Correlation of Pain and Fluoride Concentration in Allogeneic Hematopoietic Stem Cell Transplant Recipients on Voriconazole

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Supportive care guidelines recommend antimold prophylaxis in hematopoietic stem cell transplant (HSCT) recipients deemed to have high risk for invasive fungal infection, leading to long-term use of voriconazole after allogeneic HSCT in patients who remain immunocompromised. Voriconazole has been associated with periostitis, exostoses, and fluoride excess in patients after solid organ transplantation, HSCT, and leukemia therapy. The aims of this study were to describe the frequency and clinical presentation of patients presenting with pain and fluoride excess among allogeneic HSCT patients taking voriconazole, to identify when a plasma fluoride concentration was measured with respect to voriconazole initiation and onset of pain, and to describe the outcomes of patients with fluoride excess in the setting of HSCT. A retrospective review was conducted of all adult allogeneic HSCT patients receiving voriconazole at Mayo Clinic in Rochester, Minnesota, between January 1, 2009 and July 31, 2012. Of 242 patients included, 32 had plasma fluoride measured to explore the etiology of musculoskeletal pain. In 31 patients with fluoride measurement while on voriconazole, 29 (93.5%) had elevated levels. The median plasma fluoride was 11.1 μmol/L (range, 2.4 to 24.7). The median duration of voriconazole was 163 days (range, 2 to 1327). The median time to fluoride measurement was 128 days after voriconazole initiation (range, 28 to 692). At 1 year after the start of voriconazole after HSCT, 15.3% of patients had developed pain associated with voriconazole use and 35.7% developed pain while on voriconazole after 2 years. Of the patients with an elevated fluoride level, 22 discontinued voriconazole; pain resolved or improved in 15, stabilized in 3, and worsened in 4 patients. Ten patients continued voriconazole; pain resolved or improved in 7, was attributable to alternative causes in 2, and undefined in 1. Serum creatinine, estimated glomerular filtration rate, alkaline phosphatase, and voriconazole concentration did not predict for fluoride excess and associated pain. Periostitis due to fluoride excess is a common adverse effect of voriconazole that should be considered in patients presenting with pain and is often reversible after drug discontinuation. Alternative antifungal agents with a lower risk for fluoride excess should be considered in patients receiving voriconazole who develop fluoride excess and pain.

INTRODUCTION

Patients undergoing an allogeneic hematopoietic stem cell transplantation (HSCT) are at high risk for invasive fungal infections [1,2]. Clinical practice guidelines by the Infectious Diseases Society of America for the use of antimicrobial agents in neutropenic patients with cancer recommend a mold-active agent in pre-engraftment HSCT patients with a prior history of invasive aspergillosis, anticipated prolonged neutropenia of at least 2 weeks, or a prolonged period of neutropenia immediately before transplantation [3]. The Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients recommend that patients at high risk for mold infections be considered for prophylaxis with mold-active drugs during periods of risk [4]. These recommendations have led to long-term use of voriconazole in some patients after allogeneic HSCT (eg, chronic graft-versus-host disease receiving immunosuppressive therapies).

Voriconazole is a synthetic derivative of fluconazole. Broader antifungal spectrum of activity results from replacing a triazole ring on fluconazole by a fluorinated pyrimidine, as well as adding an α-methyl group [5]. Voriconazole contains 3 fluoride ions, accounting for 16.3% of voriconazole by weight. A 400 mg daily dose of voriconazole contains 65 mg elemental fluoride [6]. The typical adult daily fluoride consumption is ≤ 2.5 mg through environmental sources such as drinking water [7]. It is postulated that the fluorinated pyrimidine in voriconazole is responsible for periostitis and exostoses secondary to fluoride excess; however, this phenomenon is not well understood [6,8,9].

There is little information on the effects of long-term use of voriconazole in HSCT recipients. The objectives of this study are to describe the frequency of fluoride-related pain in

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a cohort of allogeneic HSCT recipients taking voriconazole, to identify when plasma fluoride was measured because of musculoskeletal symptoms in relationship to voriconazole initiation, and to describe the clinical presentation and outcomes of fluoride excess in HSCT recipients.

PATIENTS AND METHODS

Study Population

After institutional review board approval was obtained and patient consent for use of medical records was verified, data regarding all adult allogeneic HSCT recipients at Mayo Clinic in Rochester, Minnesota between January 1, 2009 and July 31, 2012 were retrospectively reviewed. Patients were included if they received voriconazole after allogeneic HSCT. Patients were excluded if they were treated by the pediatric service or did not consent for research.

Study Design

A retrospective review was completed, with time 0 as either the transplantation date or voriconazole start date, whichever came later. Voriconazole exposure before HSCT was not captured as many patients were managed at other centers before HSCT and patients with acute leukemia often received voriconazole as antimold prophylaxis during the post-chemotherapy period while neutropenic, but they did not have continuous exposure before HSCT. Follow-up time ended at either the voriconazole stop date or date of last follow-up if the patient was still on voriconazole. Plasma fluoride measurements were conducted with an ion-selective electrode (normal range, 0 to 4 μmol/L, resulting from exposure to fluoride from common sources such as diet, beverages, drinking water, and use of fluoride toothpaste). The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine data using the isotope dilution mass spectrometry–traceable modification of diet in renal disease study equation: eGFR (mL/minute/1.73 m^2) = 175 × (serum creatinine)$^{-1.154}$ × (age)$^{-.203}$ × (.742 if female) × (1.210 if black).

Statistical Methodology

Cox proportional hazards models were used to measure associations of variables with toxicity. Variables measured during follow-up were modeled as time-dependent covariates. Kaplan-Meier methodology was used to estimate cumulative musculoskeletal pain associated with voriconazole use rates. Hazard ratios (95% confidence intervals) were used to summarize these associations. SAS software, version 9.2 (SAS Institute, Cary, NC) was used for all analysis.

RESULTS

Patient Characteristics

From January 1, 2009 through July 31, 2012, 292 patients received an allogeneic HSCT at Mayo Clinic's campus in Rochester, Minnesota, of whom 50 were excluded because they did not consent to research (n = 4), they were treated by the pediatric service (n = 7), or they did not receive voriconazole (n = 39). The median age of patients included was 54 years (range, 19 to 71), 44% of patients were female, and 95% of patients were Caucasian. The diseases leading to transplantation included acute myeloid (36.7%) or lymphoblastic (13.6%) leukemia, myelodysplastic syndrome (13.2%), and chronic lymphocytic leukemia (12.4%); 89.7% of patients received peripheral blood stem cells, 6.6% received bone marrow, and 3.7% received cord blood. Forty-nine percent received a transplant from a matched related donor, 38% from a matched unrelated donor, 12% from a mismatched unrelated donor, and 1% from a mismatched related donor. The median duration of voriconazole for all patients was 163 days (range, 2 to 1327). More than one half of patients (56%) received voriconazole for less than 6 months, 60 patients (25%) received voriconazole for 6 to 12 months, 35 patients (14%) received voriconazole for more than 1 year, and 12 patients (5%) received voriconazole for more than 2 years.

Fluoride and Voriconazole Testing

Of 242 adult allogeneic HSCT patients who received voriconazole, 32 patients developed musculoskeletal pain and underwent subsequent serum fluoride measurement. Of those, 31 patients had a plasma fluoride measurement while on voriconazole. Twenty-nine (93.5%) had elevated fluoride concentrations (> 4 μmol/L). One patient who developed musculoskeletal pain after 1.5 years of voriconazole therapy had a normal plasma fluoride measured 1 month after voriconazole discontinuation (Table 1). The median plasma fluoride concentration in patients on voriconazole at the time of the plasma fluoride measurement was 11.1 μmol/L (range, 2.4 to 24.7). The median time to fluoride measurement was 128 days after voriconazole initiation (range, 28 to 692). At 1 year after the start of voriconazole after HSCT, 15.3% of patients developed pain associated with voriconazole use and 35.7% developed pain while on voriconazole after 2 years (Figure 1). Only 1 patient had radiographic findings consistent with fluoride excess; this was noted on shoulder radiograph as benign-appearing new bone formation of both shoulders. Serum creatinine, eGFR, and alkaline phosphatase did not predict the development of pain associated with voriconazole (Table 2). Voriconazole trough concentrations were measured in 119 patients at any time point after transplantation. Of the 32 patients with fluoride measurement, 24 patients also had a voriconazole concentration measured. There was no association between elevated fluoride concentration and voriconazole concentration (hazard ratio, .799; 95% confidence interval, .577 to 1.108).

DISCUSSION

We observed a significant number of allogeneic HSCT patients develop musculoskeletal pain while on voriconazole. The development of voriconazole-associated pain in 15.3% of our patients within 10 months is consistent with the 15% of patients reported to have pain and an elevated plasma fluoride level by Gerber et al. in a smaller cases series of 20 patients [10]. In the multistate outbreak of invasive fungal infections due to contaminated compounded methylprednisolone, Moon et al. found 14.4% of evaluable patients received bone scans and fluoride levels concurrently for concern of periostitis and, of those, 21 were confirmed to be positive (75%) [11]. We did not prospectively measure fluoride levels in all patients so we cannot confirm the finding of Gerber et al. that all patients receiving voriconazole develop elevated plasma fluoride levels. However, most plasma fluoride levels measured after the development of pain while on voriconazole in our cohort were elevated. This is consistent with a previous study from our institution, which primarily consisted of solid organ transplantation patients on voriconazole, where all patients had elevated plasma fluoride levels, but the range of elevation was broad [6]. Taken together, these various investigations suggest that plasma fluoride levels are often elevated in patients taking voriconazole, including allogeneic HSCT patients.

Fluoride excess has well-known adverse clinical effects. Gastrointestinal symptoms and lower extremity pain were noted in 54% of subjects treated with 75 mg of sodium fluoride daily for 4 years [12]. Plasma fluoride levels were only 8 μmol/L in this trial, which is significantly lower than that of most of the patients in our study of voriconazole. The skeletal pain associated with voriconazole has typically been attributed to periostitis. Although fluoride is covalently bound in voriconazole, 5% of voriconazole is metabolized to free fluoride [13,14]. The fluoride ion