Novel Formulation SUBA--itraconazole: Prophylaxis in Hematological Malignancy or Undergoing Allogeneic Stem Cell Transplantation: Follow Up Survival Data

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INTRODUCTION

Invasive fungal infections (IFIs) in patients with hematological malignancies and those undergoing hematopoietic stem cell transplantation (HSCT) are associated with significant morbidity, mortality and cost to the health care system.

Despite the advantageous spectrum of activity of itraconazole, it is rarely used as a prophylactic agent due to limited bioavailability and intolerance of the conventional formulation. After the development of a novel formulation SUBA-itraconazole (SU; per bioavailability), we undertook a study to assess therapeutic levels, safety, tolerability and IFI rates of this novel formulation when compared to the conventional itraconazole liquid in patients undergoing allogeneic hematopoietic stem cell transplantation or in hematological malignancy patients.

AIMS

This prospective comparative cohort study was designed to assess the time to achieve therapeutic levels of SUBA-itraconazole compared to a retrospective control group of conventional itraconazole liquid in patients undergoing allogeneic hematopoietic stem cell transplantation or in hematological malignancy patients.

METHODS

Following a single centre, prospective study of SUBA-itraconazole 200mg BID vs conventional liquid itraconazole 200mg BID, the SUBA-itraconazole group was assessed one year post allogeneic stem cell transplant for incidence of IFI and survival. In the experimental group SUBA-itraconazole was given at an initial dose of 200mg (4x50mg capsules) twice daily, on an empty stomach, half an hour before food. Trough plasma concentrations were measured twice weekly throughout the study period. If trough concentrations were above 2000ng/mL, the dose was reduced by 50mg/dose every week until therapeutic levels were achieved in 69% of the SUBA-itraconazole group vs 21% (p<0.001). The mean trough serum concentrations at steady state of SUBA-itraconazole were significantly higher, with less interpatient variability (1577ng/mL, CV 35%) vs (1218ng/mL, CV 60%) (p<0.001).

FOLLOW UP SURVIVAL AT ONE YEAR POST HSCT

After one year post allogeneic stem cell transplant in the SUBA--itraconazole group there were 2 deaths (10%) due to disease progression and no further IFIs were reported.

PHARMACOKINETIC RESULTS

A total of 57 patients (29 SUBA--itraconazole and 30 liquid itraconazole) were assessed. Therapeutic concentrations were achieved significantly more quickly in the SUBA-itraconazole group; median of 6 days vs 14 (p<0.001). At day 10, therapeutic concentrations were achieved in 69% of the SUBA-itraconazole group vs 21% (p=0.001). The mean trough serum concentrations at steady state of SUBA-itraconazole were significantly higher, with less interpatient variability (1577ng/mL, CV 35%) vs (1218ng/mL, CV 60%) (p<0.001). Future randomized trials will be necessary to determine the exact role of the SUBA-itraconazole preparation when used as IFI prophylaxis in patients undergoing allogeneic HSCT or in patients considered to have an intermediate/high risk of IFI associated with treatment of a hematological malignancy. Efficacy and tolerability of treatment in both groups were also assessed.

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SAFETY AND TOLERABILITY

There were 2 (7.5%) treatment failures in the SUBA--itraconazole group, both due to cessation of therapy for mucositis, compared to 7 (23.3%) treatment failures in the liquid-itraconazole group, due to subtherapeutic levels (5), mucositis (1) and gastrointestinal intolerance (1), (p = 0.096). There was one confirmed IFI in the SUBA-itraconazole treatment failure group defined by a blood culture that yielded yeast; however, this was after the cessation of SUBA-itraconazole for mucositis. No other Probable/Possible IFIs were observed.

CONCLUSION

The use of the SUBA--itraconazole formulation was a safe and effective prophylactic agent. It was associated with more rapid attainment of therapeutic levels with less interpatient variability when compared to conventional liquid itraconazole. This study has demonstrated that the SUBA-itraconazole formulation is associated with more rapid attainment of therapeutic levels with less interpatient variability when compared to conventional liquid itraconazole. Future randomized trials will be necessary to determine the exact role of the SUBA-itraconazole preparation when compared to currently accepted alternative mold-active agents as IFI prophylaxis in settings where itraconazole may be considered as a reasonable alternative in patients with an intermediate to high risk of fungal infection.