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Editorial

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Cyclophosphamide- Antifungals Interactions in Patients Undergoing Hematopoietic Stem Cell Transplantation: What Should We Know About it?

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INTRODUCTION

Cyclophosphamide (Cy) is a chemotherapy agent used as a conditioning regimen in autologous and allogeneic hematopoietic stem cell transplantations (HSCTs). This drug is metabolized in the liver through cytochrome P (CYP) oxidation, glutathione conjugation, and aldehyde dehydrogenase conversion. Cy is a prodrug that activates to 4-hydroxy-cyclophosphamide (HCy) via the CYP450 isoenzymes CYP2A6, CYP2B6, CYP2C9, CYP2C19, and CYP3A4. Subsequently, HCy undergoes further metabolism, producing several toxic metabolites, such as acrolein. Cy is also detoxified via CYP3A4 to an inactive metabolite, deschloroethyl-cyclophosphamide (DCCy)[1]. Drug interactions that affect the hepatic metabolism of Cy or its metabolites may lead to increased serum concentrations of Cy and associated toxicities.

The Influence of Antifungal Agents on Cyclophosphamide

Antifungal agents, extensively used to prevent and treat invasive fungal diseases (IFD) in HSCT recipients, may interact with Cy, potentially causing significant complications[2]. The complexity of drug-drug interaction, coupled with its potential complications, can pose challenges for clinicians in delivering optimal care to their HSCT patients.

Azole antifungals

Among antifungal agents, azoles are potent competitive inhibitors that reduce the metabolism of drugs metabolized by CYP450 isoenzymes, resulting in significant interactions when administered concurrently with Cy[3]. This interaction leads to increased plasma concentrations of Cy and heightened toxicity by inhibiting its Cy-mediated metabolism.

Fluconazole: Fluconazole strongly inhibits CYP2C19 and moderately inhibits CYP2C9 and CYP3A4. The moderate inhibition of CYP3A4-mediated activation of Cy by fluconazole can elevate the risk of adverse effects. A retrospective case series of nine children with established Cy metabolism profiles revealed a 43% reduction in Cy clearance when given daily 5 mg/kg fluconazole, compared to 13 children not receiving fluconazole[4]. However, early toxicity data

from a randomized trial comparing fluconazole with itraconazole as antifungal prophylaxis in HSCT recipients demonstrated that fluconazole's inhibition of CYP2C9 may reduce the synthesis of HCy, resulting in elevated levels of DCCy and less toxic metabolites[5]. This data was supported by a further retrospective pharmacokinetic study on high doses of fluconazole (400 mg per day) co-administered with Cy in HSCT patients[6]. While this protective effect may reduce toxicity, it may also decrease Cy's efficacy. Overall, in clinical practice, fluconazole has been considered safe with limited impact on Cy's PK compared to other triazoles.

Itraconazole: Itraconazole is a more potent CYP3A4 inhibitor than fluconazole, significantly affecting Cy metabolism[7]. A study on patients receiving fluconazole or itraconazole for IFD prophylaxis after allogenic HSCT found that itraconazole recipients had higher bilirubin and creatinine levels during the first 20 days post-HSCT. It was also reported that itraconazole recipients had a 20% greater Cy clearance than fluconazole recipients, resulting in increased exposure to toxic metabolites associated with hepatic veno-occlusive disease (VOD)[4]. Additionally, itraconazole's potential negative inotropic effects may exacerbate congestive heart failure and is recommended to be avoided in patients receiving drugs that could be cardiotoxic, such as high-dose Cy. Therefore, itraconazole therapy should be suspended during Cy-containing chemotherapy administration[8].

Voriconazole: Voriconazole, the preferred antifungal for invasive aspergillosis prevention and treatment, strongly inhibits CYP3A4, moderately inhibits CYP2C19, and weakly inhibits CYP2C9. While the theoretical interaction between voriconazole and Cy has not been formally evaluated, recent animal studies suggest that CYP2B6-mediated inhibition may contribute to the voriconazole-Cy interaction[9]. In patients scheduled for undergoing HSCT who are receiving voriconazole for a preexisting fungal infection, holding voriconazole therapy or switching to non-azole antifungals is recommended. If voriconazole is temporarily discontinued, it should be stopped at least 30 hours before starting chemotherapy and resumed after five half-lives have passed [10]. However, further clinical investigations are needed to fully understand the impact of this interaction.

Posaconazole: Posaconazole is a broad-spectrum azole antifungal that strongly inhibits CYP3A4, similar to voriconazole. The interaction-related adverse effects of posaconazole when combined with Cy have not been studied [11].

Ketoconazole*:* Ketoconazole use has been replaced by newer antifungals due to its risks of drug interactions, endocrine dysregulation, and hepatotoxicity [12]. Ketoconazole, a strong inhibitor of CYP3A4 and a weak inhibitor of CYP2C19, significantly influences Cy metabolism. Combining these two drugs can lead to nephrotoxicity and hepatotoxicity, making the avoidance of this combination highly recommended.

Echinocandins

Echinocandins are widely used to treat invasive candidiasis in neutropenic patients, such as those undergoing HSCT. Three echinocandins—caspofungin, micafungin, and anidulafungin—have been developed for clinical use, are known for their mild and infrequent toxicity. Notably, these agents do not significantly inhibit or induce CYP450 enzymes, resulting in a lower risk of PK drug-drug interactions. However, they necessitate daily intravenous infusions and come at a relatively high cost[13]. In some transplant centers, caspofungin is substituted for triazole antifungals during Cy conditioning to minimize drug-drug interactions and ensure uninterrupted antifungal therapy. Nevertheless, it remains uncertain whether this approach significantly improves transplant survival outcomes. Further research is needed to establish its superiority in this regard.

Amphotericin B

Amphotericin B (AmB), known for its broad-spectrum antifungal properties, does not typically engage in clinically significant metabolism-based interactions. However, it can potentially lead to renal dysfunction, especially when used alongside

nephrotoxic medications. In the pre-engraftment phase of HSCT, low doses of liposomal amphotericin B (LAmB) have been proposed as a replacement for azole prophylaxis. Research has shown no significant difference in the development of IFI or all-cause mortality between these two options[14]. In cases of high azole resistance or contraindications, inhaled amphotericin B (InAmB) offers an alternative for invasive pulmonary aspergillosis (IPA) prophylaxis in HSCT patients. It does not pose systemic adverse effects or medication interactions. However, its tolerance is contingent on local reactions, and factors such as an unpleasant taste, cough, nausea, and technical challenges may limit its use[13].

Table 1 provides a summary of the interactions between high-dose Cy and antifungals, presenting information on the mechanism, severity, outcome, and degree of documentation in HSCT patients.

The Role of Therapeutic Drug Monitoring (TDM)

Despite the widespread use of Cy, there has been insufficient research on its therapeutic drug monitoring (TDM). While the exact role of Cy metabolites in efficacy and toxicity remains unclear, a connection between Cy exposure and toxicity has been suggested. This implies that TDM could provide valuable data on toxicity outcomes associated with Cy. Cy is known to cause various side effects, including nausea, vomiting, alopecia, immunosuppression, gonadal damage, and cardiotoxicity. These adverse effects are often exacerbated by high-dose regimens such as those used in HSCT. Given the close relationship between Cy delivery regimens and toxicological consequences, TDM for Cy is highly recommended. Monitoring Cy concentrations in circulation can offer insights into the drug's actual levels in the body, potentially prompting further PK investigations and refinement of the therapeutic index[15].

DISCUSSION

The interactions between Cy and antifungal agents pose significant clinical challenges, potentially resulting in serious side effects. Among the triazoles, fluconazole appears to be a safe choice for co-administration with Cy. In contrast, itraconazole and ketoconazole therapies should be discontinued during Cy-containing chemotherapy. The clinical impact of theoretical interactions between Cy and voriconazole or posaconazole remains incompletely understood, necessitating further research.

Echinocandins, such as caspofungin, do not interact significantly with immunosuppressants and chemotherapy drugs used in HSCT. Therefore, they can be administered during the conditioning treatment phase before transplantation, minimizing interruptions in antifungal therapy and enabling prophylaxis in high-risk patients.

For antifungal prophylaxis in the pre-engraftment period, low-dose L-AmB may offer a safe and effective alternative. InAmB can be a preferable option for prophylaxis against IPA in HSCT recipients with contraindications. TDM is essential to ensure that drug concentrations remain within the therapeutic range without reaching potentially toxic levels and should be integrated into routine practice. When combining intractable antifungals with Cy, close monitoring of hepatic and renal function, as indicated by serum bilirubin and serum creatinine levels, along with vigilant cardiac monitoring, is imperative.

CONCLUSION

In summary, the management of Cy-antifungal interactions demands a deep understanding of potential drug-drug interactions, appropriate dosage adjustments, and the necessity for therapeutic and clinical monitoring. These aspects are crucial when initiating and discontinuing Cy. Due to the limited available data, further studies are warranted to assess the clinical impact of antifungal medication interactions with Cy on transplant outcomes and the role of TDM in these patients.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

Table 1: Summary of clinical interactions between high-dose cyclophosphamide and antifungal agents in patients undergoing HSCT

Antifungal agent	Mechanism of interaction	Severity	Outcome	Documentation	Ref.
Fluconazole	Strong inhibition of CYP2C19-mediated activation of Cy Moderate inhibition of CYP2C9-mediated activation of Cy Moderate inhibition of CYP3A4-mediated activation and detoxification of Cy	Moderate	↕Toxicity	Suspected	[4, 5]
Itraconazole	Strong Inhibition of CYP3A4-mediated activation of Cy Synergist cardiotoxicity effects	Moderate	↑↑ Cardiotoxicity ↑↑ Nephrotoxicity ↑↑ Hepatotoxicity ↑↑ VOD	Suspected	[4, 7, 8]
Ketoconazole	Strong inhibition of CYP3A4-mediated activation and detoxification of Cy Week inhibition of CYP2C19-mediated activation of Cy	Major	↑↑↑ Nephrotoxicity ↑↑↑ Hepatotoxicity	Suspected	[12]
Voriconazole	Strong inhibition of CYP3A4-mediated activation and detoxification of Cy Moderate inhibition of CYP2C19-mediated activation of Cy Week inhibition of CYP2C9-mediated activation of Cy Inhibition of CYP2B6-mediated activation of Cy	Moderate	N/A	Suspected	[9, 10]
Posaconazole	Strong inhibition of CYP3A4-mediated activation and detoxification of Cy	Moderate	N/A	Suspected	[11]
Echinocandins	No significant interaction	-	-	-	[13]
Amphotericin B (parenteral)	Synergist nephrotoxicity effects	Moderate	↑ Nephrotoxicity	Suspected	[14]
Amphotericin B (inhalation)	No significant interaction	-	-	-	[13]

Abbreviations: CYP: cytochrome P; Cy: cyclophosphamide; HSCT: hematopoietic stem cell transplantation; N/A: not available; Ref.: reference; VOD: veno-occlusive disease; ↑ increased; ↕ increased or decreased

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