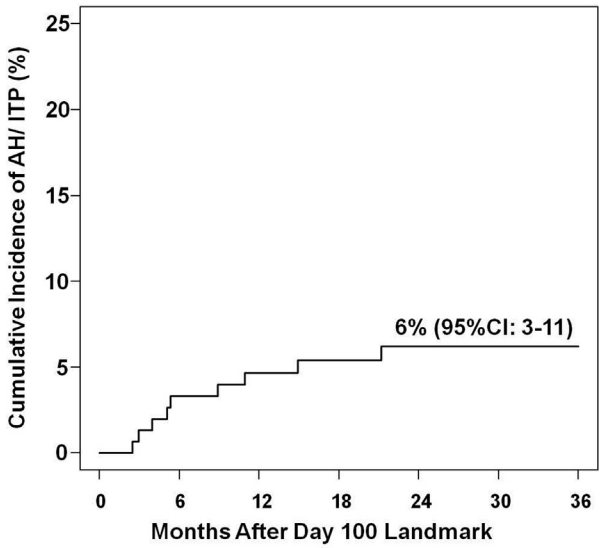

Figure.

rituximab only, and 1 received corticosteroids/IVIg. Overall, all 9 patients received rituximab at 2-18 days (4-6 doses) after diagnosis. Early rituximab ($\leq$ 7 days) reduced time to CR (Hb $\geq$ 8 &/or platelets $\geq$ 100): median 13 days (7-49 days) if early rituximab in 4 patients versus 58 days (19-98 days) in 5 without early rituximab. Moreover, an initial IVIg/corticosteroids/rituximab combination was best (CR 7-13 days). Four patients flared at 28-393 days but all achieved CR with further treatment. Drug therapy was well tolerated whereas 2 of 3 patients who underwent splenectomy with initial therapy or with relapse had complications. Eight of 9 AH/ITP patients are alive & disease free. Seven of them are in CR from AH/ITP at a median of 30 months (range 9-102) follow-up after AH/ITP diagnosis whereas one has recurrent AH requiring therapy.

Conclusions: While AH/ITP is infrequent it can have sudden onset and be life-threatening. The mechanism is likely transient B-cell immune dysregulation during immunosuppression taper, and thus patient monitoring and prompt recognition during this period are warranted. Early rituximab treatment is both mandated at presentation in severe disease and will likely reduce corticosteroid exposure & could avoid splenectomy.

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CMV and EBV Reactivation after Allogeneic Transplantation

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Background: Reactivation of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) following allogeneic stem cell transplant occurs in 60-70% and 5-15% of patients respectively. CMV disease can present as pancytopenia, disordered liver function, pneumonitis, retinitis or neurological disorders. EBV reactivation can result in post transplant lymphoproliferative disorder (PTLD). At risk patients are monitored using DNA PCR assays and pre-emptive therapy commenced. The optimum timing for intervention has not been established.

Methods: We identified at-risk patients receiving an allogeneic transplant during the period 2012-2013 from our institutional database and retrospectively collected data from the electronic and paper records.

Results: Complete data was available for 27 patients. The diagnoses were AML/MDS (14), ALL (6), CLL (3), CML (1), aplastic anaemia (1) and myelofibrosis (1). 26 were at risk for EBV reactivation and 13 were at risk for CMV reactivation. 5/13 (38%) patients developed CMV reactivation at a median of 26 days post transplant (range 22-49). The median CMV DNA peak titre was 3647 IU/ml (range 603-62616). 4/5 patients were treated with valganciclovir and none developed CMV disease. Valganciclovir was well tolerated and effective in all cases. 7/26 patients (27%) developed EBV reactivation after a median 60 days (range 10-221). 2 patients (12.5%) developed lymphadenopathy and received rituximab with a complete response. Two patients developed late onset recurrent EBV reactivation following treatment with rituximab. One patient had a rising titre from day +165, continuing to rise from $<$137 to 37944 IU/ml on day +494. The second patient reactivated on day +225 with a titre continuing to rise to 23693 IU/ml on day +264. Neither patient was on immunosuppression or has developed clinical or radiological evidence of PTLD.

Conclusion: CMV reactivation was less frequent than previously reported and pre-emptive therapy was effective. It is possible that some patients were treated unnecessarily although treatment was well tolerated. EBV reactivation rates were consistent with those previously reported. Two cases of PTLD highlight the importance of regular EBV titre monitoring and early treatment. The late re-emergence of EBV reactivation in patients who are not on immunosuppression is not well described in the literature and its pathogenesis and clinical significance may be different from early reactivation.

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Withdrawn

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Micafungin Anti-Fungal Prophylaxis in Pediatric Patients Undergoing Hematopoietic Cell Transplantation (HCT) - Can We Give Higher Dose, Less Frequently? - a Pharmacokinetic (PK) Study

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Background: Disseminated fungal infection is a major cause of morbidity and mortality in children undergoing HCT. Anti-fungal prophylaxis with intravenous micafungin has a distinct advantage over amphotericin-B and oral triazoles due to its better safety profile, specifically in terms of hepatic and renal toxicity, and lack of drug-drug interactions

with common medications used in the HCT setting. Currently, children who receive prophylactic micafungin are given daily dosing (1mg/kg/dose) or alternate day dosing (3mg/kg/dose). We hypothesized that higher dose micafungin (5 mg/kg) every 4 days will provide effective anti-fungal prophylaxis, and improve patient compliance (with essentially twice a week dosing regimen).

Objectives: To examine micafungin PK when given at 5mg/kg dose for anti-fungal prophylaxis to children undergoing HCT.

Methods: Nine children with various hematological, metabolic and immune deficiency disorders undergoing HCT received a single dose of micafungin (5 mg/kg) intravenously over 1 hour. Dose selection was based on published PK data in pediatric neutropenia patients (Seibel et al. 2005), our alternate day micafungin PK study (Mehta et al. 2010), along with Monte Carlo PK/PD simulation. Blood samples were drawn around the micafungin infusion and at regular intervals until 96 hours after. Plasma concentration data were analyzed by noncompartmental (WinNonlin) and population PK analysis (NONMEM).

Results: Micafungin at 5 mg/kg dose was well tolerated in all subjects along with measurable plasma concentrations at 96 hours (Table 1). PK was best described by a 2-compartment model in all subjects (Figure 1). The mean concentration at 96 hours was 0.11 μg/mL (Range: 0.03-0.26 μg/mL). Concentrations at the end of the 96 hours remain above the minimum inhibitory concentration (MIC) of susceptible fungal pathogens (MIC >0.2 μg/ml) in 1 patient (11%) only. However, target concentrations were achieved in 7/9 (78%) patients at the end of 72 hours. When accounted for the post-antifungal effect, all 9 (100%) patients were in the goal range at the end of 72 hours.

Conclusion: Our data suggest that although micafungin at 5 mg/kg dosing generates suboptimal levels at the end of 4 days, observed levels at the end of 3 days were in the target range, to cover susceptible fungal pathogens and provide an attractive alternative for anti-fungal prophylaxis in children undergoing HCT.

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Table 1
Micafungin concentrations

Patient	At 24 hrs (μg/ml)	At 48 hrs (μg/ml)	At 72 hrs (μg/ml)	At 96 hrs (μg/ml)
Mean	4.60	1.19	0.34	0.11
SD	1.07	0.36	0.15	0.08

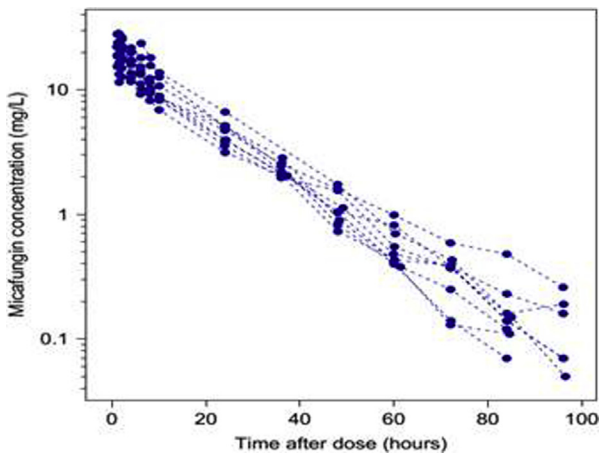

Figure 1. PK profile of micafungin

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The Incidence and Outcomes of Oral Mucositis Among Allogeneic Stem Cell Transplantation Patients: A Systematic Review and Meta-Analysis

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Background: Oral mucositis (OM) is the most debilitating adverse effect of treatment from patient perspective during Allogeneic Stem Cell Transplantation (ASCT).The intensity of the conditioning regimen relates to both incidence & severity of OM; however no previously published study has analyzed this relationship. We sought to perform a meta-analysis and systemic review on the incidence and outcomes of OM in ASCT patients, and analyze this association.

Methods: A comprehensive search of several databases (Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane CRCT, Ovid Cochrane DSR and Scopus) from 1990-2014 for studies of OM in ASCT patients was conducted by an experienced medical librarian. To avoid file-drawer bias, professional society meeting (ASH, EHA, ASBMT, EBMT, AAD) abstracts were searched. Studies were included with strict eligibility - if they reported the grade & incidence of OM with validated scales, and provided details of conditioning regimen and Graft-versus-host-disease (GVHD) prophylaxis (including doses e.g. methotrexate). Grade of OM was analyzed based on the WHO or NCI-CTCAE scales. For studies not utilizing these scales, only overall incidence of OM was reported. Severe mucositis was defined as either Grade 2-4 or Grade 3-4 depending on the studies' definition of severity. Cohorts were analyzed based on regimen intensity i.e. Reduced Intensity Conditioning (RIC) [including Non-myeloablative] and Myeloablative (MA).

Results: A total of 624 studies generated from the search were reviewed. Of the 582 patients in 14 eligible MA regimen studies, 75.4% experienced any OM, while in 245 patients reviewed in the 6 eligible RIC regimen studies, 86.1% experienced any OM (figures 1&2). A majority of studies utilized the WHO or NCI-CTCAE scales. Severe OM occurred in 73.3% of the WHO/NCI graded MA conditioning patients and 67.8% of WHO/NCI graded RIC conditioned patients. Other grading scales included in the studies were Oral Mucositis Index, the Southwest Oncology Group (SWOG) Criteria, and the Eastern Cooperative Oncology Group (ECOG) scale. Due to the lack of randomized controlled trials focusing on OM as the primary outcome variable and heterogeneity of scales used to measure OM, a meta-analysis could not be performed; however pooled analysis indicated significant differences in incidence of OM with respect to different conditioning regimens (figures 1&2).

Conclusions: To our knowledge, this is the first analysis on OM in ASCT patients and we found that RIC regimens led to a very high incidence of OM similar to that of MA regimens. Clinical trials on treatment of OM are lacking emphasizing the essential need for prospective studies in this arena. A significant variance in the criteria for grading OM undermines the importance of establishing standard grading system for OM measurement in future ASCT clinical trials globally.