documented measurable disease after at least three prior regimens, with adequate hematologic parameters (ANC 1,000/mm³, platelets 50,000/ mm³), adequate liver tests (total bilirubin 1.5 x ULN, AST and ALT 3 x ULN), and creatinine clearance of 45 mL/ min. Initially, patients received metformin alone, as a single agent, for 7 days, with a possible extension up to 21 days in the event the drug was not initially well tolerated. In the absence of dose-modifying adverse events, participants took metformin 500 mg twice daily for the first three days, and 1000 mg twice daily for the remaining four days. Participants then initiated the combination regimen in 28-day treatment cycles. Ritonavir was added to metformin, initiated at 300 mg twice daily and increased by 100 mg twice daily after being on each dose for at least three days up to a maximum of 800 mg twice daily ritonavir. Subjects received study agents until experiencing either unacceptable toxicity or disease relapse/progression by International Myeloma Working Group criteria (10-12).

The first patient, a 61-year-old woman, received single-agent metformin for two weeks and developed anticipated gastrointestinal (GI) toxicity (grade 2 diarrhea). When that event abated, ritonavir was added. The ritonavir dose was escalated up to the maximum dose of 800 mg twice daily. She received this regimen for 3 weeks, at which point she developed grade 3 lactic acidemia (classified as an unacceptable toxicity), grade 3 hypokalemia, grade 2 nausea, grade 2 dehydration, and grade 2 urinary tract infection. We reasoned that the lactic acidemia was multifactorial due to dehydration from nausea, diarrhea, and the urinary tract infection, all considered possibly related to the regimen. Given that metformin can cause lactic acidosis/acidemia, albeit rarely, and that this toxicity met the definition of unacceptable, the patient was taken off study treatment. At the time of this event, the patient's lactate level was 4.6 mmol/L (normal range 0.5 to 2.2 mmol/L). The creatinine level was 1.49 mg/dL, increased from her baseline creatinine level of 0.7 mg/dL. Her lactate levels resolved to 2.2 mmol/L the next day and additionally to 1.8 mmol/L after 5 days, and her creatinine levels returned to normal at 0.9 mg/dL within the next day; She was unable to complete the first cycle of therapy, receiving <75% of the regimen. Since she received less than one cycle of therapy on the trial, disease response could not be assessed. She went on to receive carfilzomib as the subsequent line of therapy, achieving a likely partial response.

The second patient, a 63-year-old woman, received single-agent metformin for 3 weeks because of nausea (grade 1) and headaches (grade 3 that resolved); both adverse events were considered possibly related to metformin. The patient went on to receive combination therapy with ritonavir for 5 weeks. She experienced persistent headaches (grade 1), dizziness (grade 1), nausea (grade 1), diarrhea (grade 1) and severe fatigue (grade 2) despite dose reduction of ritonavir from 300 to 200 mg twice daily. She also developed grade 3 hyponatremia, but that event was thought to be pseudohyponatremia due to high paraprotein levels. Although none of the events experienced by the patient were considered unacceptable by definition, she decided to withdraw from treatment. Her disease was stable while on treatment, but she progressed on a subsequent clinical trial study drug. She proceeded to receive BCMA-directed CAR T cell therapy, to which a complete response was achieved.

The third patient, a 59-year-old woman, received single-agent metformin for 2 weeks, then started combination therapy with 300 mg twice-daily ritonavir for a total of 2 weeks. While receiving the combination, the patient developed lactic acidemia at a lactate level of 3.74 mmol/L (grade 3), grade 3 hyponatremia, grade 3 hypomagnesemia, and grade 2 acute kidney injury (creatinine 1.4 mmol/L). She was taken off treatment because of the lactic acidemia (classified as unacceptable) and progressed soon thereafter. She subsequently responded to carfilzomib-based treatment and likely achieved a partial response (without formal disease assessment, as in the first patient).

Serial blood samples were collected around the morning doses administered on Day 1 and 15 of combined treatment for the measurement of metformin and ritonavir. Median steady-state metformin C_{max} and AUC on Day 1 (N=3) were 1063 ng/mL (range 849, 1143) and 10099 ng x hr/mL (range 7855, 10510), respectively. Day 15 steady-state metformin C_{max} and AUC (N=2) were 1027 ng/mL (1043, 1011) and 10257 ng x hr/mL (8996, 11517), respectively. Median ritonavir C_{max} after doses of either 300 mg (N=3) or 800 mg (N=2) were 3.0 µg/mL (2.5, 5.8) and 7.3 µg/mL (2.9, 11.8), respectively.

To summarize the toxicity among the three patients, there were five serious adverse events (SAEs) at least possibly related to the treatment during cycle 1. There were two events of grade 3 lactic acidemia, one grade 3 hypomagnesemia, one grade 3 hyponatremia, and one grade 2 acute kidney injury. No SAEs were reported during the single-agent metformin stage. The two events of grade 3 lactic acidemia were considered unacceptable toxicities. One SAE of grade 3 hyponatremia was thought to be unrelated to treatment (pseudohyponatremia due to high paraprotein levels). At the last contact in February 2020, all 3 patients were alive. Clinical data are summarized in Table 1.

Discussion

A hallmark of cancer is the development of increased dependence on glucose to fuel aerobic glycolysis, which is essential for the generation of new biomass and facilitation of nutrient signaling. The cells consequently produce lactic acid, affecting pH levels, which can promote tumor invasion and suppression of anticancer immune effectors. The alteration in glucose metabolism occurs throughout carcinogenesis (13). Ritonavir affects many cellular and tissue processes including angiogenesis, tumor growth and invasion, inflammation, antigen processing and presentation, cell survival, and tissue remodeling. It results in inhibition of NF κ B, inhibition of Akt-regulated cell proliferation, and enhancement of protein ubiquitination (4, 14-16). Metformin has been widely used in diabetic and non-diabetic patients, has an acceptable safety profile, and use of this agent in diabetic patients with MM predicted an increase in overall survival when compared to the control group administered insulin or insulin analogues (9). The combination of ritonavir and metformin was found to be safe and well-tolerated in non-diabetic patients with HIV for the treatment of retroviral therapy-induced insulin resistance and lipodystrophy (8).

We decided to use the metformin extended release (XR) formulation, which typically results in less toxicity than the traditional formulation. In routine clinical practice, metformin is generally dose escalated over 1 to 2 weeks to diminish gastrointestinal toxicities present upon initiation or dose escalation. In an effort to provide patients with maximal drug doses as quickly as possible, we attempted a more rapid intra-patient escalation, but in our small group of 3 patients, we found that in all 3 patients, it took 2 weeks for the transient GI toxicity from metformin to resolve. In our study consistent with the package insert, we found that although gastrointestinal toxicities are uncomfortable, they do not typically exceed grade 2. Other than GI toxicity, metformin is generally very well-tolerated. One patient also reported headaches, which have been reported in about 6% of patients receiving metformin.

Several considerations contributed to the decision to increase metformin to its maximum dose before initiating ritonavir. Pre-clinical *in vivo* experience showed better efficacy when metformin administration began 7 days before ritonavir (7). Metformin may take time to cross the plasma membrane of target cells (17, 18). Furthermore, both metformin and ritonavir cause transient GI toxicity via distinct mechanisms (19-21).

Ritonavir is known to cause paresthesia, fatigue, dizziness, GI toxicity, and peripheral neuropathy. Notably, there are several drug interactions with ritonavir because of its ability

to act as both a potent inducer and inhibitor of CYP3A4. Therefore, we prohibited concomitant therapy with other strong CYP3A4 inhibitors/inducers. Ritonavir is not thought to be particularly myelosuppressive. (There has been some myelosuppression observed with higher doses of ritonavir, but this finding was in patients with HIV taking other antiretroviral drugs, which are known to cause myelosuppression.) In the subject population with RRMM, we did not anticipate significant myelosuppression, a contrast to many of the agents in current use in this setting.

The incremental (100 mg twice daily) dose increase of ritonavir is consistent with that described in the package insert. However, in this study we decided to explore up to 800 mg twice daily of ritonavir, a 33% increase over the 600 mg twice daily dose (FDA-approved) for several reasons. First, the anti-neoplastic ability of ritonavir *in vitro* is dose dependent (4, 7, 16, 22-25). Second, the FDA-approved dose of 600 mg twice daily appears to have been based on the biological threshold for HIV protease inhibition and not safety or tolerability (IC₉₀ of HIV-PI achieved at 2.9 μ M) (26-29). Third, plasma concentrations (C_{min}, C_{max}, AUC) of ritonavir vary greatly between individuals taking the same dose and regimen, and plasma concentrations directly tie to tolerability (26, 27, 29-32), suggesting that an individually targeted maximum dose is appropriate. Ritonavir has a three- to four-hour half-life, and the twice daily ritonavir administration results in a large difference between C_{min} and C_{max} (26, 27, 29-32). The same total daily dose administered with more frequency has been proposed and explored in the literature (26, 27, 29-32), but twice daily dosing was pursued in this study to facilitate patient compliance. Because ritonavir induces its own metabolism, and plasma concentrations vary greatly between patients and directly link to tolerability, during the dose escalation phase, patients had a 7-day window to determine whether the toxicity experienced was transient, after which appropriate dose reductions were made.

Our observation of lactic acidemia in two out of three patients prompted study closure. In this era of numerous potential novel therapies for MM, it is reasonable to pursue other alternatives. Although lactic acidosis/acidemia is a well-described complication of metformin therapy, it is rare and typically occurs at very high concentrations (e.g., > 5 μ g/mL) (33, 34). Our pharmacokinetic analysis revealed that metformin levels were $\cong$ 1 μ g/mL and consistent with previously reported results following single-agent administration (35). Furthermore, metformin concentrations were not different between Days 1 and 15 despite co-administration of higher ritonavir doses (i.e., 300 mg versus 800 mg). Therefore, we did not observe any apparent drug-drug interactions leading to increased metformin exposures.

It is possible that metabolic perturbations induced by metformin and ritonavir led to lactic acidosis through mechanisms that are not clearly understood. Mitochondrial toxicity is a cause of lactic acidosis and was reported to be an effect of several other HIV drugs, although those agents were in the nucleoside reverse transcriptase inhibitor class (36). Liver disease is considered a risk factor for the development of lactic acidosis during metformin therapy. However, continued use of metformin in diabetics with liver dysfunction, including cirrhosis, has been used successfully and may be associated with a survival benefit in certain patients. Nevertheless, we were cautious and excluded patients with >Grade 1 AST or ALT

elevation (37, 38). Neither of the patients who developed lactic acidemia in our study had evidence of liver disease. Notably, both of those patients developed transient elevation in creatinine levels, and the risk of lactic acidosis increases with renal insufficiency. While a meta-analysis suggested to cautiously expand use of metformin in patients with type 2 diabetes and eGFR of at least 30 mL/min/1.73 m² (39), and another large study showed that metformin did not increase the risk of lactic acidosis even with chronic kidney disease (40), we were conservative in our study, and required creatinine clearance above 45 mL/min for study entry. Conditions predisposing to hypoperfusion and hypoxemia include renal impairment, heart failure, acute pulmonary decompensation, dehydration, and sepsis (41-43). This population of patients with relapsed or refractory multiple myeloma is prone to renal impairment, particularly in the setting of poor oral intake and dehydration, and they are also prone to infections.

Conclusion

Although there is a sound biological rationale for combining a protease inhibitor such as ritonavir with metformin, our pilot feasibility and safety study showed that the combination was toxic in this population, even at lower doses of ritonavir. The anorexia and GI toxicity associated with the regimen may predispose these fragile patients with RRMM to develop dehydration, acute kidney injury, and subsequent risk of serious complications. Other protease inhibitors have been studied in this setting, and an encouraging phase 2 clinical trial using nelfinavir in combination with bortezomib and dexamethasone was conducted in a heavily pretreated population of 34 RRMM patients with an average of 5 prior lines of treatment. In this setting, bortezomib-refractory patients showed an impressive overall response rate of 65% (44). This combination has been shown to overcome proteasome inhibitor-based resistance (44-46). A trial using an entirely oral regimen of nelfinavir in combination with lenalidomide and dexamethasone showed a minor response or greater in 55% of patients (47), a favorable example of repurposing drugs (48). Nelfinavir has obtained orphan drug status for MM treatment, and it is commercially available for off-label use in RRMM. Although nelfinavir also impacts glucose uptake, it does so to a weaker extent and through a mechanism of impaired GLUT4 translocation, rather than the reversible binding seen with ritonavir (49). A combination with metformin may result in less severe toxicities, but adverse events should be closely monitored. Certainly, the combination of ritonavir and metformin, regardless of the rationale, warrants caution and a careful assessment of the potential risks and benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Practice Points

- The combination of metformin and the protease inhibitor ritonavir was associated with unacceptable toxicities in patients with multiple myeloma.
- Ritonavir has the off-target effect of reversibly inhibiting the glucose transporter GLUT4, which may have contributed to the regimen's toxicity.
- A combination of metformin with other protease inhibitors, including nelfinavir, may result in less severe toxicities, but adverse events should be closely monitored.

Table 1.

Summary of clinical data. Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; GI, gastrointestinal.

	Monoclonal protein at initiation of combination treatment	Monoclonal protein subtype	Monoclonal protein at end of treatment	Grade 2 toxicities associated with metformin/ritonavir treatment (CTCAE v4)	Response to metformin/ritonavir treatment	Subsequent line of therapy, with response given
Patient 1	1.68 g/dL	IgA kappa	1.22 g/dL	GI toxicity, lactic acidemia, hypokalemia, dehydration, urinary tract infection	Unable to be assessed, received <1 cycle of therapy	Carfilzomib, partial response
Patient 2	3.4 g/dL	IgG kappa	3.96 g/dL	Headaches, fatigue, hyponatremia	Stable disease	BCMA-directed CAR T cells, complete response
Patient 3	88 mg/dL	Lambda light chain	114.9 mg/dL	Lactic acidemia, hyponatremia, hypomagnesemia, acute kidney injury	Unable to be assessed, received <1 cycle of therapy	Carfilzomib, partial response