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CASE REPORT

Therapeutic Drug Monitoring-Guided Antifungal Therapy Under Tyrosine Kinase Inhibitor Treatment in an Advanced Osteosarcoma Patient with Invasive Pulmonary Aspergillosis

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Abstract: Antifungal therapy for invasive pulmonary aspergillosis (IPA) can be challenging in cancer patients due to interpatient variability in pharmacokinetic properties of antifungals and potential drug-drug interactions (DDIs). This case report describes a 14-year-old boy with advanced osteosarcoma diagnosed with invasive pulmonary aspergillosis (IPA) after chemotherapy. Initial treatment of voriconazole showed poor improvement, as therapeutic drug monitoring (TDM) revealed exceptionally low trough concentration (0.28 μg/mL) even after dose increase. When voriconazole was switched to isavuconazole, favorable antifungal response was observed with isavuconazole trough concentrations ranging from 2.43 μg/mL to 4.12 μg/mL. Moreover, TDM also detected no obvious pharmacokinetic DDI between isavuconazole and apatinib but potential DDI between voriconazole and anlotinib in this patient. This case highlights the importance of individualized pharmacokinetic considerations in antifungal therapy in cancer patients. TDM may be a useful aid for therapeutic regimen decision and optimization.

Keywords: invasive pulmonary aspergillosis, voriconazole, isavuconazole, apatinib, pharmacokinetics

Introduction

Invasive pulmonary aspergillosis (IPA) is a life-threatening opportunistic fungal infection in advanced neoplasia patients, who are often immunocompromised under radiotherapy or chemotherapy.[1,2] Early diagnosis and appropriate antifungal therapy are essential to prevent dissemination and death. According to current guidelines, voriconazole (VOR) and isavuconazole (ISA) are recommended as the first-line treatment for IPA. Notably, efficacy and safety of these agents is closely related to their pharmacokinetic properties.[3,4] Insufficient or toxic exposure represents as important causes for treatment failure or adverse events. Moreover, drug-drug interaction (DDI) between azole antifungals and antineoplastics though hepatic cytochrome P450 (CYP450) enzymes-mediated metabolism is also of great concern. In sight of these factors, therapeutic drug monitoring (TDM) may be of particular importance to optimize drug exposure and avoid unexpected drug toxicity or DDIs.

Here we present a case of IPA after chemotherapy of advanced osteosarcoma. TDM was performed for medication regimen decision and potential DDI detection, indicating the importance of individualized pharmacokinetic considerations in antifungal therapy in cancer patients.

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Case Presentation

A 14-year-old boy with a known case of osteosarcoma of left tibia and pulmonary metastasis received surgical treatment for left tibia (1 year ago) and right upper lobe (5 months ago). After lung surgery, his chemotherapy was adjusted to ifosfamide, vincristine and trelizumab. Two months ago, he began to take anlotinib (12mg qd), a novel multi-target, anti-angiogenic tyrosine kinase inhibitor (aa-TKI).[5] Neutropenia occurred during the treatment period with specific values unknown. One month ago, he developed fever (Tmax 39.0°C), cough and pain in left back. A week later, he presented to the local hospital and was diagnosed with IPA by thoracic computed tomography (CT) scan and metagenomic next-generation sequencing (mNGS) of bronchoalveolar lavage (BAL) (*Aspergillus fumigatus*, sequence count: 18). BAL cultures were negative. Chemotherapy except anlotinib was discontinued. Intravenous voriconazole (VOR, 200 mg q12h) andamphotericin B liposome (25 mg qd) was initially administered for 8 days, with caspofungin (50 mg qd) added for the next 8 days due to the poor control of body temperature. Despite the use of methylprednisolone, his CT features still worsened, but the body temperature gradually reduced to normal. Then, he was transferred to our hospital. The anthropometric assessment documented a weight of 47 kg, a height of 1.75 m and a body mass index (BMI) of 15.35 kg/m^2 upon admission. CT scan showed extensive consolidation predominantly in the left upper lobe with ground-glass opacities (Figure 1A). Laboratory data revealed white blood cell (WBC) count 12.00 × 10^9/L with 70.5% neutrophils and 13.7% monocytes. Serum c-reaction protein, procalcitonin, liver and kidney function were normal. Microscopy, Gram staining, and cultures of BAL were all negative, while galactomannan antigen index was positive in BAL (6.64) but negative in serum (0.28). According to the updated consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group, the diagnosis of IPA is "probable".[6] Regarding the limited efficacy of previous treatment, anlotinib intake was suspended. Intravenous VOR was continued as the single antifungal treatment with dose increase to 250 mg q12 h, for serum VOR trough concentration (Cmin) was 0.93 μg/mL (therapeutic target 2–6 μg/mL) on day 2 of admission (VOR day 18). Unexpectedly, VOR-Cmin decreased to 0.28 μg/mL on day 10 (VOR day 26). Thoracic CT scan also showed poor improvement (Figure 1B) with WBC count at 10.10 × 10^9/L. The physician asked clinical pharmacist for consultation.

Considering this patient might be an ultra-rapid (UM) or rapid metabolizer (RM) of the primary metabolism enzyme of VOR, CYP2C19,[7] the clinical pharmacist suggested to refer to ISA therapy instead. Intravenous ISA was initiated on day 16 of admission with 6 loading dose (200 mg tid) and the maintenance dose of 200 mg qd. To ensure sufficient exposure, ISA-Cmin was measured on day 22 (ISA day 7) and turned out as 2.43 μg/mL. This level was in accordance with the mean ISA-Cmin described in the SECURE trial (a mean ISA-Cmin on day 7 of 2.6 ± 1.0 μg/mL).[8] WBC count decreased rapidly to 5.94 × 10^9/L. As early assessment of ISA-Cmin was probably not at steady state, ISA was continued at original dose and switched to oral intake for convenient administration on day 23 (ISA day 8). After 14-day treatment,

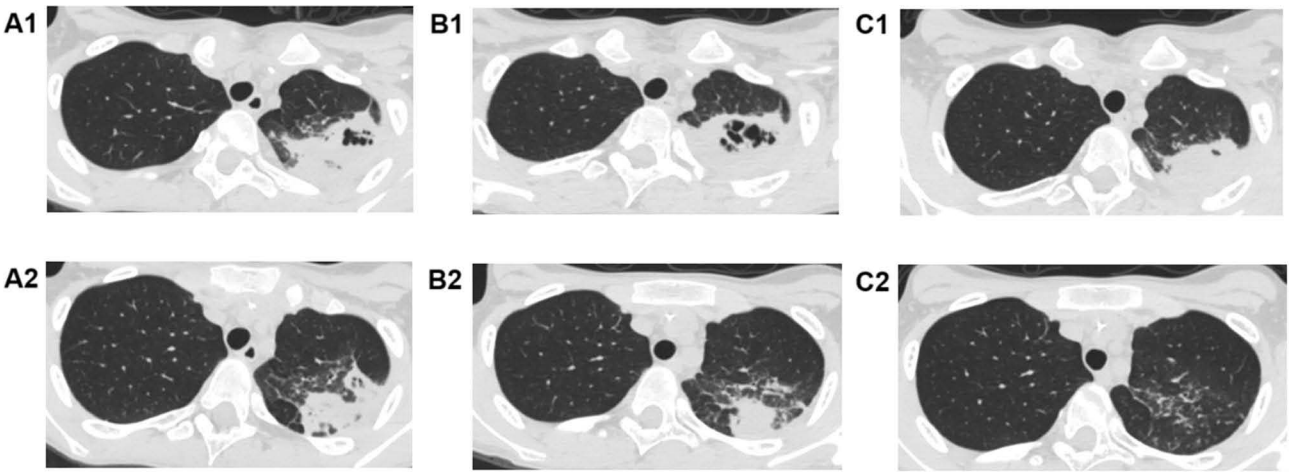

Figure 1 Thoracic CT features of the patient during different antifungal therapy. (**A1** and **A2**) day 2 of admission (voriconazole day 18); (**B1** and **B2**) day 13 of admission (voriconazole day 29); (**C1** and **C2**) day 36 of admission (isavuconazole day 23).

ISA-Cmin reached 3.96 μg/mL. Markedly improvement was observed in thoracic CT features (Figure 1C) on day 37. Based on the favorable response on antifungal therapy, the physician planned to restart chemotherapy of another novel aa-TKI, apatinib (APA, 375 mg qd). The metabolism of APA primarily relies on CYP 3A4/5. Previous research has reported that co-administration of ketoconazole or VOR significantly increased APA exposure in rats.[9] Whether the similar pharmacokinetic DDI existed between ISA and APA, which might lead to dose-related adverse reactions, such as hand-foot syndrome, hypertension, proteinuria and neutropenia, remained unknown.[10] To solve this problem, the clinical pharmacist proceeded TDM of APA by liquid chromatography–tandem mass spectrometry according to the published methodology study.[11] Cmin of ISA and APA at the second day of APA intake (day 39) was 3.82 μg/mL and 24.66 ng/mL, respectively. On day 44 (APA day 7), steady state Cmin of ISA and APA was 4.12 μg/mL and 30.41 ng/mL. For the quantitative-effectiveness relationship of APA has not been conclusively established, we also measured the $AUC_{0\text{-}24}$ of these two agents at steady state as 116.5 mg·h/L for ISA and 5283 mg·h/L for APA, comparable with those reported in clinical trials (ISA 200mg qd: $AUC_{0\text{-}24}$ 106 ± 32.1 mg·h/L, APA 500mg qd: $AUC_{0\text{-}24}$ 8991 ± 3139 mg·h/L).[11,12] The patient showed no obvious adverse reactions during the whole treatment process and discharged from hospital with prescriptions for ISA (200 mg qd) and APA (375 mg qd) at day 45 (Figure 2). A week later in outpatient re-examination, Cmin of ISA and APA was measured as 3.40 μg/mL and 24.41 ng/mL, respectively. Then, the patient was transferred to local hospital. ISA was suspended after 12-week treatment with markedly improved CT feature.

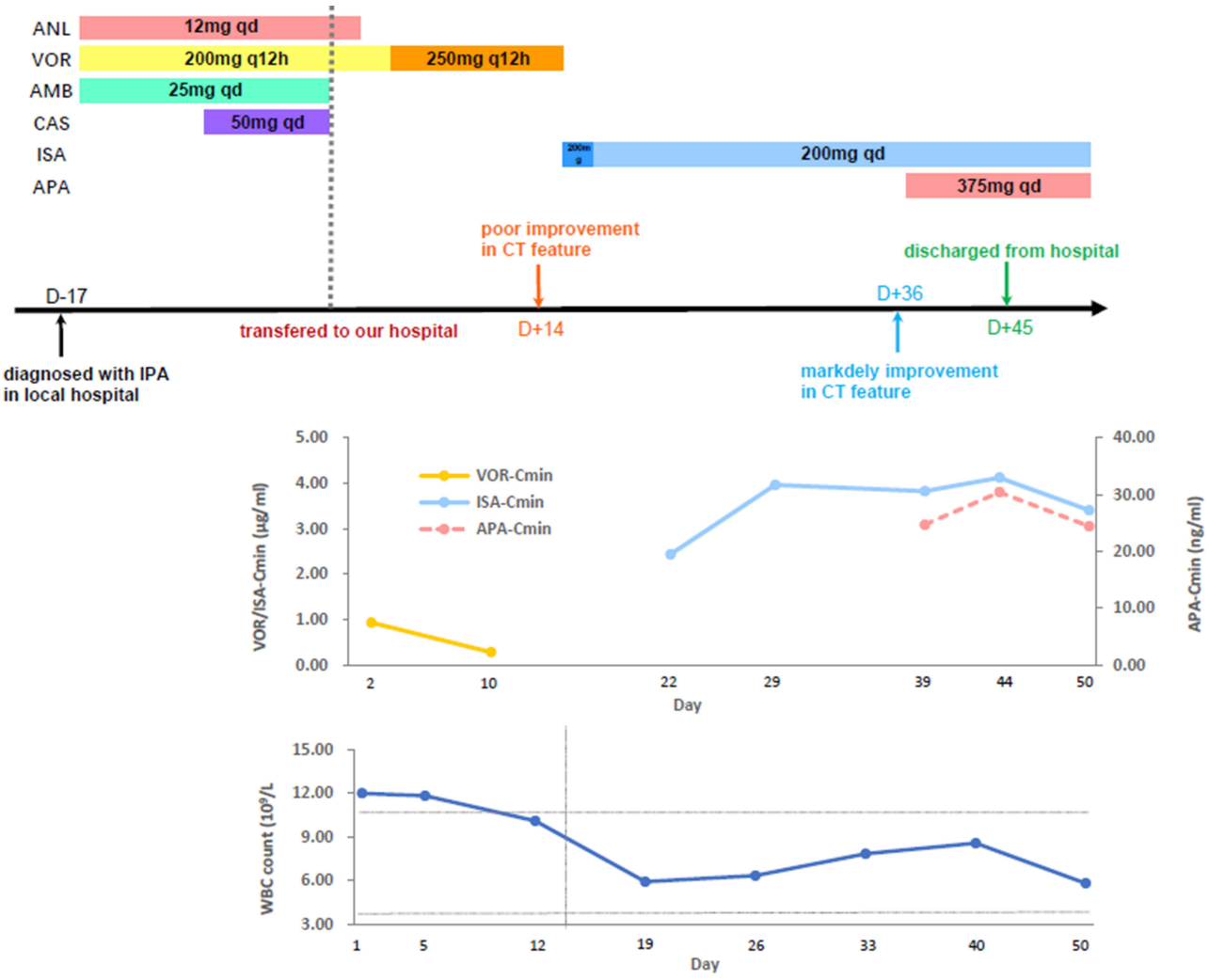

Figure 2 The timeline of antifungal and TKI therapy, and trough concentrations.
Abbreviations: ANL, anlotinib; VOR, voriconazole; AMB, amphotericin B; CAS, caspofungin; ISA, isavuconazole; APA, apatinib.

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Discussion

To our knowledge, this is the first case report that discuss TDM-guided antifungal therapy under new-generation aa-TKI treatment in cancer patients with IPA. TDM was used to ensure medication efficacy and safety, highlighting the significance of individualized antifungal therapy in cancer patients.

Invasive aspergillosis is a serious and complicated medical condition in patients with oncological malignancies, and the mortality is increasing. Being the most frequent therapeutic choice, VOR can exhibit significant interpatient pharmacokinetic variability. VOR is mainly metabolized by the hepatic CYP2C19. Genetic polymorphisms of CYP2C19 are crucial determinant of VOR exposure.[4] According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) recommendation, UMs and around 50% of RMs were unable to achieve therapeutic Cmin with standard dosing, and were suggested to use an alternative agent that does not depend on CYP2C19 metabolism, such as ISA, liposomal amphotericin B, or posaconazole.[7] In the current case, inadequate VOR exposure possibly induced by rapid metabolism might account for initial treatment failure. A genotype test may help certify the metabolism activity of CYP2C19. However, it was not performed as the assay was unavailable in the local hospital and VOR administration was discontinued. On the other hand, the relatively higher VOR-Cmin (0.93 μg/mL) on admission might be attributed to pharmacokinetic DDI with anlotinib. Previous study has reported that CYP2C19 genetic polymorphism was closely related to anlotinib exposure and adverse reactions.[13] Whether it is an inhibitor of CYP2C19 remains unknown. The DDI between VOR and anlotinib has not been reported to date. Further studies are required to assess the underlying mechanisms.

ISA is a relatively new triazole antifungal with comparable efficacy of VOR in clinical trials of IPA.[6] It has several advantages over other azoles, such as linear pharmacokinetics, low interpatient pharmacokinetic variability, and relatively low risk of DDIs.[14] Routine TDM of ISA is not necessary in most circumstances but may be beneficial in cases with potential pharmacokinetic DDIs. However, the concentration thresholds for efficacy and safety of ISA have not yet been defined in current guidelines.[2,3] Some studies have suggested that therapeutic range of ISA-Cmin could be 2–5 μg/mL.[15] In our case, TDM of ISA was proceeded to ensure appropriate exposure. Different form VOR-Cmin, ISA-Cmin exhibited rapid and stable attainment of the reported target range with favorable antifungal response, indicating the lower interpatient variability of both pharmacokinetic properties and therapeutic effect for ISA.

New generation aa-TKIs, including anlotinib and APA, are increasingly used in the treatment of advanced bone and soft tissue sarcoma. Their anti-tumor effects have been demonstrated in several single-center or multi-center clinical studies.[16,17] Both anlotinib and APA are primarily metabolized by CYP3A4/5. Thus, CYP3A4/5-based DDIs are of great concern for their exposure and therapeutic outcome. The elevated exposure of anlotinib and APA with azole antifungals co-administration has been predicted or proved in preclinical studies.[8,18] However, in our case, the Cmin of ISA and APA was relatively stable and no obvious adverse reactions was observed during the whole treatment process. Moreover, $AUC_{0\text{-}24}$ of these two agents was comparable with those reported in clinical trials, indicating low risk of pharmacokinetic DDIs. Well-designed studies are still needed to further confirm this inference. The limitation of this case report is that ISA and APA concentrations were not measured through the whole period of treatment, for the patient was transferred to local hospital shortly after discharge.

Conclusion

With the increased application of new generation aa-TKIs in malignant tumors, individualized antifungal therapy for IPA is of particular importance to ensure efficacy and safety. Our case showed low risk of pharmacokinetic DDI between ISA and APA, but potential DDI between VOR and anlotinib, with the aid of TDM. Further studies are required to systematically analyze the potential DDIs between azole antifungals and aa-TKIs.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author (Ruiting Wen) upon reasonable request.

Consent Statement

Informed consent was obtained from the patient to TDM and publish any findings. As this is a case report (and no clinical study) there is no ethics statement included, because monitoring of serum levels in this patient is regular health care in our hospital. An Ethical Board is therefore not consulted.

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Disclosure

Ruiting Wen, Wentao Ni and Xiaotong Gu contributed to the work equally and should be regarded as co-first authors. Ruiting Wen and Xiaohong Zhang contributed to the work equally and should be regarded as co-corresponding authors. All authors have no conflicts of interests to report relevant to this article.

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